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Regional Hypoperfusion Predicts Decline in Everyday Functioning at Three-Year Follow-Up in Older Adults without Dementia

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Abstract.
Background: Increasing evidence indicates that cerebrovascular dysfunction may precede cognitive decline in aging and Alzheimer's disease (AD). Reduced cerebral blood flow (CBF) is associated with cognitive impairment in older adults. However, less is known regarding the association between CBF and functional decline, and whether CBF predicts functional decline beyond cerebrovascular and metabolic risk factors.
Objective: To examine the association between regional CBF and functional decline in nondemented older adults.
Method: One hundred sixty-six (N = 166) participants without dementia from the Alzheimer's Disease Neuroimaging Initiative underwent neuropsychological testing and neuroimaging. Pulsed arterial spin labeling magnetic resonance imaging was acquired to quantify resting CBF. Everyday functioning was measured using the Functional Assessment Questionnaire at baseline and annual follow-up visit across three years.
Results: Adjusting for age, education, sex, cognitive status, depression, white matter hyperintensity volume, cerebral metabolism, and reference (precentral) CBF, linear mixed effects models showed that lower resting CBF at baseline in the medial temporal, inferior temporal, and inferior parietal lobe was significantly associated with accelerated decline in everyday functioning. Results were similar after adjusting for conventional AD biomarkers, including cerebrospinal fluid (CSF) amyloid-β (Aβ) and hyperphosphorylated tau (p-tau) and apolipoprotein E (*APOE*) ε4 positivity. Individuals who later converted to dementia had lower resting CBF in the inferior temporal and parietal regions compared to those who did not.
Conclusion: Lower resting CBF in AD vulnerable regions including medial temporal, inferior temporal, and inferior parietal lobes predicted faster rates of decline in everyday functioning. CBF has utility as a biomarker in predicting functional declines in everyday life and conversion to dementia.

Keywords: Activities of daily living, aging, Alzheimer's disease, biomarkers, cerebrovascular circulation, dementia, magnetic resonance imaging, neuropsychology, perfusion, regional blood flow

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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INTRODUCTION

The pathophysiological process of Alzheimer's disease (AD) begins many years before clinical symptoms emerge [1]. Goals of AD research include identification of biomarkers to facilitate early detection of pathology and prediction of clinical outcome. Identifying those individuals who are most likely to progress at predementia stages is essential so that treatments can be applied before extensive brain, cognitive, and everyday functioning changes occur. Thus, identifying early, reliable, and easily obtainable markers of brain changes in individuals at risk for AD is critical.

The association between cerebrovascular changes and AD has gained increasing attention, given growing evidence that vascular changes may accelerate cognitive decline associated with AD pathology, or, may be part of the earliest phase of AD pathogenesis [2–6]. Brain functioning requires constant cerebral blood flow (CBF) to ensure adequate delivery of oxygen, glucose, and nutrients, as well as removal of carbon dioxide and cellular waste [6]. Given the tight interactions between CBF and neuronal activity, CBF provides critical insights into how the brain is functioning [7]. Furthermore, the two-hit vascular hypothesis of AD proposes that blood vessel damage is the initial insult through which reduced brain perfusion leads to amyloid-β (Aβ) accumulation, suggesting that CBF could be a useful, early biomarker of downstream AD pathogenesis [5, 6, 8].

Quantification of CBF using arterial spin labeling (ASL) magnetic resonance imaging (MRI) is non-invasive and has advantages over other methods [9, 10]. Unlike positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) that use invasive radioactively labeled tracers, in ASL protons in arterial blood are magnetically labeled with a radiofrequency pulse and used as an endogenous tracer. The magnetization of arterial blood is altered in a region proximal to the image slice. This is followed by a delay to allow labeled blood to arrive at the capillary bed in the tissue of interest. The labeled blood diffuses into the tissue resulting in the local alteration of the longitudinal magnetization. Difference images are generated by subtracting images acquired with ASL from control images that are acquired in the absence of labeling. The resulting MRI difference image is proportional to CBF. ASL studies of AD patients demonstrate similar patterns of regional hypoperfusion as those revealed with PET and SPECT [9, 11].

Previous ASL MRI studies have revealed a complex pattern of associations between CBF and cognition such that both hypoperfusion and hyperperfusion have been associated with poorer cognition across the clinical AD spectrum, depending on the stage of AD (e.g., cognitively normal [CN] versus preclinical/"at-risk" versus mild cognitive impairment [MCI] versus dementia) and brain region of interest being investigated [6, 12–17]. The existing studies examining associations of resting CBF and cognitive functioning have most often been cross-sectional. The few existing longitudinal studies have typically shown that baseline CBF predicts cognitive impairment or cognitive decline [18–21]. Although few studies have examined longitudinal associations of regional CBF and cognitive functioning, even fewer have assessed the associations of CBF and everyday function. A previous SPECT imaging study reported cross-sectional associations of cerebral perfusion and instrumental activities of daily living (IADL) in individuals with mild AD [22]. To the best of our knowledge, there are no published studies that have examined regional ASL MRI CBF as a predictor of IADL in older adults without dementia.

Everyday functioning, and particularly complex IADL, has been associated with a number of cognitive functions, including general cognitive abilities, memory, and executive functioning [23–27]. However, the literature examining the specific cognitive correlates of everyday function is mixed. For example, some studies have observed that executive function, but not memory, is important in predicting functional abilities in older adults [26, 28] yet other studies have observed the reverse [29, 30]. Other research has found that executive dysfunction and memory difficulties may lead to different types of errors being more prominently committed during completion of everyday activities (e.g., inefficient actions versus omission errors) [27]. In addition, multiple studies have suggested that behavior including depression, apathy, and dysexecutive behaviors may be more strongly associated with functional abilities than neuropsychological measures [23, 31, 32]. Taken together, previous research suggests that, although cognitive function and everyday functioning are related, they are not redundant. Ultimately, it is impairment in everyday function that reduces a person's independence and quality of life, increases burden and stress on caregivers and families, and contributes to greater health service use and financial costs [33–36].

Although altered CBF (characterized by both hypoperfusion and hyperperfusion) has been associated with poorer cognitive functioning, it remains unclear whether CBF alterations measured with ASL MRI predict functional decline in older adults without dementia. Therefore, we examined the longitudinal association between regional resting CBF at baseline and later functional decline in a well-characterized sample of nondemented older adults.

METHODS

The ADNI dataset

Data used in the preparation of this manuscript were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). ADNI was initiated in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the latency of cognitive decline and the progression of MCI and early AD.

Participants

Enrollment criteria for ADNI have been previously described in detail elsewhere [37]. In brief, participants from ADNI were 55–90 years old, had $\geq$6 years of education or work-history equivalent, were fluent in English or Spanish, had a Geriatric Depression Scale (GDS) <6 (possible score range is 0–15) [38], had a Hachinski Ischemic Scale (HIS) scores $\leq$4, adequate vision and hearing to perform neuropsychological tests, were in generally good health and without significant head trauma or neurologic disease, were stable on permitted medications, and had a study partner. The current study included 166 participants without dementia (61 CN, 105 MCI) who had ASL MRI data within 12 months of their baseline visit, whose ASL data passed quality control inspection, and who also had available baseline neuropsychological testing and [^{18}F] fludeoxyglucose (FDG) PET imaging.

ADNI criteria for MCI were: 1) subjective memory complaints reported by themselves, study partner, or clinician, 2) objective memory loss defined as scoring below an education-adjusted cut-off score on delayed recall of Story A of the WMS-R Logical Memory Test (score $\leq$8 for those with $\geq$16 years of education; score $\leq$4 for those with 8–15 years of education; score $\leq$2 for those with 0–7 years of education), 3) global Clinical Dementia Rating (CDR) score of 0.5, and 4) general cognitive and functional abilities sufficiently preserved such that a diagnosis of dementia could not be made by the site physician at the screening visit.

ADNI criteria for AD diagnosis were met by the National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer's disease. Criteria for probable Alzheimer's disease are Mini-Mental State Examination (MMSE) [39] scores of 20 or above and CDR scores of 0.5 or 1 [40].

Functional Assessment Questionnaire (FAQ) data was available for all 166 participants at baseline, 147 participants at 12-months follow-up, 132 participants at 24-months follow-up, and 92 participants at 36-months follow-up. Given reductions in available data at 48 months of follow-up that resulted in less than half of the sample having FAQ data at that timepoint ($n = 80$), our analyses focused on follow-up to 36 months. This study was approved by the Institutional Review Boards of all participating institutions. Informed written consent was obtained from all participants at each site.

Assessment of everyday functioning

The FAQ, a standardized assessment of IADL, was administered as a measure of everyday functioning. As previously described [41–43], the FAQ was completed by each participant's study partner at baseline and annual follow-up visits. The study partner rated each participant's functional difficulties in the past 4 weeks on the following activities: 1) writing checks, paying bills, or balancing a checkbook; 2) assembling tax records, business affairs, or other papers; 3) shopping alone for clothes, household necessities, or groceries; 4) playing a game of skill such as bridge or chess, or working on a hobby; 5) heating water, making a cup of coffee, turning off the stove; 6) preparing a balanced meal; 7) keeping track of current events; 8) paying attention to and understanding a TV program, book, or magazine; 9) remembering appointments, family occasions, holidays, medications; 10) traveling out of the neighborhood, driving, or arranging to take public transportation. The study partners were asked to rate each participant's ability to perform the tasks on a 4-point scale: 0 (*normal*), 1 (*has difficulty but does by self*), 2 (*requires assistance*), or 3 (*dependent*). The FAQ total score was calculated as the sum

of the 10 individual activity scores (range = 0–30), with higher scores indicating a greater level of difficulty. Previous research has showed that a score of 6 or higher on the FAQ best indicates significant functional difficulties [44].

Arterial spin labeling and structural MRI data acquisition and processing

A detailed description of ADNI MR imaging data acquisition and processing can be found online (http://www.loni.usc.edu). Briefly, MR imaging was performed on a 3.0 Tesla MR scanners from a single vendor (MAGNETOM Trio, Verio, Skyra, and Siemens). Pulsed ASL scans were acquired using QUIPS II with thin-slice T11 periodic saturation sequence ("Q2TIPS") with echo-planar imaging [45]. The sequenced incorporated the following set parameters: inversion time of arterial spins (T11) = 700 ms, total transit time of the spins (T12) = 1900 ms, tag thickness = 100 mm, tag to proximal slice gap = 25.4 mm, repetition time = 3400 ms, echo time = 12 ms, field of view = 256 mm, 64×64 matrix, 24 4 mm thick axial slices [52 tag + control image pairs], time lag between slices 22.5 ms.

The ASL MRI data processing pipeline has been previously described [2]. Briefly, the processing was largely automated and included motion correction, aligning each ASL frame to the first frame using a rigid body transformation, and least squares fitting using SPM8. Perfusion-weighted images are computed as the difference of the mean-tagged and mean-untagged ASL datasets. Perfusion-weighted images were intensity scaled to account for signal decay during acquisition and to generate intensities in meaningful physiological units. After geometric distortion correction, ASL images were aligned to structural T1-weighted images. Given that we are interested in CBF in gray matter and therefore want to minimize the effects of the lower perfusion in white matter on our CBF estimates, a partial volume correction was performed that assumes that CBF in gray matter is 2.5 times greater than in white matter. The partial volume corrected perfusion-weighted images were normalized by the reference image (i.e., an estimate of blood water magnetization) to convert the signal into physical units (mL/100 g tissue/min). Quality control procedures include inspecting image quality and rating quality as either pass or fail. Those individuals whose ASL images failed quality control were excluded from the present study.

A T1-weighted 3D MPRAGE structural MRI scan was acquired during the same session as the ASL scan. The structural scan parameters were as follows: field of view = 256 mm, repetition time = 2300 ms, echo time = 2.98 ms, flip angle = 9, and resolution = $1.1 \times 1.1 \times 1.2\,\text{mm}^3$. FreeSurfer was used to skull-strip, segment, and parcellate the structural scans. In addition, T2-weighted fluid-attenuated inversion recovery (FLAIR) scans were collected. Parameters were as follows: field of view = 280 mm, field of view phase = 100.0%, slice thickness = 8.0 mm, TR = 20 ms, TE = 5 ms, flip angle = 40°.

FreeSurfer-derived anatomical regions of interest (ROIs) were applied and used to extract mean CBF for each participant. We examined the following four *a priori* ROIs: 1) medial temporal lobe (MTL), which included the hippocampus and entorhinal cortex, 2) inferior parietal lobe (IPL), 3) inferior temporal gyrus (ITG), and 4) pericalcarine cortex. The first three regions were chosen given prior work showing these regions were vulnerable to early AD-related changes [46] and showed associations between CBF and AD risk [2, 14, 15]. The pericalcarine ROI was selected as a control region given that there are no expected changes in AD as well as to be consistent with prior CBF analyses conducted in ADNI [14]. Also consistent with other CBF work in ADNI [6, 14, 15], CBF of the precentral gyrus was selected to serve as a reference region as it is not thought to be impacted in early AD and was used as a covariate in our statistical models. Mean CBF corrected for partial volume effects was extracted for each of the ROIs and reference region for each hemisphere separately. However, to reduce the number of comparisons, averaged bilateral CBF estimates for each ROI were used as the outcome variable in our models. Bilateral CBF estimates were calculated by averaging the mean CBF of each hemisphere. If participants were missing baseline ASL data but had ASL data within the first year of their baseline visit, the first occasion of ASL data was used in our analyses.

Cerebral metabolism

As previously described, brain glucose metabolism was measured by FDG PET [6]. Detailed information describing the FDG PET data acquisition, processing, and analysis is available online (http://www.loni.usc.edu). In brief, FDG scanning began 30 min after intravenous injection of an approximately 5 mCi dose of tracer. PET images

were spatially normalized to a Montreal Neurological Institute (MNI) PET template. Consistent with prior FDG PET studies in ADNI, a composite meta-ROI that is comprised of the standardized uptake value ratios (SUVRs) of the left and right angular gyri, left and right middle/inferior temporal gyri, and bilateral posterior cingulate gyrus. These brain regions show metabolic changes in MCI and AD that are associated with cognitive functioning [47, 48]. The meta-ROI was intensity normalized by dividing by the mean value for a pons and cerebellum reference region [48]. FDG PET of the meta-ROI was included as a covariate so that the CBF effects could be interpreted as independent of global cerebral glucose metabolism.

White matter hyperintensity (WMH) volume

Detailed methods for WMH volumetric quantification have been previously described in detail [6, 49–52]. Briefly, WMH volume was calculated using a Bayesian approach to segmentation of the high resolution T1-weighted and FLAIR scans. Non-brain tissues were removed from T1-weighted and FLAIR images, the FLAIR image was spatially aligned to the T1-weighted image, and MRI field artifacts were removed. Images were warped to a standard template space. The likelihood of WMH was estimated from FLAIR signal characteristics, prior probability maps of WMH occurrence calculated from previously supervised segmentations of independent FLAIR images from more than 700 individuals, and tissue class constraints. The segmented WMH masks were back-transformed to native space for volume calculation. If an individual was missing WMH data at the baseline visit, the first visit with WMH data was used as long as it was within 12 months of their baseline visit.

Additional AD genetic and CSF markers

Apolipoprotein E (*APOE*) ε4 positivity (*APOE* ε4+) was based on presence of at least one copy of the ε4 allele. A subset of participants underwent a lumbar puncture ($n = 146$) for collection of cerebrospinal fluid (CSF). CSF biomarkers of AD including Aβ and hyperphosphorylated tau (p-tau) levels were measured using Elecsys ® immunoassays.

Statistical analyses

Baseline demographic and clinical characteristics were examined with chi-square tests for categorical variables and *t*-tests for continuous variables. Linear mixed effects (LME) models examined the effect of regional CBF on rate of change in FAQ score over the 3-year interval as a function of baseline regional CBF. A separate model was run for each of the CBF ROIs (MTL, ITL, IPL, and pericalcarine). FAQ data from 4 timepoints including baseline, 12-, 24-, and 36-month follow-up visits was used in analyses. These models adjusted for baseline age, education, and sex as well as baseline depression (GDS total score), cognitive status (i.e., MCI versus CN), WMH volume, FDG SUVR, and reference (precentral) CBF.

We compared demographics and relevant variables of participants who had FAQ scores at 36-months to those who were missing data at 36-months. Baseline age, education, depression (GDS total score), WMH volume, FDG SUVR, regional CBF, CSF p-tau, and *APOE* ε4+ did not differ between those participants with and without FAQ data at 36-months (all p-values >0.05), but the participants with missing data were more likely to be cognitively normal ($\chi^2 = 54.57$, $p < 0.001$) and had higher CSF Aβ (reflecting lower Aβ in the brain; $t = 2.51$, $p = 0.013$) compared to those without missing data. Thus, cognitive status (MCI versus CN) was included as a covariate in primary models. CSF Aβ and p-tau were included as covariates in secondary analyses. Individual differences in intercept and slope were modeled as random effects. Full information maximum likelihood estimation was used to allow for all available data to be included [53, 54], which has been demonstrated to be less biased than list-wise deletion [55]. All continuous independent variables and covariates in the model were standardized to have a mean of zero and a standard deviation of one using z-score transformations.

To address potential inflation of type I error resulting from multiple comparisons, we applied the Benjamini-Hochberg procedure [56] to the two-way regional CBF x time interactions from the longitudinal primary models. We corrected for three comparisons given that we expected significant effects for the MTL, ITG, and IPL ROIs. We assessed results when the false discovery rate (FDR) was controlled at 0.05.

To determine whether the observed pattern of findings was significantly influenced by cognitive status (i.e., MCI versus normal cognition), we performed secondary analyses where we ran LME models adjusting for age, education, sex, depression, WMH volume, FDG SUVR, and reference (precentral) CBF and also added a cognitive group (MCI versus normal cognition) x time two-way interaction, a cognitive

Table 1
Demographics and clinical characteristics across the entire sample and by cognitive status

	Total $n = 166$		Normal Cognition $n = 61$		MCI $n = 105$			
	Mean	*SD*	Mean	*SD*	Mean	*SD*	T or χ^2	*p*
Baseline Characteristics								
Age, y	71.32	6.85	71.62	6.44	71.01	7.10	0.56	0.578
Education, y	16.57	2.61	16.38	2.45	16.69	2.70	–0.74	0.464
Sex (% female)	50.0%	—	44.6%	—	55.4.%	—	4.38	**0.036**
GDS	1.36	1.39	0.69	1.12	1.74	1.39	–5.35	**<0.001**
APOE ε4 (%+)	40.0%	—	30.3%	—	69.7%	—	1.75	0.186
Aβ, pg/ml	1244.59	665.81	1466.07	700.48	1125.69	617.99	3.03	**0.003**
P-tau, pg/ml	24.00	11.94	22.35	10.75	24.89	12.49	–1.23	0.221
LN WMH	1.11	1.18	0.92	1.17	1.22	1.17	–1.55	0.124
FDG SUVR	1.27	0.13	1.30	0.10	1.25	0.14	2.25	**0.026**
FAQ								
FAQ, baseline ($n = 166$)	1.44	2.67	0.16	0.49	2.18	3.11	–6.52	**<0.001**
FAQ, 12 months ($n = 147$)	2.47	4.80	0.19	0.57	3.58	5.50	–6.07	**<0.001**
FAQ, 24 months ($n = 132$)	2.99	6.04	0.23	0.66	4.57	7.11	–5.56	**<0.001**
FAQ, 36 months ($n = 92$)	5.07	8.34	0.36	0.67	5.70	8.69	–5.41	**0.001**

Results from independent samples t-tests for continuous variables and chi-square tests for dichotomous variables. Data are summarized as mean (standard deviation), unless otherwise indicated. Significant group differences ($p < 0.05$) appear in bold font. MCI, mild cognitive impairment; SD, standard deviation; GDS, Geriatric Depression Scale total score; *APOE*, apolipoprotein; Aβ, amyloid-β pg/ml, picograms per milliliter; P-tau, hyperphosphorylated tau; LN, natural log transformation; WMH, white matter hyperintensity; FDG, fludeoxyglucose; SUVR, standardized uptake value ratio; FAQ, Functional Assessment Questionnaire.

group x CBF two-way interaction, and a cognitive group x CBF x time three-way interaction. In addition, we performed a second set of secondary analyses wherein we re-ran the primary LME models above but additionally adjusted for *APOE* ε4 positivity and CSF Aβ and p-tau. We did not include these three additional covariates in our primary analyses given that a substantial number of participants ($n = 20$) were missing data on at least one of these variables. Therefore, the models with CSF biomarkers and *APOE* ε4 included 146 participants. Given that a steeper decline on FAQ score among those with greater age, greater WMH volume, or lower neuronal metabolism (who also likely have lower CBF) may represent potential sources of confounding, we performed a third set of secondary analyses wherein we re-ran the primary models including three additional interactions: age × time; WMH × time; and FDG × time.

Additional analyses of covariance (ANCOVA) were performed to compare those who converted to dementia within three years and those who did not. Adjusting for age, sex, education, GDS, and reference region CBF, we compared those who converted to dementia and those who did not in terms of baseline CBF in the MTL, ITL and IPL. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (SPSS IBM, New York, USA) and figures were created using the ggplot2 package in R (https://cran.r-project.org/web/packages/ggplot2/index.html).

RESULTS

Participants' baseline demographic data are presented in Table 1. Across the whole sample, participants' mean age at baseline was 71.32 (range = 55–85). The sample was 50% female and generally well-educated (mean years of education = 16.57; range = 9–20). The sample included 105 individuals with MCI and 61 with normal cognition. The CN group had a significantly higher proportion of women compared to the MCI group ($p = 0.036$). Relative to the CN group, the MCI group on average had lower baseline neuronal metabolism ($p = 0.026$) and lower CSF Aβ, which reflects higher Aβ in the brain ($p = 0.003$). The MCI group also had significantly higher GDS scores ($p < 0.001$) although the mean of both groups was low. As expected, there were significant differences in FAQ scores across cognitive group whereby the MCI group had higher scores (i.e., greater functional difficulties) relative to the CN group ($p < 0.001$). There were no group differences in terms of age, education, or baseline WMH volume.

LME models, adjusting for baseline age, sex, education, depression, cognitive status, WMH volume,

Table 2
Estimates for the full longitudinal model of the association of baseline CBF and functional abilities across the entire sample

	Medial Temporal			Inferior Temporal			Inferior Parietal			Pericalcarine		
	b	S.E.	*p*	b	S.E.	*p*	b	S.E.	*p*	b	S.E.	*p*
Intercept	1.684	0.639	**0.009**	1.766	0.641	**0.006**	1.430	0.640	**0.027**	1.435	0.647	**0.028**
Time	0.975	0.176	**<0.001**	0.906	0.179	**<0.001**	0.929	0.175	**<0.001**	0.923	0.176	**<0.001**
Age	–0.285	0.333	0.394	–0.294	0.345	0.394	–0.164	0.335	0.625	–0.331	0.337	0.327
Education	–0.390	0.312	0.214	–0.681	0.320	**0.035**	–0.485	0.314	0.125	–0.521	0.312	0.097
Sex	–0.641	0.605	0.291	–0.769	0.610	0.209	–0.308	0.615	0.618	–0.527	0.615	0.393
Cognitive status	2.163	0.677	**0.002**	2.161	0.682	**0.002**	2.151	0.673	**0.002**	2.257	0.679	**0.001**
GDS	0.783	0.321	**0.016**	0.819	0.325	**0.013**	0.813	0.319	**0.012**	0.841	0.319	**0.009**
WMH	0.343	0.342	0.318	0.370	0.340	0.278	0.365	0.342	0.288	0.220	0.347	0.526
FDG	–1.778	0.304	**<0.001**	–1.686	0.314	**<0.001**	–1.537	0.317	**<0.001**	–1.676	0.309	**<0.001**
Reference CBF	0.346	0.381	0.364	0.231	0.397	0.562	0.631	0.494	0.203	0.418	0.387	0.282
ROI CBF	–0.825	0.379	**0.031**	–0.647	0.394	0.102	–1.041	0.513	**0.044**	–0.756	0.388	0.053
ROI CBF × Time	–0.374	0.178	**0.037**	–0.420	0.177	**0.019**	–0.478	0.177	**0.007**	–0.274	0.177	0.124

All continuous variables in the model were standardized to have a mean of zero and a standard deviation of one using z-score transformations. Significant effects ($p < 0.05$) appear in bold font. CBF, cerebral blood flow; S.E., standard error of the estimate; Cognitive status, normal cognition versus mild cognitive impairment; GDS, Geriatric Depression Scale total score; WMH, white matter hyperintensity; FDG, fludeoxyglucose; ROI, region of interest.

FDG-PET, and reference (precentral) CBF examined whether baseline regional CBF predicted rate of decline in functional abilities across the 36-month follow-up period. Table 2 shows all parameter estimates and test statistics. Across all models, there were no significant main effects for age, education, sex, WMH volume, or reference CBF (all *p*-values >0.05) although the main effect for time was significant (all *p*-values <0.001), suggesting that, on average, participants had higher FAQ scores over time. As shown in Table 1, across the entire sample (as well as in the cognitively normal and MCI groups), the mean FAQ score across all time points was less than 6, suggesting that, on average, the sample did not show significant functional difficulties. Table 1 depicts changes in FAQ scores over the course of the three years. Across all LME models, the main effects for cognitive status and GDS total score were significant suggesting that, on average, MCI and greater depressive symptoms, respectively, were associated with more functional difficulties (all *p*-values <0.05). In addition, the main effect of FDG-PET was significant, suggesting that, on average, lower metabolism was associated with more functional difficulties (all *p*-values <0.001).

In the model examining MTL CBF, there was a significant main effect of CBF ($p = 0.031$, $r = 0.162$) as well as a significant interaction between MTL CBF and time, such that lower baseline MTL CBF predicted faster rates of functional decline (i.e., higher FAQ scores) ($p = 0.037$, $r = 0.151$). In the model wherein ITG CBF served as the independent variable, there was not a significant main effect of CBF ($p = 0.102$, $r = 0.128$) although there was a significant interaction between ITG CBF and time, such that decreased baseline ITG CBF predicted increased rates of functional decline ($p = 0.019$, $r = 0.181$). In the model examining IPL CBF, there was a significant main effect of CBF ($p = 0.044$, $r = 0.154$) and there was a significant visit x CBF interaction whereby decreased baseline IPL CBF predicted faster rates of functional decline ($p = 0.007$, $r = 0.193$). As expected, there was no significant main effect of pericalcarine CBF or interaction between pericalcarine CBF and time (all *p*-values >0.05). Of note, statistical significance of the regional CBF × time interactions described above for the MTL, ITG, and IPL ROIs was retained using a 0.05 FDR.

We performed secondary analyses where we reran the LME models described above but added a cognitive group (MCI versus normal cognition) × time interaction, a cognitive group × CBF interaction, and a cognitive group × CBF × time interaction. Across models for each of the 3 ROIs and the control region, there were no significant three-way cognitive group × CBF × time interactions (all *p*-values >0.05), indicating that the interaction between CBF and time was not significantly moderated by cognitive group (i.e., the CBF × time interaction did not significantly differ between cognitively normal and MCI participants).

In addition, we performed secondary analyses where we re-ran the LME primary models described above but additionally adjusted for *APOE* ε4+, CSF Aβ, and CSF p-tau. Table 3 shows all parameter estimates and test statistics. Across all models for each of

Table 3
Estimates for the full longitudinal model of the association of baseline CBF and functional abilities additionally adjusting for *APOE* ε4+, Aβ, and p-tau in the subset of participants with CSF data ($n = 146$)

	Medial Temporal			Inferior Temporal			Inferior Parietal			Pericalcarine		
	b	S.E.	*p*	b	S.E.	*p*	b	S.E.	*p*	b	S.E.	*p*
Intercept	1.583	0.776	**0.043**	1.759	0.786	**0.027**	1.329	0.773	0.088	1.260	0.787	0.111
Time	0.962	0.190	**<0.001**	0.931	0.195	**<0.001**	0.917	0.189	**<0.001**	0.911	0.190	**<0.001**
Age	–0.427	0.364	0.243	–0.442	0.375	0.240	–0.367	0.361	0.311	–0.492	0.372	0.189
Education	–0.178	0.343	0.606	–0.498	0.352	0.160	–0.263	0.346	0.448	–0.257	0.348	0.461
Sex	–0.508	0.653	0.438	–0.611	0.659	0.356	–0.169	0.653	0.796	–0.356	0.664	0.592
Cognitive status	2.096	0.735	**0.005**	2.115	0.741	**0.005**	2.109	0.727	**0.004**	2.229	0.746	**0.003**
GDS	0.689	0.345	**0.048**	0.801	0.352	**0.024**	0.706	0.341	**0.040**	0.761	0.346	**0.029**
APOE ε4+	0.323	0.810	0.691	0.063	0.818	0.939	0.268	0.804	0.739	0.459	0.835	0.583
Aβ	–0.399	0.420	0.344	–0.436	0.415	0.295	–0.402	0.417	0.337	–0.403	0.415	0.333
P-tau	0.876	0.335	**0.010**	0.751	0.334	**0.026**	0.979	0.333	**0.004**	0.779	0.365	**0.034**
WMH	0.290	0.369	0.433	0.297	0.370	0.424	0.313	0.370	0.398	0.252	0.373	0.501
FDG	–1.604	0.343	**<0.001**	–1.579	0.348	**<0.001**	–1.356	0.347	**<0.001**	–1.529	0.349	**<0.001**
Reference CBF	0.277	0.406	0.496	0.162	0.429	0.706	0.700	0.523	0.183	0.401	0.406	0.326
ROI CBF	–0.614	0.436	0.161	–0.418	0.438	0.342	–1.016	0.549	0.066	–0.658	0.423	0.122
ROI CBF × Time	–0.395	0.192	**0.042**	–0.429	0.189	**0.025**	–0.436	0.188	**0.022**	–0.252	0.191	0.190

All continuous variables in the model were standardized to have a mean of zero and a standard deviation of one using z-score transformations. Significant effects ($p < 0.05$) appear in bold font. CBF, cerebral blood flow; CSF, cerebrospinal fluid; S.E., standard error of the estimate; Cognitive status, normal cognition versus mild cognitive impairment; GDS, Geriatric Depression Scale total score; *APOE*, apolipoprotein E; Aβ, amyloid-β; P-tau, hyperphosphorylated tau; WMH, white matter hyperintensity; FDG, fludeoxyglucose; ROI, region of interest.

the 3 ROIs and the control region, the results remained similar to those from the primary analyses. Specifically, there were significant main effects for time, cognitive status, GDS score, and FDG-PET (all *p*-values <0.05) but no significant main effects for age, education, sex, WMH volume, or reference CBF (all *p*-values >0.05). The main effects of ROI CBF were no longer significant (all *p*-values >0.05). There were no main effects of *APOE* ε4+ or Aβ (all *p*-values >0.05), although the main effect of p-tau was significant indicating that individuals with greater p-tau burden showed greater functional difficulties (all *p*-values <0.05). Similar to the results from the primary analyses, there were significant CBF × time interactions whereby decreased baseline CBF in each of the three ROIs predicted faster rate of functional decline (MTL: $p = 0.042$, $r = 0.158$; ITG: $p = 0.025$, $r = 0.183$; IPL: $p = 0.022$, $r = 0.177$) yet there was no significant CBF × time interaction for the control region ($p = 0.190$).

We re-ran the primary LME models, adjusting for baseline age, sex, education, depression, cognitive status, WMH volume, FDG-PET, and reference (precentral) CBF as well as the following additional two-way interactions: age × time, WMH volume × time, and FDG-PET × time. Supplementary Table 1 shows all parameter estimates and test statistics. Findings remained similar to those from the primary analyses. That is, the CBF × time interaction remained significant for the MTL, ITG, and IPL ROIs. The CBF × time interaction for the model with the pericalcarine ROI remained nonsignificant. In addition, across all models, the FDG × time interaction was significant suggesting that, on average, reduced neuronal metabolism predicted accelerated FAQ decline (all *p*-values <0.001). In contrast, across all models, neither the age x time interaction nor the WMH × time interaction was significant (all *p*-values >0.05).

We also compared those who converted to dementia during the three years of follow up and those who did not adjusting for age, sex, education, GDS, and reference region CBF. Of the 166 participants in the sample, 17 converted to dementia across the three years of follow-up. Those who converted to dementia showed significantly lower baseline CBF relative to those who did not convert in ITG ($p = 0.008$; partial eta squared = 0.046) and IPL ($p = 0.026$; partial eta squared = 0.031). However, in the model examining baseline MTL CBF, there was no significant difference between those who converted to dementia across three years and those who did not ($p = 0.186$; partial eta squared = 0.011).

DISCUSSION

The current study showed that lower resting CBF in AD vulnerable regions including medial temporal lobe and inferior parietal and temporal cortices predicted faster rate of decline in everyday functioning

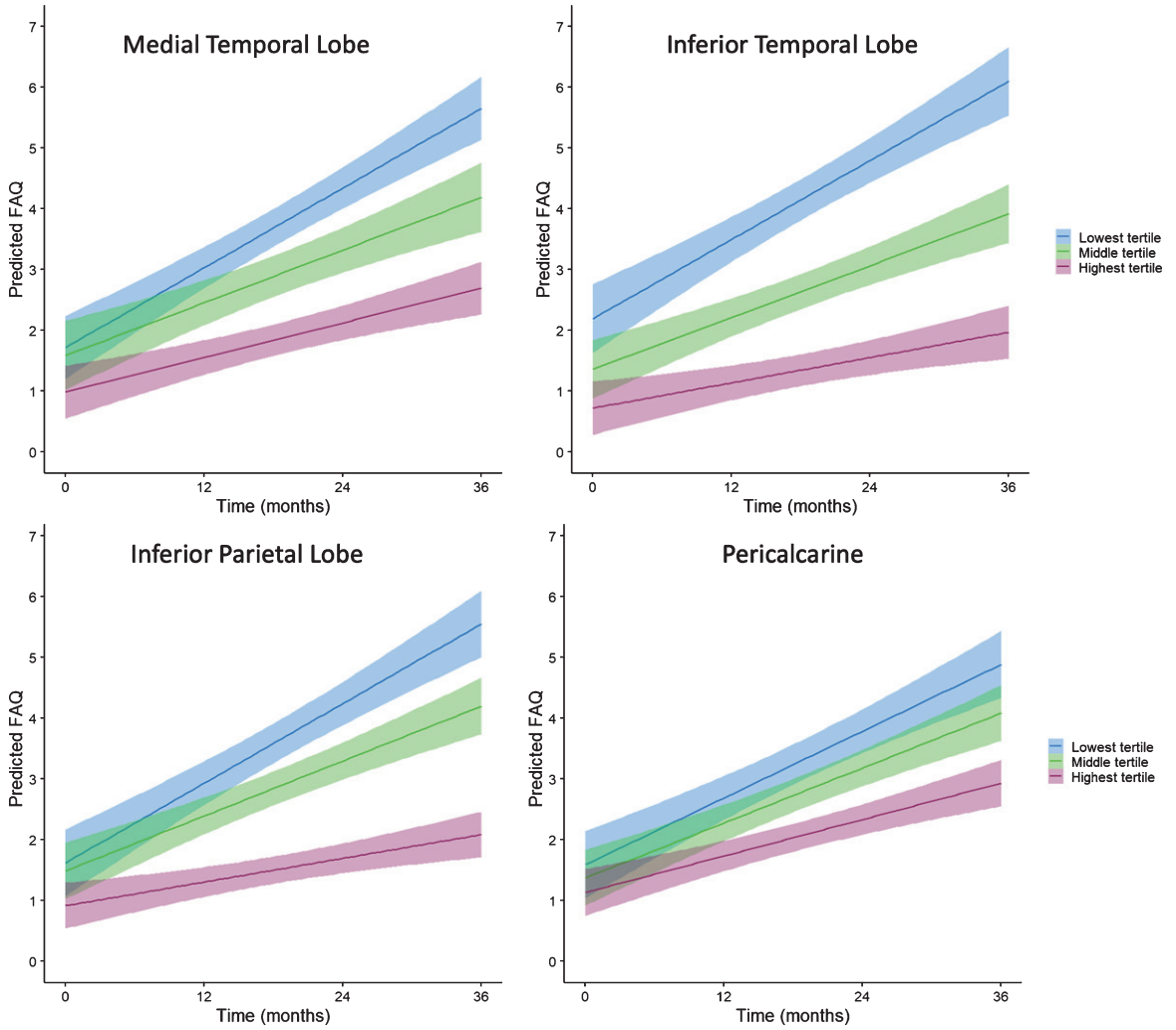

Fig. 1. Fitted plots displaying model predicted Functional Activities Questionnaire (FAQ) values over the 3-year interval, adjusting for age, education, sex, cognitive status (normal cognition versus mild cognitive impairment), depression, white matter hyperintensity volume, cerebral metabolism, and reference (precentral) cerebral blood flow (CBF) for each of the regions of interest. For visual comparison, the graphs display results for low, middle, and high CBF which were determined by a tertile split of the values in the analytic sample. Higher FAQ scores indicate greater functional difficulty. Shaded regions represent the 95% confidence interval for the regression line. Cut-off scores of >6 on FAQ have been shown to best indicate significant functional difficulties [44].

over three years of follow-up in a well-characterized sample of nondemented older adults. Our study extends prior work that has examined the utility of ASL MRI has as a biomarker of AD risk by examining the association of baseline CBF as a predictor of rate of later functional decline. Our findings also corroborate a prior study using SPECT which found cross-sectional associations between poorer overall IADL abilities and lower perfusion in AD patients [22]. Here we extend this prior work to a longitudinal design, a sample of older adults without dementia, and ASL MRI measures of CBF.

We have previously shown that elevated vascular risk burden influences the clinical expression of AD [3], although the mechanisms linking vascular changes and AD remain poorly understood. Previous MRI studies of brain changes underlying cognitive decline in AD risk have typically used conventional structural MRI to identify structural changes, such as hippocampal atrophy or white matter lesions. The use of noninvasive ASL MRI to measure CBF may help clarify the mechanisms that precede the development of irreversible parenchymal damage. The ADNI cohort is a well-characterized sample and

potential participants are excluded for neurologic disease, significant depressive symptoms, or HIS scores suggesting vascular contributions to cognitive dysfunction. Nonetheless, we adjusted for potentially confounding variables including self-reported depressive symptoms and small vessel cerebrovascular disease (i.e., WMH volume). Given the design and methods of the ADNI study together with our statistical modeling approach, for those participants in our study who showed decline, it is likely that an underlying AD process may be contributing rather than non-AD forms of cognitive impairment and dementia (e.g., vascular cognitive impairment) although the precise nature and extent of underlying neuropathological processes would not be confirmed until autopsy.

We found that CBF predicted functional decline, even after adjusting for CSF Aβ and p-tau, suggesting that CBF predicts decline independent of these hallmark AD biomarkers. These findings are in line with models such as the two-hit vascular hypothesis of AD, which proposes that reduced brain perfusion may be an early insult that may trigger neurodegeneration and Aβ accumulation, which contribute to downstream cognitive impairment in AD [5, 6, 8, 15, 57]. Within this framework, CBF alterations may modify and/or act together with Aβ accumulation to contribute to cognitive decline [5]. It is noteworthy that the observed CBF effects remained after including two-way interactions of time with age, WMH volume, and FDG-indexed neuronal metabolism in the model. Although CBF has frequently been attributed to neuronal metabolism, [15, 58, 59], our findings suggest that CBF effects are distinct from metabolic dysfunction and white matter lesions. The present findings provide additional support that CBF could be useful as an early biomarker of downstream AD pathogenesis. Future studies will be needed with longitudinal collection of Aβ, p-tau, and CBF to better delineate the individual trajectories of these biomarkers over the course of AD.

In our prior work we have shown that ASL MRI has utility as a biomarker of cognitive functioning and dementia risk in normal aging as well as across various risk groups including older adults with MCI, objectively-defined subtle cognitive decline, *APOE* ε4 allele, elevated vascular risk burden, and Aβ positivity [2, 6, 12, 60–62]. The present findings add to this work by demonstrating that regional hypoperfusion predicts later functional decline in older adults without dementia. Our findings are also in line with prior work showing associations between ASL CBF and cognitive functioning (e.g., [21, 61, 62]). Although cognition and everyday function are related, they may differ in important ways [33]. Ultimately, it is impairment in everyday function that reduces a person's independence and quality of life, increases burden and stress on caregivers and families, and contributes to greater health service use and financial costs [33–36]. By definition, dementia (or major neurocognitive disorder) is associated with impaired everyday function. MCI, which is thought to represent a transition between normal aging and dementia, has been shown to involve mild functional difficulties intermediate between subtle changes that may be evident in normal aging and significant impairment seen in dementia [24, 33, 63, 64]. It is often the extent and severity of functional impairments that differentiates between MCI versus a frank dementia. Also, among individuals with MCI, more severe functional difficulties are at increased risk of cognitive decline and progression to dementia [65, 66]. Despite the importance of everyday function to the diagnosis and prognosis of neurocognitive disorders, research examining markers predictive of functional decline in aging and dementia risk has been limited [33]. Here we showed that regional CBF predicts functional decline and is associated with conversion to dementia. Although it should be noted that the sample was, on average, still functionally independent at the 36-month visit. A score of 6 or higher on the FAQ has been shown to best indicate significant functional difficulties [44]. Although the average decline in IADL observed in our sample did not reach the level of dependence, increasing functional difficulty is an important risk factor for future disability and cognitive decline [67, 68].

There are limitations that should be considered when interpreting the current findings and should be addressed in future studies. The sample was predominately White, relatively well educated, and medically healthy which may reduce the generalizability of the results. Future studies should examine the observed associations in a more inclusive sample including more people of color. These studies should also include individuals with a wider range of FAQ scores including those diagnosed with dementia to determine whether CBF is a useful predictor of decline in those who are already showing impaired everyday function. Despite these limitations, the finding that baseline ASL CBF predicts later functional decline in nondemented older adults has not been previously reported to the best of our knowledge. Strengths of the current study include the ability to characterize and

statistically adjust for vascular and metabolic markers that could impact CBF including WMH volume and cerebral metabolism measured with FDG PET. Given this, the finding that baseline CBF predicted rate of functional decline after these adjustments suggests that CBF is an independent contributor or biomarker rather than a byproduct of cerebral small vessel disease or altered cerebral metabolism. ASL MRI may prove useful for predicting future declines in everyday life in individuals at risk for dementia early in the AD process, when interventions are likely to be most beneficial.

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SUPPLEMENTARY MATERIAL

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