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Arterial-Spin-Labeling (ASL) perfusion MRI predicts cognitive function in elderly individuals: a four-year longitudinal study

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Abstract

Background—With the disappointing outcomes of clinical trials on patients with Alzheimer's disease or Mild-Cognitive-Impairment (MCI), there is increasing attention to understanding cognitive decline in normal elderly individuals, with the goal of identifying subjects who are most susceptible to imminent cognitive impairment.

Purpose/hypothesis—To evaluate the potential of cerebral blood flow (CBF) as a biomarker by investigating the relationship between CBF at baseline and cognition at follow-up.

Study type—Prospective longitudinal study with a 4-year time interval.

Population—Three hundred and nine healthy subjects aged 20 to 89 years old.

Field strength/sequence—3T Pseudo-Continuous-Arterial-Spin-Labeling MRI.

Assessment—CBF at baseline and cognitive assessment at both baseline and follow-up.

Statistical tests—Linear regression analyses with age, systolic blood pressure, physical activity, and baseline cognition as covariates.

Results—Linear regression analyses revealed that whole-brain CBF at baseline was predictive of general fluid cognition at follow-up. This effect was observed in the older group (age≥54 years, β=0.221, p=0.004), but not in younger or entire sample (β=0.018, p=0.867 and β=0.089, p=0.098, respectively). Among major brain lobes, frontal CBF has the highest sensitivity in predicting future cognition, with a significant effect observed for fluid cognition (β=0.244 p=0.001), episodic memory (β=0.294, p=0.001), and reasoning (β=0.186, p=0.027). These associations remained

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significant after accounting for baseline cognition. Voxel-wise analysis revealed that medial frontal cortex and anterior cingulate cortex, part of the default-mode-network (DMN), are among the most important regions in predicting fluid cognition.

Data conclusion—In a healthy aging cohort, CBF can predict general cognitive ability as well as specific domains of cognitive function.

Keywords

cerebral blood flow; cognition; arterial spin labeling; aging; episodic memory; Alzheimer's disease

INTRODUCTION

Alzheimer's disease (AD) and related dementia affects 47 million people worldwide (1). Disappointing outcomes from a large number of clinical trials suggest that once a patient's cognitive impairment has reached a level of clinical significance, treatment options are very limited (2). Therefore, the focus of recent research has shifted toward understanding cognitive changes in non-demented elderly population and their neurobiological correlates (3). Along the same lines, anti-amyloid clinical trials have started focusing on high-risk, but cognitively normal individuals with the goal to delay the onset of their cognitive decline (4).

It is known that cognitive abilities, especially those related to performing tasks (i.e. fluid cognition), decline with age starting from the third decade of life (5). An extensive body of neuroimaging literature indicates that brain structure and function both deteriorate with age, including reduced brain volume and cortical thickness (6) diminished tissue microstructural integrity (7), elevation in iron content (8), and alterations in neural activation patterns (9). What is not fully understood is how these biological changes can be associated with cognition and, more importantly, whether a particular biomarker can predict cognitive performance at a future time point.

Cerebral blood flow (CBF) indicates the amount of blood supply to the brain tissue. CBF decreases with age (10), and this age-related CBF reduction has been attributed to changes in cerebral blood vessel density, fibrogenesis of basement membranes, degeneration of pericytes, and a decreased elasticity of arteries, arterioles and capillaries (11). Compared to cerebrovascular reactivity measurements which evaluate the elasticity of blood vessels (12), CBF measurements have the advantage that they can also report neural dysfunction or reduced neural activity because of a tight coupling between these two parameters, known as the neurovascular coupling. In comparison to structural properties, CBF may be more sensitive in predicting cognitive changes and is more amenable to interventions. Compared to functional magnetic resonance imaging (MRI), CBF represents a more direct assessment of brain physiology as it provides a quantitative measurement of brain perfusion in ml/100g/min. To date, there are limited studies on the relationship between CBF and cognition in cognitively normal elderly individuals (3). Furthermore, existing studies have only examined cross-sectional relationship, but do not address the predictive value of CBF in future cognitive performance.

Thus, the purpose of the present study was to examine the relationship between CBF and cognitive function in a longitudinal setting.

MATERIALS AND METHODS

Subjects and study design

Subjects were recruited from the cohort of a large-scale aging study, the Dallas Lifespan Brain Study (DLBS). The DLBS is a longitudinal life span study on cognitive aging and neuroimaging (13). The study protocol of the DLBS was approved by the Institutional Review Board of the University of the Texas Southwestern Medical Center, and conformed to the standards set by the latest revision of the declaration of Helsinki. All subjects included in the DLBS study signed written informed consent.

A total of 309 subjects aged between 20 and 89 years old were included in this study. The subjects were of generally good health with no serious or unstable medical conditions such as neurological or psychiatric disease, brain injury, uncontrollable shaking, history of bypass surgery or chemotherapy, or use of medications that affect cognitive function. The subjects had no contra-indications for MRI, were all native English speakers with at least high school education and a Mini-Mental State Exam (MMSE) score of 26 or higher at initial enrollment (14).

During the first visit of the study (‘baseline’) which took place between 2008 and 2011, each participant received an MRI scan that included a Pseudo-Continuous-Arterial-Spin-Labeling (pCASL) CBF sequence. A comprehensive cognitive assessment (see below for details) was performed through two separate visits. During the follow-up visit, which took place between 2012 and 2015, the cognitive assessment procedures were repeated.

Assessment of general cardiovascular health

Participant characteristics (age, gender, race and ethnicity) were collected in each subject. Since cognitive function could be affected by general cardiovascular health in addition to CBF, we also included cardiovascular indices of blood pressure and physical activity measured at baseline in our study. Five blood pressure measurements were performed, which include one blood pressure measurement during the MRI visit and two blood pressure measurements during each of the two cognitive assessment visits. Blood pressure was measured using a calibrated mercury sphygmomanometer and a stethoscope. Measurements were taken while the participant was seated with forearm positioned horizontally and at heart level. The mean systolic blood pressure of the 5 measurements was calculated and used as a measure for blood pressure (15).

An ‘activity lifestyle’ questionnaire was administered. In this questionnaire, subjects reported on 64 activities using a 9-point likert scale (never, less than once a year, about once a year, 2 or 3 times a year, about once a month, 2 or 3 times a month, about once a week, 2 or 3 times a week, or daily) (16). Four of the 64 activities (gardening indoors or outdoors; engaging in outdoor activities such as sailing, fishing or backpacking; engaging in recreational sports such as tennis, bowling or golf; engaging in exercise activities such as jogging, swimming, bicycling or walking) were used to create an item pool of ‘physical

activity'. Score on this item pool was used as a physical activity index, where a higher score indicates a greater level of activity.

Magnetic Resonance Imaging

Magnetic Resonance Imaging was performed on a 3T system (Philips Healthcare, Best, the Netherlands) with a body coil for radiofrequency transmission and an 8-channel head coil with parallel imaging capability for signal reception. Foam padding was used to stabilize the head and minimize head motion. The MRI protocol consisted, among other sequences, of a T_1-weighted magnetization-prepared rapid acquisition of gradient echo sequence (T_1-MPRAGE) and a pCASL sequence (17). The scan parameters of the T_1-MPRAGE sequence were as follows; TR/TE/TI = 8.1 ms/3.7 ms/1100 ms, shot interval 2100 ms, flip angle = 18°, voxel size 1×1×1 mm^3, number of slices 160, sagittal slice orientation and duration 3 min and 57s. Scan parameters of the pCASL sequence were: FOV = 240×240 mm^2, matrix = 80×80, 27 axial slices, thickness = 5mm, TR/TE = 4020 ms/14 ms, labeling duration = 1.65s, post-labeling delay = 1.5 s, single-shot echo-planar imaging (EPI), 30 pairs of label and control images, and duration 4 min. The post-labeling delay was slightly shorter than that recommended in the 'ASL white paper' (18) because the study started in 2008, seven years before the white paper was published.

Cognitive assessment

Four domains of cognitive function were assessed: processing speed, working memory, reasoning, and episodic memory. *Processing speed* was evaluated using the Digit Comparison Task, adapted from Letter Comparison Task of Salthouse & Babcock (19), and WAIS-III Digit Symbol (20). *Working memory* was measured using the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (21) and WAIS-III Letter Number Sequencing (20). *Reasoning* was estimated using the Raven's progressive matrices (22), ETS letter sets (23) and CANTAB Stockings of Cambridge (21). *Episodic memory* was assessed using the modified Hopkins Verbal Learning Task (HVLT) (24) and the CANTAB Verbal Recognition Memory Task (21). A detailed description of each of the cognitive tests is given in the Supplementary Text. Additionally, MMSE was also administered (14).

Data analysis

MRI data analysis—MRI data analysis was performed using MRICloud (www.mricloud.org) (25). MRICloud is a cloud-based computational platform for MR image analysis, and can be accessed through a web-based user interface. In this study, T_1-multi-atlas and ASL toolboxes of the MRICloud were used. Briefly, the pCASL control and label images were realigned for motion correction. Pairwise subtraction was performed to obtain a CBF-weighted image (24). Quantification of CBF in physiological units (ml/100g/min) followed recommendations provided in the ASL white paper (18):

$$CBF = \frac{6000 \cdot \lambda \cdot SI_{difference} \cdot e^{\frac{PLD}{T_{1blood}}}}{2 \cdot \alpha \cdot T_{1blood} \cdot M_0 \cdot (1 - e^{\frac{-\tau}{T_{1blood}}})} [\text{ml}/100\text{g}/\text{ min }] \quad \text{Eq.1}$$

where λ is the brain/blood partition coefficient, assumed to be 0.9 ml/g; $SI_{difference}$ is the signal difference between the control and label images; T_{1blood} is the longitudinal relaxation time of blood and was set at 1650 ms; α is the labeling efficiency and was assumed to be 0.85; M_0 reflects the signal intensity of spins at equilibrium and was estimated from the control images after T_1 correction; τ is the label duration (1650 ms) and PLD is the post-labeling delay (1525 ms). This procedure yields CBF map in pCASL image space.

The MRICloud toolboxes then transformed CBF image in individual space to template space, i.e. Montreal Neurological Institute (MNI) 152 standard-space, using the T_1-MPRAGE image as an intermediate. Specifically, CBF map in the individual space was first co-registered to the individual MPRAGE image by means of a 12-parameter affine transformation. Then, the individual MPRAGE was normalized to the MNI template, in which multiple brain atlases were used to transform (elastic transformation (13)) the individual image to the template and the warped images were automatically segmented into major brain regions (26). The transformation was also applied to the CBF map to convert it into the MNI space. Although the MRICloud is capable of segmenting the entire brain into several levels of discrete regions (up to 289 regions), for the purpose of this study, we focused on CBF in gray matter of major brain lobes, including frontal, parietal, temporal, and occipital, as well as in whole-brain cortical gray matter. Potential partial voluming effects were accounted for by using subject-specific gray-matter ROIs (obtained from the MRICloud T1-parcellation toolbox) that minimize the inclusion of any white matter or CSF voxels.

Analysis of cognitive data—Each cognitive test results in a numeric score. These raw scores were first transformed into z-values using the mean and standard deviation of the subject group on that test. Next, z-values of multiple tests in the same cognitive domain were averaged to compute a domain-specific construct score. Four cognitive domains were evaluated, including processing speed, working memory, reasoning, and episodic memory. If data from one or more tests within a domain was missing, the construct z-score was not calculated for the subject. Finally, a fluid ability construct (27), which reflects the overall intelligence or problem-solve capacity, was calculated by computing a mean z-score across all domains. The above calculation was performed separately for baseline and follow-up data.

In addition, change in cognition over time was also calculated. Baseline data for each test was converted to z-scores which were followed by a transformation of follow-up data using the baseline mean and standard deviation. The change in cognition was calculated as the difference between follow-up and baseline z-scores. Based on this calculation, a negative value in the difference score would suggest a decline while a positive value suggests an

improvement in cognition over time. These calculations were performed for individual cognitive domains as well as for the general fluid ability.

Statistical analysis

Analyses were performed using Matlab R2009a (Mathworks Inc., Natick, MA, 2009) and SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp.).

Since the main goal of this study is to examine whether CBF measured at baseline can predict cognition at follow-up, the planned analysis was the association between these two measures. Furthermore, to account for the influence of baseline cognition on the follow-up measure, when a potential association between CBF and follow-up cognition was observed, we conducted an additional analysis by including baseline cognition as a covariate in the model. An association was considered meaningful only when the results remained significant after accounting for baseline cognition. For age stratification, because cognitive changes and variations are more relevant in the older population, our primary analyses focused on the CBF-vs-cognition association in participants 54 years (mean age in our sample) and above, with the whole-sample examination as a secondary analysis.

The relationship between CBF and cognition was explored using bidirectional step-wise linear regression analyses. Cognitive scores were used as the dependent variable and CBF in major lobes (i.e. frontal, parietal, temporal, and occipital) served as the independent variables, with age, blood pressure and physical activity serving as covariates. The rationale for including these covariates was as follows. Previous studies have shown associations between cognition and age (5), physical activity (28) or blood pressure (29), and we wanted to remove their influence on the CBF-cognition relationship. In a separate analysis, whole-brain gray matter (GM) CBF was used as the independent variable. For cognition, fluid and domain constructs (processing speed, working memory, reasoning, and episodic memory) were considered.

For all analyses, the significance threshold was set at $p<0.05$. Corrected p-values were also calculated and provided. The correction for multiple comparisons was performed using the method described by Šidák (30). The multiple comparison corrections account for the multiple brain lobes investigated. All p values were based on two-tail results except for the analyses of investigating the influence of adding baseline cognition as a covariate on the predictive results, because in those analyses the direction (i.e. positive or negative) of association is known from the basic model analyses.

To corroborate the lobar results, a voxel-wise multiple regression analysis was performed in which fluid cognition at follow-up was the independent variable and voxel-wise baseline CBF was the dependent variable. The voxelwise analysis was performed on whole-brain CBF maps including both gray and white matter voxels. Age, blood pressure, and physical activity were covariates. The analysis was performed in MNI space using Statistical Parametric Mapping (SPM, University College London). Significant clusters were delineated using a voxel-wise threshold of $p=0.001$ and a cluster size of 379 voxels. This corresponds to a family-wise error (FWE) threshold of $p=0.01$.

As an exploratory analysis, we investigated the association between baseline CBF and changes in cognition, i.e. z-score at follow-up minus z-score at baseline. A step-wise linear regression similar to the one described above was used. We examined the association between whole-brain CBF and general fluid cognition. We also examined the association between each of the brain lobes with each of the cognitive domains. Multiple comparison corrections similar to the one described above were performed.

RESULTS

Characteristics of the participants

At baseline, three hundred and nine participants received MRI scan and cognitive assessment. Of these, 10 subjects had poor pCASL image quality as determined by an experienced rater and were excluded from further analysis. Of the remaining 299 subjects, cognitive assessment was performed in 216 subjects at follow-up. The time interval between baseline and follow-up was 4.1±0.2 (mean±SD) years. The participants who did not return for follow-up were not different from those who returned in terms of age range ($p=0.33$), education ($p=0.87$), physical activity ($p=0.12$), or systolic blood pressure ($p=0.82$), but were found to have a trend of lower MMSE ($p=0.09$).

Quantitative mean CBF maps (in ml/100g/min) stratified by age ranges are displayed in Figure 1. As we can see, CBF continuously decreases with age but the quality of the images is satisfactory throughout the lifespan.

Demographic information and characteristics of the participants, including age, gender, race and ethnicity, mean systolic blood pressure, physical activity, and MMSE at baseline and at follow-up, are given in Table 1. Information on the older subcohort (aged ≥ 54 years) is also shown in this table. Based on MMSE scores, all participants were considered free of mild cognitive impairment or dementia at year 4 follow-up. The lowest MMSE score of the participants was 25 (N=3). Figure 2 displays whole-brain CBF, systolic blood pressure, physical activity and fluid cognitive function at baseline, stratified by age decades. There was an age-related decrease in CBF ($p<0.001$) and cognition ($p<0.001$) and an age-related increase in blood pressure ($p<0.001$), while physical activity was not age-dependent ($p=0.63$). From the baseline and follow-up cognitive data, changes in fluid cognition were calculated and are also shown in Figure 2. As can be seen, older participants manifested a faster decline in cognitive function compared to younger subjects. Additionally, we evaluated the stability of the cognitive data between baseline and follow-up. Their scatter plot is shown in Supplementary Figure S1. As expected, a strong association is observed between cognition measured at baseline and at follow-up.

Whole-brain CBF is predictive of cognition

In older individuals, whole-brain CBF at baseline was predictive ($\beta=0.221$, $p=0.004$) of fluid cognition (i.e. a construct of four cognitive domains including processing speed, working memory, reasoning and episodic memory) four years later at follow-up, after accounting for age, blood pressure, and physical activity. Higher blood flow at baseline is associated with better cognitive performance at follow-up. Figure 3 shows a scatter plot between whole-

brain CBF at baseline and fluid cognition at follow-up in the older group. After accounting for cognition at baseline, the association between whole-brain CBF at baseline and fluid ability at follow-up was weaker but remained significant (β=0.099, p=0.031). Across the entire cohort, whole-brain CBF was not predictive of fluid cognition (p=0.098).

In terms of specific cognitive domains, whole-brain CBF was predictive of follow-up episodic memory in older individuals, with (β=0.207, p=0.008) or without (β=0.270, p=0.002) accouting for memory scores at baseline. A similar association was observed when using data from the entire cohort.

Frontal lobe CBF plays an important role in cognitive function

Among all lobes examined, frontal lobe was found to be the most sensitive in predicting cognitive performance. Frontal CBF at baseline was predictive of follow-up fluid ability in the older group (β=0.244, uncorrected p=0.001, corrected p=0.004). This association remained significant after adjusting for baseline fluid ability (β=0.109, p=0.021). No such association was observed in the entire cohort.

For individual cognitive domains investigated, frontal CBF was most strongly predictive of episodic memory and this relationship was observed in the older group (β=0.294, uncorrected p=0.001, corrected p=0.004) and, to a lesser extent, in the entire cohort (β=0.205, uncorrected p=0.006, corrected p=0.024). Figure 4 shows a scatter plot between frontal CBF at baseline and episodic memory at follow-up in the older group. These associations remained significant after adjusting for baseline episodic memory, in both the older group (β=0.204, p=0.009) and the entire cohort (β=0.143, p=0.019).

Frontal CBF also showed a predictive value for reasoning ability, although this relationship was only observed in the older group (β=0.186, uncorrected p=0.027, corrected p=0.104). This relationship remained significant after adjusting for baseline reasoning ability (β=0.152, p=0.006).

Frontal CBF was not associated with other cognitive domains.

CBF and cognition in parietal, temporal and occipital lobes

Baseline CBF in the occipital lobe, parietal lobe, and temporal lobe was not predictive of any cognitive domains at follow-up.

Relationship between CBF and *changes* in cognition

We conducted an exploratory analysis to investigate the potential association between CBF and cognitive changes. Reasoning change between baseline and follow-up was dependent on parietal CBF and this relationship was observed in the older group (β=0.209, uncorrected p=0.029, corrected p=0.111) and the entire cohort (β=0.163, uncorrected p=0.018, corrected p=0.070). Additionally, changes in reasoning ability were also associated with whole-brain CBF (β=0.142, p=0.040) in the entire cohort. No other associations were observed between lobar CBF and changes in cognitive functions.

Voxel-wise analyses

Figure 5 illustrates brain regions where baseline CBF was associated with follow-up fluid ability in the older group, after accounting for the effects of age, blood pressure, and physical activity on cognitive performance. Consistent with the lobar analysis, significant clusters were observed in the frontal lobe, in particular in the medial frontal cortex and anterior cingulate cortex (ACC). Table 2 summarizes the location and size of all significant clusters.

DISCUSSION

The major findings of this longitudinal aging biomarker study were: (1) Non-invasive imaging of CBF can predict general cognition, i.e. fluid ability, measured four years later; (2) Among all brain lobes, frontal lobe CBF is the most sensitive in predicting future cognition, especially in the cognitive domain of episodic memory; (3) CBF is more sensitive in predicting cognition in older than in younger individuals; (4) CBF in medial frontal cortex/anterior cingulate cortex seems to be particularly important for an individual's cognitive ability; (5) The predictive value of CBF on cognition remains after accounting for current cognition.

While cross-sectional studies are important in understanding the neurobiological underpinnings of cognitive performance (3), clinically it is of greater significance to identify biomarkers that can predict future cognitive ability. Such efforts have begun to be undertaken in patients with cognitive impairment and dementia. Park et al. examined 39 patients diagnosed with mild cognitive impairment (MCI) and revealed that patients who converted to AD over 19 months' time displayed a lower cingulate and precuneus CBF as measured by single-photon-emission-computed-tomography (SPECT) (31). Benedictus et al. studied patients with AD and observed that those who manifested a faster cognitive decline revealed a lower whole brain and parietal CBF as measured by ASL MRI (32). Similarly, Chao and colleagues followed 48 MCI patients for 2.7 years and reported that CBF in right inferior parietal and right middle frontal perfusion were predictive of conversion to dementia (33). However, no prior studies have reported a predictive value of CBF in cognitively normal individuals in a longitudinal setting. Our results showed, for the first time, that CBF measured by non-invasive ASL MRI can predict an individual's general cognitive ability four years later.

Furthermore, the comprehensive cognitive batteries used in the present study afforded us the ability to study specific cognitive domains and their association with CBF. The strongest association was found between episodic memory and CBF. Episodic memory is known to be prone to age-related decline and was found to be an early sign of AD (34). Thus, markers that can predict decline in episodic memory are of significant importance in clinical studies of dementia. Our results are in accordance with a recent study that found that frontal CBF can predict conversion from MCI to AD (33). Interestingly, frontal lobe is the region where age-related CBF reduction is most pronounced in the brain (10). Our further investigation using voxel-based regression analysis revealed that, within the frontal lobe, medial frontal cortex/anterior cingulate cortex are the most sensitive in predicting cognition. This brain region is part of the default mode network (DMN) and is intricately involved in the

pathophysiology of MCI and AD (35). Consistent with this observational study, recent interventional studies have suggested the same brain region mediating (i.e. CBF was augmented) the salutary effect of aerobic exercise on cognition, in both MCI patients (36) and elderly normal volunteers (37).

Cerebral blood flow is one of the potential biomarkers to predict cognitive performance in elderly individuals. It should be pointed out that a number of other imaging measures have also been used to relate brain biology to cognition. For example, Fjell et al. observed that entorhinal atrophy rate was predictive of memory decline, consistent with the role of medial temporal lobe in encoding memory (6). Abnormalities in white matter microstructure and functional connectivity were found in patients with dementia (38). Other studies investigated the effects of disease risk factors on cognition and reported that lacunar infarcts and white matter hyperintensities as seen on fluid-attenuated inversion recovery (FLAIR) MRI are predictive of functional decline (39). These other brain measures contain complementary information about brain health and can be used together with CBF to provide a more accurate prediction of future cognitive status.

Our results suggest that the highest correlation between CBF and future cognition is observed in the older population. When we applied a similar analysis to the younger population, no significant effect was identified for any cognitive domains or brain lobes ($p>0.05$ for all analyses). When we applied the analysis methods to the entire cohort, statistical significance level of the predictive effects was also considerably attenuated despite almost doubling the sample size (216 vs. 115). This finding underscores the idea that CBF variations across elderly individuals are more indicative of cognitive problems, whereas in young individuals such differences may be more likely attributed to other normal variations in physiology that are not related to cognitive performance. The results may also indicate that younger individuals have a greater cognitive or physiological reserve that can compensate for any reduction in blood flow. Indeed, a recent study (40) has shown that blood supply's reserve in the brain diminishes by more than 50% comparing 80 years old to 20 years old individuals.

A few earlier studies have shown that systemic cardiovascular health such as physical activity (28) and blood pressure (29) could also affect cognition. Given our primary interest to study the impact of brain health on cognitive function, we have used physical activity and blood pressure as covariates in the model and thereby factored out their influences in our analysis. We found that CBF can predict cognitive performance, independent of these systemic factors. This finding is consistent with a recent cross-sectional study in healthy middle-aged (35–60 years old) adults, which found that prehypertension and CBF are independently related to cognitive performance (15). Our results further strengthen the notion that the effect of CBF on cognition cannot be simply attributed to systemic factors of cardiovascular health.

Although the primary analysis of this study focused on the predictive value of baseline CBF on follow-up cognition, we also added baseline cognition as a covariate in the regression model and examined whether the predictive effect of CBF remained. Our results suggest that baseline CBF can explain variance in follow-up cognition beyond that explained by baseline

cognition, although the coeffient, i.e. β value, and significance level both become lower. We also conducted an exploratory analysis between baseline CBF and changes in cognition, i.e. follow-up minus baseline. Changes in reasoning ability were associated with baseline CBF and the specific brain region implicated was the parietal lobe. This finding is consistent with the observations by Rieck et al. that fMRI activation in the parietal lobe is correlated with scores of reasoning ability (9).

Strengths of our study include a large sample size (216 participants with 115 participants >54 years old at follow-up), that it examines four-year longitudinal change data, and that all participants were imaged at a single-site on one MRI system, which ensures data harmonization without the need to consider site variations in equipment or test procedures. Our cognitive tests were comprehensive and include multiple cognitive domains with each domain consisting of multiple tasks. Our CBF technique was also state-of-the-art in that we started collecting pCASL MRI data in 2008, at a time when this method was still an emerging research sequence and seven years before its recommendation by the “ASL white paper” (18).

A limitation of the study is that the present work has primarily focused on the effect of CBF in predicting future cognition, but did not compare CBF with other neuroimaging markers such as brain volume, cortical thickness, or white matter hyperintensity volume in FLAIR MRI. We reasoned that, given the complexity of this work which includes different brain regions, multiple cognitive domains, two time points, and a large age span of the cohort, the addition of more imaging modalities would make study analyses complicated and dilute the primary focus of this investigation. Therefore, we compared our results to other relevant imaging markers reported in the literature. Another limitation is that our ASL MRI sequence was only performed during baseline visit, but not follow-up. Thus, we were not able to assess CBF changes between the two time points. However, imaging biomarkers of a single time point is expected to be most useful in clinical applications, especially if a single-point measure can predict future clinical or cognitive status. Multiple imaging time points tend to increase patient burden and cost of care, and result in a high attrition rate, and reduce signal-to-noise ratio of the image data (as noise tends to add up even when performing image subtractions). Additionally, it should be highlighted that our findings are based on a relatively healthy cohort of highly educated participants. Therefore, caution should be used when extending these observations to other cohorts, especially those with poorer cognitive status. Finally, we would like to point out that, in our multiple comparison correction, we have primarily accounted for multiple brain regions investigated, but not multiple cognitive domains. This is because correction of multiple domains in addition to multiple brain regions, while minimizing false positive findings, would result in considerable false negative errors, thereby missing potentially important findings. We therefore selected to report results without accounting for multiple cognitive domains, but pointing out that future studies are needed to verify the associations observed in our study.

In conclusion, data presented in this study suggest that cerebral blood flow measured with non-invasive MRI can predict cognitive scores in older subjects four year later. In particular, cerebral blood flow in the frontal lobe was strongly predictive of episodic memory. Collectively, our findings suggest that imaging measures of brain perfusion may provide a

useful biomarker for early detection of cognitive decline, identification of suitable cohorts for clinical trials, and monitoring of treatment effects in cognitively impaired populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
AD	Alzheimer's disease
ASL	Arterial-Spin-Labeling
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBF	Cerebral blood flow
DLBS	Dallas Lifespan Brain Study
DMN	Default mode network
EPI	Echo-planar imaging
FLAIR	Fluid-attenuated inversion recovery
FWE	Family-wise error
HVLT	Hopkins Verbal Learning Task
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Exam
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
pCASL	Pseudo-Continuous-Arterial-Spin-Labeling
PLD	Post-labeling delay
Sd	Standard deviation
SPECT	Single-photon-emission-computed-tomography
SPM	Statistical Parametric Mapping

T_1-MPRAGE T_1-weighted magnetization-prepared rapid acquisition of gradient echo

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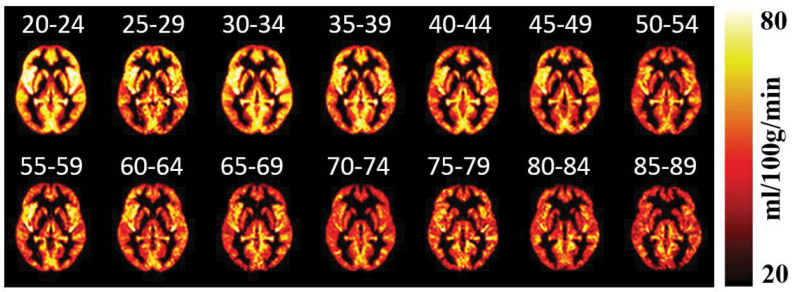

Figure 1.

Mean CBF maps stratified by age groups (at an interval of 5 years). Within each interval, all available participants were averaged after their CBF maps were normalized into the MNI space. Cerebral blood flow noticeable decreases with age.

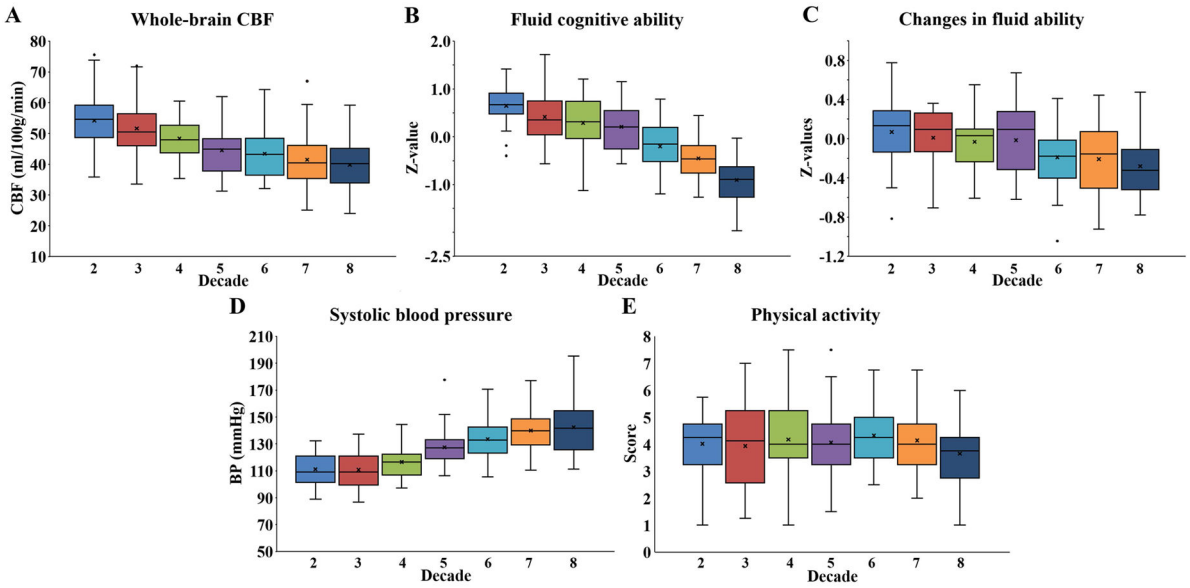

Figure 2.

Box-whisker plots of **(A)** whole-brain CBF, **(B)** fluid cognitive ability, **(C)** changes in fluid cognition, **(D)** systolic blood pressure, and **(E)** physical activity. Mean values and standard deviations per decade are shown.

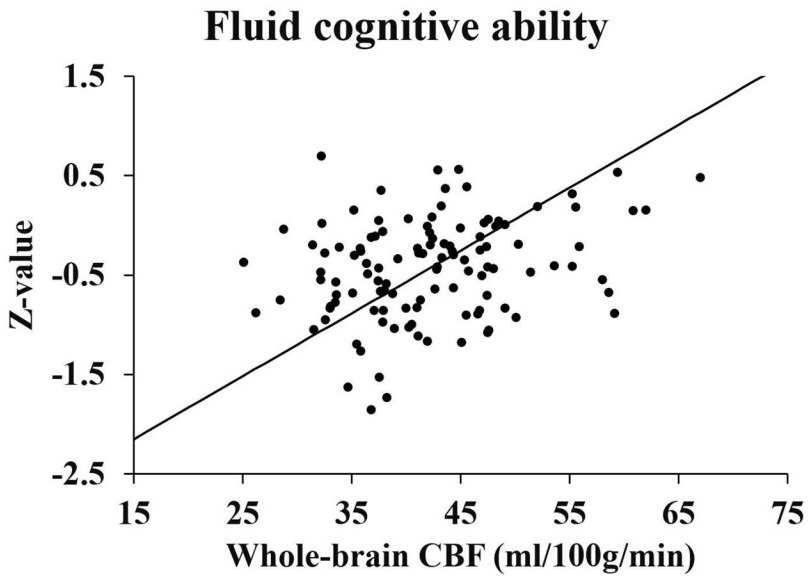

Figure 3.

Scatter plot between baseline whole-brain CBF and follow-up fluid cognitive ability in the older group. These results demonstrate a significant association between whole-brain CBF and fluid cognitive ability, corrected for age.

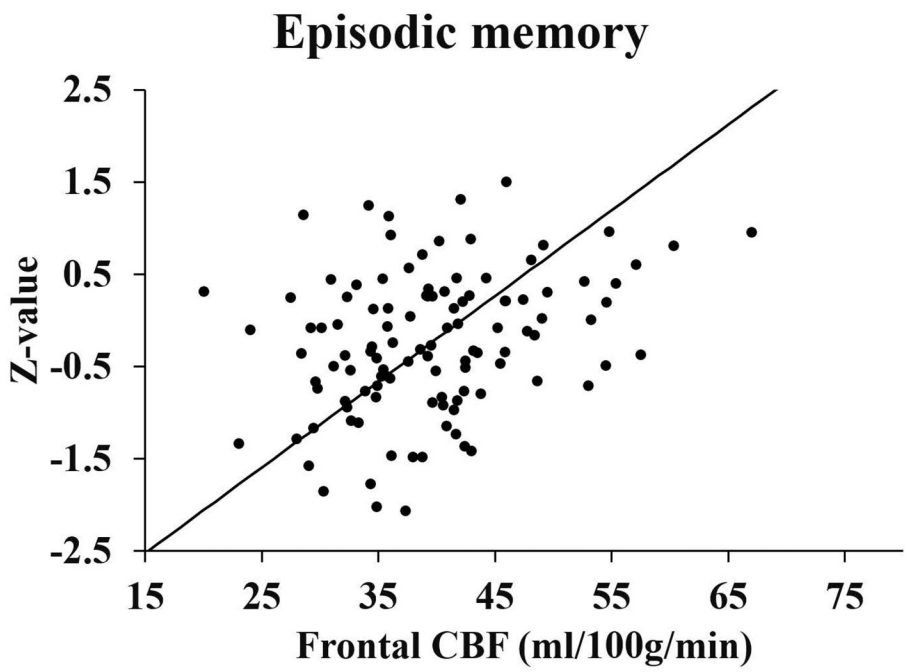

Figure 4.

Scatter plot between baseline frontal CBF and follow-up episodic memory. Stepwise linear regression analysis retained both frontal CBF and age in the prediction model of episodic memory at follow-up in the older group. This scatter plot demonstrates the relation between frontal CBF and episodic memory, corrected for age.

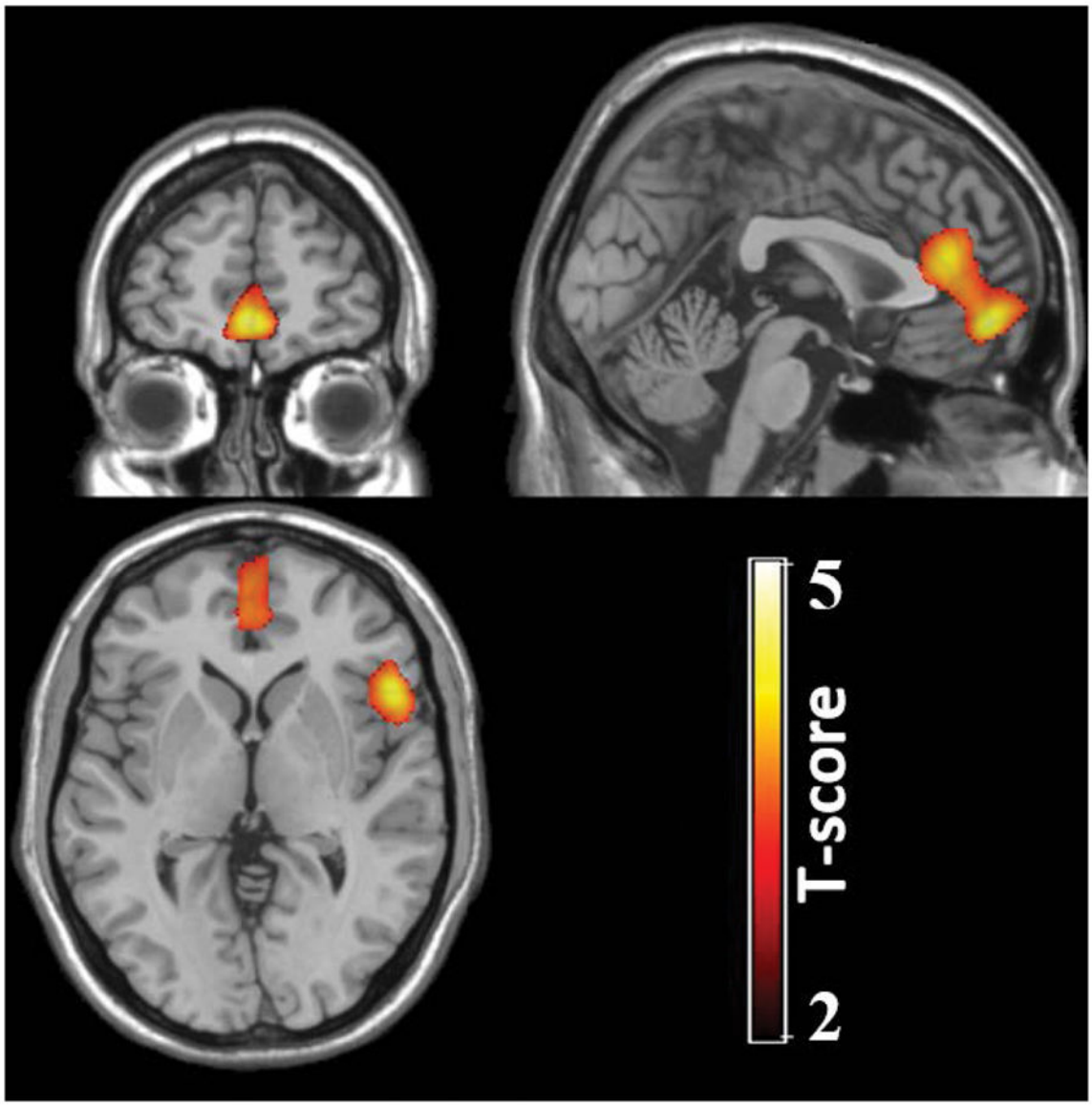

Figure 5.

Results of voxelwise analysis between baseline CBF and follow-up fluid ability in the older group, after accounting for age, blood pressure, and physical activity. The voxelwise results are overlaid on a template image (181×217×181) provided by the software MRIcro. The slice coordinates are 73, 183, and 91 for the axial, coronal, and sagittal images, respectively.

Table 1

Participants characteristics

Baseline characteristics	**Entire population N(%) or mean (±sd)**	**Subjects ≥ 54 yrs**
Age at baseline	54 (±19)	69 (±9)
Age at follow-up	58 (±19)	73 (±9)
Gender distribution at baseline	190 F – 109 M	97 F – 54 M
Gender distribution at follow-up	146 F – 70 M	80 F – 35 M
Race and ethnicity		
White caucasian/non-hispanic	248 (83%)	144 (95.4%)
Asian american/pacific islander	15 (5%)	-
Black/african americans	12 (4%)	2 (1.3%)
Hispanic/latin	10 (3%)	-
Multiracial	7 (2.3%)	1 (0.7%)
American indian/alaskan native	3 (1%)	2 (1.3%)
Middle eastern	1 (0.3%)	-
White/mediterranean	1 (0.3%)	-
Other	2 (0.7%)	2 (1.4%)
Systolic blood pressure	126 (±19) mmHg	137 (± 17) mmHg
Physical activity	4.1 (±1.2)	4.1 (±1.1)
Education	16 (±2) yrs	16 (±2) yrs
MMSE at baseline	28.3 (±1.3)	28.0 (±1.3)
MMSE at follow-up	29.3 (±1.1) *	29.0 (±1.2) *
Time between baseline *and* follow-up	4.1 (±0.2) yrs	4.0 (±0.2) yrs

* The increase in MMSE from baseline to follow-up was attributed to a training effect.

Table 2

Brain regions related to fluid cognitive ability.

Coordinates (x,y,z)			# of voxels	Regions
3	54	−8	1681	Medial frontal gyrus
				Anterior Cingulate
				Middle frontal gyrus
56	14	8	1033	Precentral gyrus
				Inferior frontal gyrus
16	10	60	413	Superior frontal gyrus
28	−70	−48	625	Inferior semi-lunar lobe
32	38	24	446	Middle frontal gyrus
28	−82	−10	411	Lingual gyrus
				Inferior occipital gyrus