Arterial Spin Labeling May Contribute to the Prediction of Cognitive Deterioration in Healthy Elderly Individuals[1]

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Purpose: To explore whether arterial spin labeling (ASL) imaging in cognitively intact elderly individuals may be used to predict subsequent early neuropsychological decline.

Materials and Methods: The local ethics committee approved this prospective study, and written informed consent was obtained from all participants. A total of 148 consecutive control subjects were included, 75 of whom had stable cognitive function (sCON) (mean age, 75.9 years ± 3.4 [standard deviation]; 43 female) and 73 of whom had deteriorated cognitive function (dCON) at 18-month clinical follow-up (mean age, 76.8 years ± 4.1; 44 female). An additional 65 patients with mild cognitive impairment (MCI) (mean age, 76.2 years ± 6.1; 25 female) were also included. Two-dimensional pulsed ASL was performed at the baseline visit. Statistical analysis included whole-brain voxelwise analysis of the ASL relative cerebral blood flow (CBF) data, receiver operating characteristic (ROC) curve analysis of the posterior cingulate cortex (PCC), and voxel-based morphometry analysis of gray matter.

Results: The voxelwise comparison of ASL revealed decreased relative CBF in the dCON group compared with that in the sCON group and slightly more pronounced relative CBF in the MCI group compared with that in the sCON group, most notably in the PCC ($P < .05$ corrected). Comparison of the dCON group with the MCI group revealed no significant differences. ROC analysis of relative CBF in the PCC enabled discrimination of dCON ($P < .001$; area under the ROC curve, 0.66). There was no confounding focal gray matter atrophy.

Conclusion: Reduced ASL in the PCC at baseline is associated with the development of subsequent subtle neuropsychological deficits in healthy elderly control subjects. At a group level, ASL patterns in subjects with dCON are similar to those in patients with MCI at baseline, indicating that these subjects may initially maintain their cognitive status via mobilization of their neurocognitive reserve at baseline; however, they are likely to develop subsequent subtle cognitive deficits.

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It is commonly believed that curative interventions in patients with Alzheimer disease (AD) could be most effective when applied in the preclinical phase either to counterbalance the biologic compromise that precedes the cognitive breakdown or to promote functional compensation (1,2). In line with this idea, the concept of preclinical AD has been introduced to refer to cognitively intact elderly patients with increased amyloid burden on positron emission tomography (PET) scans and decreased concentration of amyloid beta 42 in cerebrospinal fluid who remain cognitively stable for variable time periods but ultimately display significantly increased risk for AD (3). However, this definition implies invasive investigations are hard to perform in routine clinical settings. Unlike PET, which remains the imaging reference standard, magnetic resonance (MR) techniques may be more easily implemented.

The performance of various MR imaging techniques to depict incipient AD and to identify persons with mild cognitive impairment (MCI) has been studied by using multiple techniques, including resting-state functional connectivity (4), gray matter derived from T1 voxel-based morphometry (5–7), white matter derived from diffusion-tensor imaging (8–10), iron deposition derived from susceptibility imaging (11), and perfusion derived from arterial spin labeling (ASL) (12–19). This latter technique revealed brain hypoperfusion mainly in bilateral parietal areas and precuneus in patients with MCI and early AD; this overlaps with the patterns of hypometabolism on fluorodeoxyglucose PET scans (20) obtained later in the disease process, indicating the potential to use ASL in the early detection of cognitive decline (21).

Previous ASL contributions mainly focused on group differences between control subjects and patients with MCI or AD (12–19). The current investigation tests the hypothesis that ASL neuroimaging may depict very early and subtle alterations in brain perfusion at the baseline visit in cognitively intact elderly individuals and that this information can be used to predict very early phases of subsequent cognitive decline. Elderly individuals were classified on the basis of neuropsychologic follow-up at 18 months as having either stable cognitive function (sCON) or deteriorating cognitive function (dCON) and were compared with a group of patients with MCI.

Advances in Knowledge

- Reduced arterial spin labeling (ASL) in the posterior cingulate cortex at baseline is found in healthy elderly patients who develop subsequent cognitive deterioration ($P < .001$; area under the receiver operating characteristic curve, 0.66).
- The significant yet relatively low accuracy of ASL is consistent with very early and subtle cognitive decline.
- The posterior cingulate cortex was identified in a whole-brain analysis without prior assumptions and replicates the hypometabolism on fluorodeoxyglucose PET images observed in this area in patients with mild Alzheimer disease.
- Control subjects with deteriorated cognitive function (dCON) and patients with mild cognitive impairment have similar ASL patterns, indicating that those with dCON already have perfusion alterations at baseline imaging despite apparent normal cognition because of mobilization of the neurocognitive reserve.

Implications for Patient Care

- ASL has the potential to serve as a biomarker in the very early diagnosis of preclinical dementia.
- Structural MR imaging is routinely performed in many centers during the work-up of cognitive decline; thus, operator-independent ASL might simply be added to an existing investigation.

Materials and Methods

Participants

The local ethics committee (University Hospitals of Geneva) approved this prospective study, and all participants gave written informed consent prior to inclusion. Participants were contacted via advertisements in local media to guarantee a community-based sample. After we provided detailed information about this research, we performed telephone screening with the following inclusion criteria: normal or corrected-to-normal acuity; no history of major medical disorders (neoplasm or cardiac illness), sustained head injury, or psychiatric or neurologic disorders; no alcohol or drug abuse; no regular use of neuroleptics, antidepressants, mood stabilizers, anticonvulsant drugs, or psychostimulants; and no contraindications to MR imaging. To control for the confounding effect of cardiovascular diseases, patients

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Abbreviations:
AD = Alzheimer disease
ASL = arterial spin labeling
AUC = area under the ROC curve
CBF = cerebral blood flow
dCON = deteriorated cognitive function
MCI = mild cognitive impairment
PCC = posterior cingulate cortex
ROC = receiver operating characteristic
sCON = stable cognitive function

Author contributions:
Guarantors of integrity of entire study, C.R., E.T., K.O.L., P.G., S.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.X., C.R., M.L.M., S.T., E.T., D.Z., K.O.L., F.B., P.G., S.H.; clinical studies, A.X., C.R., M.L.M., S.T., E.T., D.Z., K.O.L., P.G., S.H.; statistical analysis, A.X., C.R., M.L.M., F.H., S.H.; and manuscript editing, A.X., C.R., M.L.M., F.H., D.Z., K.O.L., F.B., P.G., S.H.

Conflicts of interest are listed at the end of this article.

with subtle cardiovascular symptoms and a history of stroke and transient ischemic episodes were not included in the present study. There were 50 participants who did not meet the inclusion criteria for neurologic conditions, 45 who did not meet the criteria for pharmacologic treatment, 18 who had vision problems, eight who had cancer, 28 who met MR imaging exclusion criteria, five who had a cardiac illness, and 28 who were excluded for psychosocial reasons. At follow-up, we excluded one participant because of drug treatment, two because of vision problems, and 41 for psychosocial reasons. The inclusion period for control subjects and patients with MCI was from October 2010 to January 2011.

At baseline, all individuals underwent neuropsychological assessment. The control participants were evaluated with an extensive neuropsychological battery, including the Mini-Mental State Examination (or MMSE) (22), the Hospital Anxiety and Depression Scale (or HAD) (23), and the Lawton Instrumental Activities of Daily Living (or IADL) (24). Cognitive assessment included *(a)* attention (Code [25], Trail Making Test A [26]), *(b)* working memory (verbal: Digit Span Forward [25], visuospatial: Visual Memory Span [Corsi] [25]), *(c)* episodic memory (verbal: RI-48 Cued Recall Test [27]; visual: Shapes test [28]; executive functions: Trail Making Test B [26], Wisconsin Card Sorting Test [or WCST] [29], and Phonemic Verbal Fluency test [30]), *(d)* language (Boston Naming [31]), *(e)* visual gnosis (Ghent Overlapping Figures [32]), *(f)* ideomotor (33), *(g)* reflexive (34), and *(h)* constructional praxis (Consortium to Establish a Registry for Alzheimer's Disease [or CERAD] Figures copy [35]). Education level was defined according to the Swiss scholar system, as follows: level 1, less than 9 years (primary school); level 2, between 9 and 12 years (high school); and level 3, more than 12 years (university). All individuals were also evaluated with the Clinical Dementia Rating scale (or CDR) (36), and only cases with a Clinical Dementia Rating score of 0 and scores within 1.5 standard deviations of the age-appropriate mean in all other tests were included in the control group.

For participants with MCI, we confirmed their status with a shortened battery that included the Mini-Mental State Examination (22), Hospital Anxiety and Depression Scale (23), and Lawton Instrumental Activities of Daily Living (24). The cognitive assessment included *(a)* attention (Trail Making Test A [26]), *(b)* working memory (verbal, Digit Span Forward [25]), *(c)* episodic memory (verbal, RI-48 Cued Recall Test [38] and Rl/RI–16 Free and Cued Remining Test [37]), *(d)* executive functions (Trail Making Test B [26] and Phonemic Verbal Fluency test [30]), and *(e)* language (Boston Naming [31]) and Consortium to Establish a Registry for Alzheimer's Disease Figures copy [35]). All individuals were also evaluated with the Clinical Dementia Rating scale (36). In agreement with the criteria of Petersen et al (38), participants with a Clinical Dementia Rating score of 0.5 but no dementia and a score more than 1.5 standard deviations below the age-appropriate mean in any of the previously mentioned tests were confirmed to have MCI.

Eighteen months after the baseline evaluation, only control subjects underwent cognitive reassessment with the same neuropsychological battery. Participants were placed in the dCON group at follow-up if they had a performance 0.5 standard deviation lower than that at inclusion for two or more neuropsychological tests. Additionally, all individuals were clinically assessed independently by two neuropsychologists (S.T., E.T.; 4 and 2 years of experience, respectively). The final classification of dCON was made blindly by a trained neuropsychologist (C.R., 10 years of experience) who took into account both the neuropsychological test results and the clinical assessment. Within the dCON group, four subtypes were identified according to the criteria of Petersen et al (38): single-domain amnestic ($n = 2$), single-domain nonamnestic ($n = 2$), multiple-domain amnestic ($n = 53$), and multiple-domain nonamnestic ($n = 16$).

The final sample included 75 consecutive patients in the sCON group (mean age, 73.3 years ± 2.9 [standard deviation], 46 female), 73 in the dCON group (73.9 years ± 4.1, 47 female), and 65 in the MCI group (73.7 years ± 5.5, 22 female) (Table, Table E1 [online]).

MR Imaging

MR imaging was performed with a clinical routine whole-body 3.0-T MR imager (Trio; Siemens Medical Systems, Erlangen, Germany). We used a pulsed ASL sequence with the following parameters: repetition time msec/echo time msec/inversion time msec, 5000/21/700, 1800; saturation stop time, 1600 msec; matrix, 64 × 64; voxel size, 3.44 × 3.44 × 5 mm, flow limit, 5 cm/sec; 71 images acquired, with alternation of labeled and nonlabeled images; parallel imaging factor (iPAT; Siemens Medical Systems), two; and PICORE Q2Tips labeling scheme as described by Luh et al (39). A magnetization-prepared rapid gradient-echo three-dimensional T1-weighted sequence was performed for spatial normalization and gray matter segmentation with the following fundamental parameters: 2300/2.3, 256 × 256 matrix, 176 sections, and 1 × 1 × 1 mm.

Additional sequences included axial fast spin-echo T2-weighted imaging (4000/105, 30 sections, 4-mm section thickness), diffusion-tensor imaging (9000/92, 30 diffusion directions, b value = 1000 sec/mm^2 isotropically distributed on a sphere, one reference image with b value = 0 sec/mm^2, 128 × 128 × 64 matrix, 2 × 2 × 2 mm voxel size, one signal acquired), and susceptibility weighted imaging (28/20, 208 × 256 × 128 matrix, 1 × 1 × 1 mm voxel size) and were performed to exclude brain disease, such as ischemic stroke, subdural hematomas, or space-occupying lesions. In particular, white matter lesions were analyzed according to the Fazekas score (40).

Statistical Analysis

Statistical analysis of clinical data and the receiver operating characteristic (ROC) curve was performed with Graphpad Prism, version 5.0f, and

Essential Demographic and Clinical Data for the Three Study Groups

Variable	sCON Group ($n = 75$)	dCON Group ($n = 73$)	MCI Group ($n = 65$)	*P* Value			
				Group	sCON vs dCON	sCON vs MCI	dCON vs MCI
Age (y)	73.68 ± 3.4	73.39 ± 4.1	74.30 ± 5.7	NS	NS	NS	NS
Sex	48 female, 29 male	47 female, 26 male	22 female, 43 male	…	.701	.003	<.001
Education	2.4 ± 0.6	2.1 ± 0.7	2.2 ± 0.7	<.001	<.001	…	…
Mini-Mental State Examination	28.9 ± 1.1	28.4 ± 1.2	26.5 ± 2.3	<.001	…	<.001	<.001
Lawton Instrumental Activities of Daily Living	8.4 ± 1.1	8.2 ± 0.7	10.1 ± 4.2	<.001	…	<.001	<.001
Hospital Anxiety and Depression Scale	6.5 ± 1.9	6.4 ± 1.6	5.9 ± 1.7	NS	NS	NS	NS
Anxiety	5.0 ± 2.7	4.9 ± 2.9	4.2 ± 2.6	NS	NS	NS	NS
Depression	1.6 ± 1.6	2.2 ± 2.0	2.8 ± 2.2	<.001	…	<.001	…
Digit Span Forward	6.5 ± 1.9	6.4 ± 1.6	5.9 ± 1.7	NS	NS	NS	NS
RI-48 Cued Recall Test							
Total immediate cued recall	40.6 ± 4.5	38.6 ± 4.6	34.5 ± 4.7	<.001	<.05	<.001	<.001
Total cued recall	27.1 ± 4.9	27.2 ± 4.5	15.7 ± 3.5	<.001	…	<.001	<.001
Instrusions	2.1 ± 2.2	2.3 ± 2.6	5.0 ± 6.2	<.001	…	<.001	<.001
RL/RI-16 Free and Cued Remining Test							
Total immediate recall	…	…	12.3 ± 3.4	…	…	…	…
Total free recall	…	…	12.3 ± 7.8	…	…	…	…
Delayed free recall	…	…	6.3	…	…	…	…
Boston naming	19.5 ± 1.0	19.3 ± 0.8	13.4 ± 1.6	<.001	…	<.001	<.001
Praxies: constructional	10.9 ± 0.5	10.7 ± 0.8	10.6 ± 0.9	NS	NS	NS	NS
Verbal fluency	23.6 ± 6.0	22.2 ± 6.1	17.8 ± 6.7	<.001	…	<.001	<.001
Trail A							
Time	41.5 ± 17.9	43.8 ± 12.4	47.7 ± 16.6	NS	NS	NS	NS
Error	0.0 ± 0.2	0.0 ± 0.3	0.1 ± 0.4	NS	NS	NS	NS
Trail B							
Time	89.5 ± 27.9	105.7 ± 41.4	139.0 ± 92.6	<.001	…	<.001	<.001
Error	0.3 ± 0.6	0.5 ± 0.7	0.8 ± 1.3	<.05	…	<.05	<.05
Trail B time divided by trial A time	2.3 ± 0.7	2.5 ± 0.9	2.9 ± 1.7	< .01	…	<.01	…
Code	56.9 ± 11.2	50.8 ± 10.9	…	…	<.001	…	…
Wisconsin Card Sorting Test							
No. of categories completed	2.6 ± 0.7	2.6 ± 0.7	…	NS	NS	NS	NS
Error	0.2 ± 0.4	0.2 ± 0.4	…	NS	NS	NS	NS
Shapes test	11.8 ± 0.7	11.7 ± 0.8	…	NS	NS	NS	NS
Praxies							
Ideomotor transitive	9.5 ± 0.8	9.0 ± 1.3	…	…	<.01	…	…
Ideomotor intransitive	19.6 ± 0.9	19.6 ± 0.8	…	NS	NS	NS	NS
Reflexive	7.0 ± 0.9	7.0 ± 1.1	…	NS	NS	NS	NS
Visual gnosis	5.0 ± 0.1	5.0 ± 0.1	…	NS	NS	NS	NS
Visual Memory Span Forward	5.1 ± 1.5	4.7 ± 1.5	…	NS	NS	NS	NS

Note.—NS = not significant.

Stata, release 13.1 (Stata, College Station, Tex) (S.H., F.R.H.; 12 and 26 years of experience, respectively).

Demographic and neuropsychologic data were analyzed as follows: Normal distribution was tested by using the Kolmogorov-Smirnov test. At baseline, for each variable we first performed a group-level analysis for the sCON, dCON, and MCI groups (analysis of variance for parametric data, Kruskal-Wallis test for nonparametric data). If the group-level test results were significant, we additionally performed post hoc pairwise comparisons for sCON versus dCON, sCON versus MCI, and dCON versus MCI (Bonferroni multiple comparison correction for parametric data, Dunnett multiple comparison tests for nonparametric data). Binary data, such as sex, were compared by using the χ^2 test. To account for the multiple comparisons of 25 neuropsychological tests performed in control subjects at baseline, a *P* value of .002 (.05/25 = .002) indicated a significant difference, For follow-up, the paired

student *t* test and Wilcoxon test were used to compare values at baseline with those at 18-month follow-up in the dCON group.

Additionally, we performed ROC curve analysis for the ASL relative cerebral blood flow (CBF) values in the posterior cingulate cortex (PCC). The PCC was defined on basis of previous ASL studies of MCI and AD (ie, at later stages of neurodegeneration) (12–14,16). Note that the whole-brain voxelwise analysis of the current ASL data also enabled identification of the PCC. Finally, we computed ROC analyses for the two neuropsychological tests (RI-48 Cued Recall Test and Code) that revealed a significant difference between the sCON and dCON groups at baseline and compared the ROC analyses between these two tests versus ASL and their combination by using χ^2 tests. The combination of two or more parameters was performed with logistic regression analyses. Corrected $P < .05$ was considered to indicate a significant difference.

Voxelwise Whole-Brain Analysis of ASL Data

First, the relative CBF values were estimated directly by the software according to the recommendations of Luh et al (39) and Wang et al (41) and under the assumption of constant standard values for hematocrit, T1, lambda, and inversion efficiency, as follows:

$$f = \frac{\lambda \Delta M}{2\alpha M_O TI_1 \exp(-TI_2 / T_{1a})},$$

where f is regional CBF (in milliliters per 100 g per minute), λ 0.9 (in milliliters per gram) is blood and tissue water partition coefficient 0.9, α is 95% inversion efficiency, $M0$ and ΔM are fully relaxed image intensity and signal difference, respectively (control and label), TI1 and TI2 (in milliseconds) are inversion times, TI2 is TI1 plus transit time, and T1a is 1500 msec at 3 T (longitudinal relaxation time of blood).

Second, these relative CBF maps were postprocessed with FSL software (FMRIB Software Library, version 5.0.2.1; *www.fmrib.ox.ac.uk/fsl*). The following data processing techniques were applied: masking of nonbrain voxels by using the brain extraction tool (part of FSL), linear registration of the ASL data to the same subject's three-dimensional T1-weighted data by using a linear registration tool (FLIRT; *www.fmrib.ox.ac.uk/fsl*), nonlinear spatial registration of the high-resolution three-dimensional T1-weighted image to Montreal Neurologic Institute standard space by using a nonlinear image registration tool (FNIRT; *www.fmrib.ox.ac.uk/fsl*), and application of this nonlinear transformation matrix to the ASL relative CBF maps to spatially normalize the relative CBF maps onto Montreal Neurologic Institute standard space. ASL relative CBF values are higher in gray matter than in white matter. To compensate for partial volume effects of the relative CBF maps, we calculated gray matter–corrected relative CBF maps as reported previously (12,16). In principle, the individual three-dimensional T1-weighted images were preprocessed by using FSL voxel-based morphometry to create individual gray matter maps, which were then used to mask the individual ASL relative CBF maps to obtain individual gray matter–corrected relative CBF maps. Then, we performed voxelwise permutation testing implementing randomize (part of FSL software) and familywise error correction for multiple comparisons at corrected $P < .05$. The same analysis was repeated with and without age, sex, and Fazekas white matter lesions scores as coregressors. The analysis was performed twice, without and individual gray matter correction, to obtain raw relative CBF and corrected relative CBF maps, respectively (A.X., S.H.; 4 and 12 years of experience, respectively).

Gray Matter Voxel-based Morphometry Analysis

Voxel-based morphometry analysis was performed by using the previously mentioned software package, according to the standard procedure described in detail online *(www.fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM)*. The essential processing steps included brain extraction with the Brain Extraction Tool, tissue-type segmentation with the FMRIB Automated Segmentation Tool (FAST; *www.fmrib.ox.ac.uk/fsl*), and nonlinear transformation into Montreal Neurologic Institute Voxelwise general linear model with permutation-based nonparametric testing (RANDOMIZE; *www.fmrib.ox.ac.uk/fsl*), with threshold-free cluster enhancement correction for multiple comparisons at $P < .05$ (corrected) (42).

Results

Demographic and Clinical Data

There was no significant difference in age or Fazekas white matter lesion score between groups (Table). There was a significantly lower proportion of women in the MCI group as compared with the dCON group ($P < .05$); this occurred by chance because of the prospective and consecutive inclusion of participants in this study. As expected, Mini-Mental State Examination scores in the MCI group were significantly lower than those in the sCON ($P < .001$) or dCON ($P < .001$) group. Two of 25 neuropsychological tests performed in control subjects at baseline showed differences between sCON and dCON at baseline, notably RI-48 Cued Recall Test ($P < .001$) and Code ($P < .001$), while the remaining 23 tests did not reveal a difference between groups.

Voxelwise Analysis of ASL-relative CBF

The group average ASL-relative CBF maps are shown in Figure 1. The voxelwise comparison of the partial volume-corrected ASL revealed decreased relative CBF in the dCON group compared with that in the sCON group in the PCC. MCI versus sCON had notably decreased relative CBF in the PCC and to a lesser degree in the bilateral superior and middle frontal gyrus (Fig 2). The comparison of dCON with MCI revealed no significant differences. The repeated analysis with age, sex, and Fazekas white matter

Figure 1

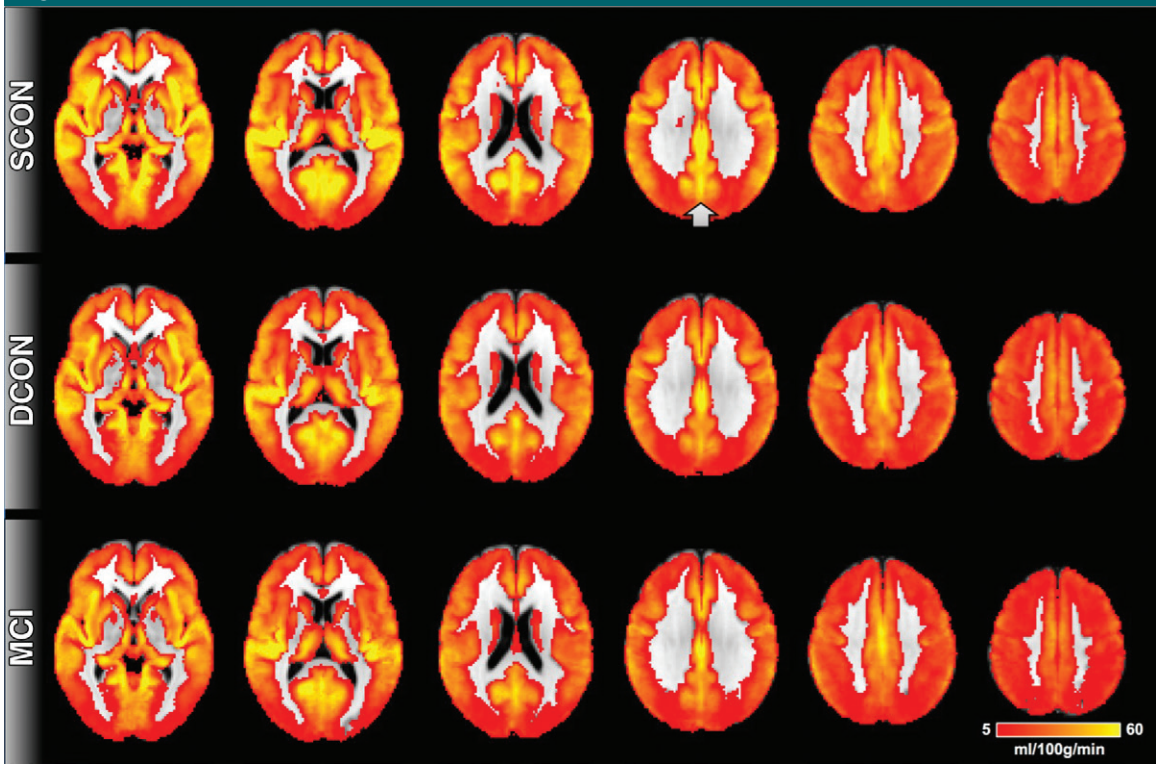

Figure 1: Group average ASL-relative CBF maps. There is a global reduction in baseline perfusion in the dCON and MCI groups compared with the sCON group, notably in the PCC (arrow). Radiologic convention with the right hemisphere on the left side, color-coded group average relative CBF (in milliliters per 100 g per minute) superimposed onto the Montreal Neurologic Institute standard brain.

scores as co-regressors did not significantly change the results (details not shown). ROC Analyses of Relative CBF in the PCC

ROC analysis of relative CBF in the PCC enabled discrimination of dCON from sCON ($P < .001$; area under the ROC curve [AUC], 0.66) and of MCI from sCON ($P < .001$; AUC, 0.71). There was no difference in AUC between dCON and MCI (Fig 3). The cutoff value of 58.5 mL/100 g/min in the PCC enabled discrimination of dCON from sCON, with a sensitivity of 58.9% and a specificity of 65.3%.

Two of the 25 neuropsychological tests performed at baseline also enabled discrimination of sCON from dCON. Buschke 48 resulted in an AUC of 0.62, and Code resulted in an AUC of 0.67. There was no significant difference between the three AUC values for ASL, Buschke 48, or Code. The combination of any two parameters did not significantly increase the AUC values. In contrast, the combination of all three parameters (ie, ASL, Buschke 48, and Code) slightly but significantly ($P < .05$) increased the AUC to 0.69.

Gray Matter Voxel-based Morphometry Analysis

There was no suprathreshold difference in gray matter concentration between sCON and dCON.

Discussion

Among 148 cognitively intact elderly individuals prospectively and consecutively included at baseline, about one-half developed subtle cognitive deficits after 18 months. At first glance, this high percentage of individuals with lower neuropsychological performance at a relatively short follow-up interval may be surprising. However, one should keep in mind that to explore the initial phases of cognitive decline in healthy control subjects we used a low threshold of neuropsychological decline (−0.5 standard deviation compared with baseline). ASL imaging was used to identify reduced perfusion in dCON already at baseline imaging, with a pattern equivalent to that in patients with MCI. ASL imaging at baseline has independent predictive value for subsequent subtle cognitive decline in cognitively intact elderly individuals. The significant yet relatively low AUCs reflect the very early and very subtle cognitive decline. Consequently, the expected ASL differences between those with sCON and those with dCON at baseline are a priori small and of similar magnitude when compared with the most predictive neurocognitive test. Correspondingly, even when comparing patients with established AD and healthy subjects

with subjective cognitive complaints, the AUC is 0.83 (16).

The significant group discrimination obtained with ASL alone is encouraging in the perspective of future multimodal studies. For instance, in our study, control subjects were not further stratified at baseline with other complementary markers, such as apolipoprotein E genotype or amyloid status (amyloid PET Pittsburgh compound B [or PiB] or amyloid beta level in the cerebrospinal fluid), and if they were considered at baseline jointly with ASL, they could further increase the power to discriminate between sCON and dCON. Note that two of 25 neuropsychological tests (Buschke 48 and Code) also enabled discrimination between sCON and dCON at baseline. These tests are not related to memory performance, and Buschke 48 in particular is not usually used in the characterization of MCI. Both neuropsychological tests had an AUC similar to that of ASL, and the combination of ASL and both neuropsychological tests slightly but significantly improved the resulting AUC value, indicating complementary information from both modalities. Since MR imaging is part of the routine work-up of cognitive decline at many centers, ASL is a cost-efficient and operator-independent tool used to assess early cognitive decline, which simply prolongs an already existing assessment for a few minutes.

Our observations of reduced CBF in the PCC in subjects with dCON (comparable to patients with MCI) are compatible with the well-established interindividual variation of functional compensation, also referred to as neurocognitive reserve (43). Because of individual predisposition, education, and social integration, some individuals may maintain normal cognitive function longer than other individuals. In our sample, individuals with dCON had alterations in cerebral perfusion, notably in the PCC, that could be detected with ASL imaging similar to patients who already had MCI at baseline imaging. While subjects with dCON were initially able to compensate for these changes and maintain normal cognitive status, patients with MCI, who had equivalent alterations at ASL imaging, already had impaired clinical cognitive status. This might indicate that subjects with dCON progressively depleted their cognitive reserve and eventually developed subtle neurocognitive changes at 18-month follow-up.

Interestingly, the most prominent reduction of ASL relative CBF in both subjects with dCON and patients with

Figure 2

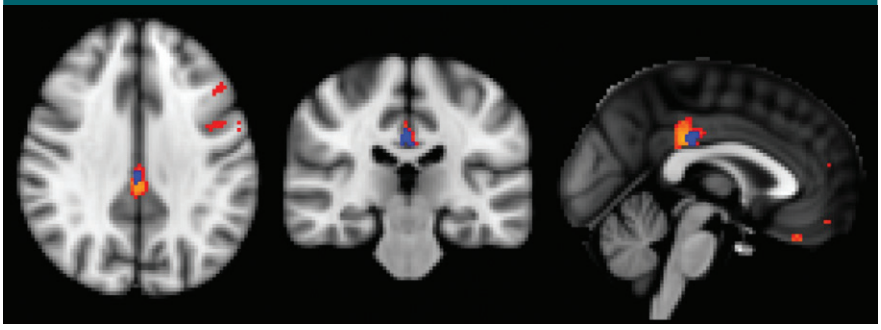

Figure 2: Voxelwise comparison of partial volume-corrected ASL revealed decreased relative CBF in dCON compared with sCON (blue) in the PCC. MCI versus sCON (orange) had decreased relative CBF, again notably in the PCC and to a lesser degree in the bilateral superior and middle frontal gyrus. Comparison of dCON with MCI revealed no significant difference. Voxelwise comparison ($P < .05$, familywise error corrected) superimposed onto the Montreal Neurologic Institute standard brain in axial, coronal, and sagittal planes.

Figure 3

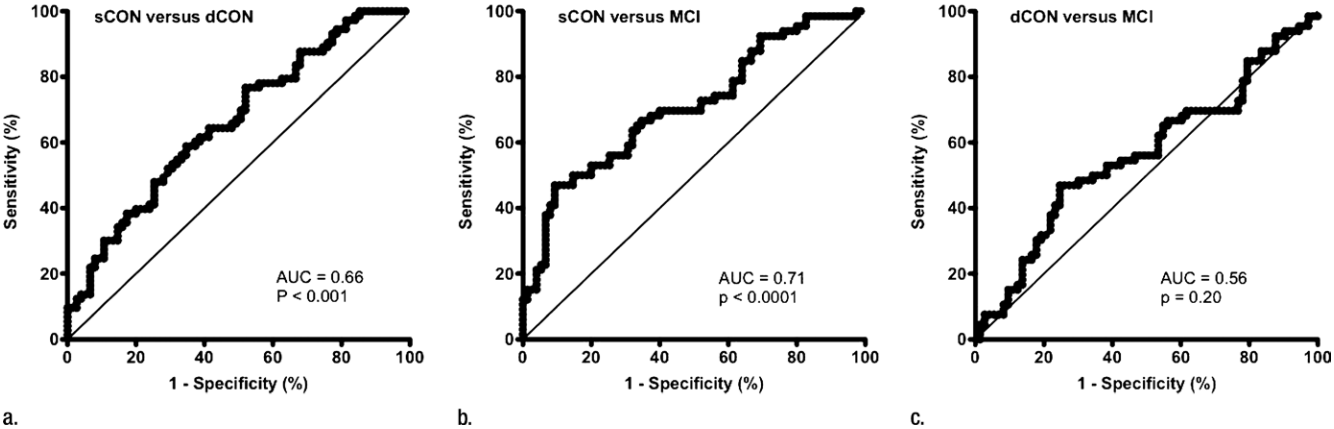

Figure 3: ROC curve analysis of the pairwise comparison between groups. ASL relative CBF in PCC enabled discrimination of **(a)** dCON ($P < .001$) and **(b)** MCI ($P < .001$) from sCON; however, there was no difference between **(c)** dCON and MCI.

MCI as compared with subjects with sCON was observed in the PCC. This area shows prominent hypometabolism in both clinically overt and incipient AD cases (20,21,44,45), a finding consistent with the known perfusion-metabolism coupling (46,47). Moreover, previous case-control studies in which researchers compared control subjects with patients with MCI and those with AD showed that this area displays not only decreased perfusion and metabolism but also decreased fractional anisotropy and volumes and decreased protein synthesis in patients with early AD (12–15,17–19,21,48). A recent ASL study in subjects with MCI and patients with AD also documented ASL deficits in the PCC (16) that may start quite early in the course of the dementing process and precede the development of significant neuropsychological deficits. Moreover, the PCC is a core component of the so-called default mode network (49), which is reliably identified with resting-state functional MR imaging (50–52). Default mode network activity decreases in the course of neurodegeneration probably as a consequence of both vascular and neuronal effects (4,52–57).

While several previous cross-sectional studies compared groups of patients with AD or MCI and control subjects (12–19), only one previous longitudinal study indicated that baseline hypoperfusion in the right inferior parietal and middle frontal cortex and in the precuneus indicated subsequent cognitive decline in patients with MCI (58). Our results suggest that ASL could be useful as a predictive preclinical AD marker and should enable identification of healthy control subjects at risk for AD dementia. In particular, because of the known coupling between brain perfusion and metabolism, ASL might be partly used as a surrogate marker for FDG PET. As an easy and cost-effective tool, in the future, ASL could be combined with amyloid and τ PET imaging in the identification of healthy individuals with already active AD who are at high risk for further cognitive decline. This subsample of elderly control subjects would be of particular interest for future curative treatments in this field.

Focal atrophy might be a confounding factor for perfusion analysis in ASL. Consequently, we used individual gray matter–corrected ASL data to eliminate this potential confounding variable. We found no significant differences in ASL values with partial volume correction versus those without partial volume correction, nor did we find voxel-based morphometry differences in gray matter between subjects with sCON and those with dCON, indicating that partial volume effects or focal atrophy did not confound the results of our sample. Finally, the implemented ASL sequence has one inversion time, which might potentially confound the estimation of relative CBF in elderly patients with a decreased speed of perfusion. Ongoing methodologic improvements, such as multiinversion time ASL sequences, will overcome this limitation in the future.

In conclusion, ASL relative CBF enabled discrimination of dCON and MCI from sCON at baseline imaging. Both dCON and MCI had similar patterns of reduced ASL, notably in the PCC, suggesting that this parameter enables early detection of regional CBF alterations before the onset of clinically overt dementia. Patients with dCON may maintain their cognitive status at baseline in spite of this CBF change because of their neurocognitive reserve; however, they will display the first neuropsychological deficits at 18-month follow-up.

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