Cerebral perfusion:
artrial spin-labeling MRI
Cerebral blood flow measured with 3D pseudocontinuous arterial spin-labeling MRI in Alzheimer’s disease and mild cognitive impairment: a marker for disease severity
ABSTRACT

**Purpose:** To compare pseudo-continuous arterial spin-labeled (PCASL) magnetic resonance (MR) imaging measured quantitative CBF of patients with Alzheimer’s disease (AD), patients with mild cognitive impairment (MCI) and subjects with subjective complaints in a region-of-interest (ROI) and voxel-wise fashion.

**Materials and Methods:** The local Institutional Review Board approved the study. All subjects provided informed consent. Whole-brain 3D fast spin echo PCASL images were acquired at 3T in 71 AD patients (age 65±7, 55% female), 35 MCI patients (age 65±8, 42% female) and 73 subjects with subjective complaints (age 60±9, 39% female) that visited our memory clinic. Analyses were performed using both uncorrected and partial volume corrected (PVC) maps. Regional CBF was compared using analyses-of-variance, permutation tests were used for voxel-wise comparisons. Associations with cognition (Mini Mental State Examination) were investigated using linear regression analyses. All analyses were corrected for age and sex.

**Results:** Uncorrected CBF was decreased in AD patients compared to subjects with subjective complaints (27±5 vs. 33±5 ml/100g/min; p<0.001), with strongest reductions in the parietal lobes (22±6 vs. 30±5 ml/100g/min; i.e. 27%). PVC cortical CBF showed similar results. In MCI patients CBF was decreased in the precuneus and the parietal and occipital lobes compared to subjects with subjective complaints. Voxel-wise comparisons confirmed our ROI-based findings, showing largest CBF differences in the precuneus and bilateral parietal cortex. Uncorrected and PVC cortical CBF were associated with cognition across diagnostic groups (β=0.46 and β=0.42, p<0.001) and within the AD group (β=0.41 and β=0.42, p<0.001).

**Conclusion:** CBF measured by 3D PCASL detects functional changes in the prodromal and more advanced stages of AD, and is a marker for disease severity.
Advances in Knowledge:

- Whole brain quantitative cerebral blood flow (CBF) measured by 3D pseudo-continuous arterial spin-labeling (PCASL) distinguishes patients with Alzheimer’s disease (AD) and mild cognitive impairment (MCI) from subjects with subjective complaints.
- The parietal regions, and more specifically the precuneus and posterior cingulate, are most severely hypo-perfused in AD and MCI.
- The association between CBF and cognition confirms the clinical relevance of this functional marker.
- Partial volume correction of CBF maps is not essential for clinical purposes, since CBF measured by 3D PCASL distinguishes AD and MCI patients from subjects with subjective complaints both with and without correction for partial volume effects.

Implications for Patient Care:

The advantages of 3D pseudo-continuous arterial spin-labeling, e.g. its non-invasive nature, the short acquisition time and its widespread accessibility, make it a potential alternative for currently used functional markers, such as FDG-PET, in the workup of dementia.

Summary statement:

Quantitative CBF measured by 3D PCASL detects functional brain injury caused by AD pathology both in the prodromal and more advanced stages of the disease; its relation to cognition indicates the clinical relevance of this functional marker.

INTRODUCTION

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder, characterized by the accumulation of amyloid-β and hyperphosphorylated tau.¹ The hallmark of AD on magnetic resonance (MR) imaging is cortical atrophy, particularly located in the medial temporal and parietal lobes.² However, with the prospect of disease-modifying therapies, it is desirable to detect signs of neurodegeneration at an earlier stage of the disease, before neuronal cell destruction is detectable on MR imaging as atrophy.

Molecular markers, e.g. amyloid binding positron emission tomography (PET) tracer uptake, show the earliest detectable changes in the course of AD. Amyloid plaque
deposition occurs prior to cognitive decline but reaches a plateau in a very early stage of the disease. Preceding structural damage reflected by volume loss on MR imaging, functional changes are also present in an early stage of the disease but gradually change as the disease progresses. Functional markers such as glucose metabolism representing \(^{18}\)F-fluorodeoxyglucose (FDG) PET are therefore more suitable to monitor disease progression.

Arterial spin-labeled (ASL) MR imaging is a technique that non-invasively measures cerebral blood flow (CBF) by using magnetically labeled arterial blood water, flowing through the carotid and vertebral arteries, as an endogenous contrast medium. Important advantages of this technique are its non-invasiveness and short acquisition time at higher magnetic field strengths (3T), allowing routine clinical application in the workup of dementia. Since CBF and glucose metabolism are closely linked, ASL may be a promising alternative functional marker for the early diagnosis and monitoring of the disease progression in AD. To date several smaller studies have studied relative and absolute perfusion in (prodromal) AD, mainly using pulsed and continuous ASL sequences with partial brain coverage. These studies show decreased perfusion in AD in similar patterns as found using FDG-PET.

The purpose of this study was to compare quantitative CBF values of patients with AD, patients with mild cognitive impairment (MCI) and subjects with subjective complaints, using a whole brain 3D pseudo-continuous ASL (PCASL) technique at 3T. We studied both uncorrected CBF (i.e. not corrected for partial volume effects) and partial volume corrected (PVC) cortical and white matter CBF, in a region-of-interest (ROI) and a voxel-wise fashion. Secondly, we aimed to investigate whether changes in CBF correlated with cognition as measured using the Mini Mental State Examination (MMSE).

**METHODS**

GE Medical Systems (Milwaukee, WI, USA) provided the below described 3D PCASL sequence. The authors had full control of the data and the information submitted for publication.

**Subjects**

In this prospective study we included 71 AD patients, 35 MCI patients and 73 subjects with subjective complaints that underwent brain MR imaging according to our dementia protocol at 3T between 6 October 2010 and 14 September 2011. All subjects underwent
a standard dementia screening that included medical history, physical and neurological examinations, screening laboratory tests, neuropsychological testing and brain MR imaging. Clinical diagnosis was established by consensus in a multidisciplinary team. AD patients met the NINCDS-ADRDA criteria for probable AD. Diagnosis of MCI was based on the Petersen criteria. When all investigations were normal (i.e. criteria for MCI or psychiatric disorder were not fulfilled and other underlying neurological diseases were ruled out), patients were considered to have subjective complaints and served as a control group. The local Institutional Review Board approved the study. All patients provided written informed consent.

MR imaging acquisition

MR imaging was performed on a 3T whole body MR system (Signa HDxt, GE Medical Systems Milwaukee, WI, USA) using an 8-channel head coil. Structural images included a sagittal 3D T1-weighted sequence (IR-FSPGR, echo time=3.0ms, repetition time=7.8ms, inversion time=450ms, flip angle=12°, matrix 256x256, 176 slices, voxel size 1x0.9x0.9mm) for anatomical information, and a sagittal 3D fluid attenuated inversion recovery (FLAIR) sequence (CUBE, echo time=123.6ms, repetition time=8000ms, inversion time=2351ms, echo-train length=230, acquisition matrix 224x224, reconstruction matrix 256x256, 132 slices, voxel size 1.2x1x1mm) to determine the severity of white matter hyperintensities (WMH) using the Fazekas scale. PCASL perfusion images (3D-FSE acquisition with background suppression, post-label delay 2.0s, echo time=9ms, repetition time=4.8s, spiral readout 8 arms x 512 samples; 36x5.0mm axial slices, 3.2x3.2mm in-plane resolution, reconstructed pixel size 1.7x1.7mm, acquisition time 4 minutes) were calculated using a single compartment model after the subtraction of labeled from control images. An approximately proton-density (PD) weighted image was obtained by a saturation recovery (SR) acquisition with identical parameters.

CBF was described using the following formula:

\[ CBF = \lambda \left(1 - e^{-T_{SAT}/T_{1GM}}\right) \frac{e^{w/T_{1B}}}{2 T_{1B} (1 - e^{-\tau/T_{1B}})} \frac{\Delta S}{S_0} \]

with post-label delay \( w=2.0s\), labeling time \( \tau=1.5s\), partition coefficient \( \lambda=0.9\), labeling efficiency \( \varepsilon=0.8*0.75\) (label PCASL * background suppression), T1 of blood \( T_{1B}=1.4s\), SR time for PD image \( T_{SAT}=2.0s\) and correction for SR in PD image \( T_{1GM}=1.2s\). \( \Delta S \) stands for ASL difference image and \( S_0 \) for PD reference image.
Pre-processing and MR imaging data analysis

Both T1-weighted and PCASL images were corrected for gradient non-linearities in all three directions. Further data analyses were carried out using FSL (version 4.1; http://www.fmrib.ox.ac.uk/fsl). Pre-processing of T1 images consisted of non-brain tissue removal, linear registration to standard space and tissue segmentation yielding partial volume estimates. PCASL images were linearly registered to the brain-extracted T1 images. The brain mask was used to calculate uncorrected mean whole brain CBF. Partial volume estimates were transformed to the ASL data space and used in a regression algorithm, using a Gaussian kernel of 9.5mm full width at half maximum, to create PVC cortical and white matter CBF maps. Partial volume estimates were subsequently used as a weighting factor to calculate mean cortical and white matter CBF. Additionally, the MNI152 atlas and the Harvard-Oxford cortical atlas (both part of FSL) were used to create regions-of-interest (ROIs) of the frontal, parietal, temporal, occipital and cerebellar brain areas, and additionally of the precuneus and posterior cingulate (PPC) and the hippocampus, to extract mean regional uncorrected and PVC CBF.

Figure 1. Examples of an uncorrected cerebral blood flow (CBF) map and a partial volume corrected (PVC) cortical CBF map of a subject with subjective complaints (female, 49 years old, mean uncorrected CBF 41 ml/100g/min, mean PVC cortical CBF 63 ml/100g/min), an MCI patient (female, 68 years old, mean uncorrected CBF 30 ml/100g/min, mean PVC cortical CBF 44 ml/100g/min) and an AD patient (female, 65 years old, mean uncorrected CBF 26 ml/100g/min, mean PVC cortical CBF 42 ml/100g/min). Red to yellow colors represent CBF values in ml/100g/min. Additionally, corresponding T1-weighted images of the same subjects are displayed.
values (M.A.A.B. (expertise: image analysis, 4 years of experience), J.P.A.K. (expertise: MR physics and image analysis, 15 years of experience) and M.R.B. (expertise: image analysis, 1 year of experience)). In Figure 1 an example of an uncorrected and a PVC cortical CBF map are displayed of a subject with subjective complaints, an MCI patient and an AD patient.

Complementary, voxel-wise comparisons of both uncorrected CBF maps and PVC cortical CBF maps were performed using nonparametric permutation tests (5000 permutations) to detect voxel-wise CBF differences between groups (M.A.A.B., J.P.A.K. and A.M.W. (expertise: image analysis, 12 years of experience)). Analyses were corrected for age and sex. After threshold-free cluster enhancement (TFCE), significant voxels were found by applying a family-wise error (FWE) corrected threshold corresponding to $p = 0.05$. To visualize percentual CBF changes between diagnostic groups, the difference in mean CBF between groups was divided by the mean CBF of the subjective complaints group within the regions of significantly decreased CBF between AD patients and subjective complaints subjects according to the voxel-wise comparisons.

Data quality

All MR images were visually inspected (M.A.A.B. and M.R.B.). One subjective complaints subject was excluded due to poor quality of the PCASL sequence caused by field inhomogeneities at the level of the labeling plane, visible as an artifact on T1-weighted images. Two MCI patients were excluded due to the presence of large vessel infarctions. One MCI patient with a history of meningitis was excluded because of hydrocephalus. One MCI patient was excluded due to failure of structural image pre-processing with unknown cause. Finally, two outliers were excluded from the subjective complaints group because their CBF values differed more than two standard deviations from the mean. Data of 71 AD patients, 31 MCI patients and 70 subjects with subjective complaints were used for further analyses.

Statistics

All other statistical analyses were performed using SPSS (version 15.0; SPSS, Chicago, Ill, USA) (M.A.A.B and W.M.F. (expertise: statistical analysis, 13 years of experience)). For continuous measures, differences between groups were assessed using one-way analyses-of-variance (ANOVA) with post-hoc Bonferroni tests to correct for multiple comparisons. A chi-squared test was used to compare frequency distributions of sex. Differences in CBF between male and female subjects were analyzed using independent samples t-tests. Relationships between age, WMH and CBF were explored using
Pearson’s correlation analyses. Differences in CBF between diagnostic groups were analyzed using ANOVA with post-hoc Bonferroni tests, correcting for the effect of age and sex, and additionally for WMH. Linear regression analyses were performed across the diagnostic groups and within the patient groups to assess relationships between CBF (independent variable) and cognition, using MMSE-scores (dependent variable). Age and sex, and additionally WMH, were entered into the model as covariates. A receiver operating characteristic (ROC) curve was generated for AD patients and subjective complaints subjects to determine the optimal cut-off value of uncorrected CBF in the PPC region at a sensitivity of 80%.

RESULTS

Demographics and MR imaging findings are shown in Table 1. There were no differences in sex between patient groups. Subjects with subjective complaints were younger than patients with MCI (p=0.005) and AD (p=0.001). Patients with AD had lower MMSE-scores compared to MCI patients and subjects with subjective complaints (both p<0.001). MCI and AD patients had more WMH than subjects with subjective complaints (p<0.001 and p=0.005 respectively). Normalized gray matter volume (NGMV) was decreased in AD patients compared to MCI patients and subjects with subjective complaints (both p<0.001).

Relevance of covariates

Within the subjective complaints group females showed higher CBF in the PPC region (uncorrected CBF p=0.01, PVC cortical CBF p=0.02 and PVC white matter CBF p=0.006), the occipital region (PVC cortical CBF p=0.02, PVC cortical CBF p=0.01, and PVC white matter CBF p=0.001) and the cerebellum (uncorrected CBF p<0.001, PVC cortical CBF p=0.002, and PVC white matter CBF p<0.001). Furthermore, females showed higher total and parietal PVC white matter CBF than males within the subjective complaints group (p=0.02 and p=0.04 respectively). There were no differences in CBF between males and females within the MCI and AD groups. Age was associated with uncorrected CBF in the frontal and temporal lobes within the subjective complaints group (r=-0.37 with p=0.002 and r=-0.26 with p=0.03 respectively). Similar results were found within the MCI patient group (r=-0.33 with p=0.07 and r=-0.38 with p=0.04 respectively), but there was no association with age in the AD group. Severity of WMH was associated with CBF within the AD group in the occipital region (uncorrected, PVC cortical and PVC white matter CBF) and in the cerebellum (PVC white matter CBF).
Total and regional CBF differences

Total uncorrected and PVC cortical and white matter CBF differed between groups. Post-hoc tests showed that AD patients had lower uncorrected CBF (p<0.001), PVC cortical CBF (p<0.001) and white matter CBF (p<0.001) compared to subjects with subjective complaints (Table 2) (Figure 2). Uncorrected CBF (p=0.006) and PVC white matter CBF (p=0.006) were decreased in AD patients compared to MCI patients. MCI patients showed trends of lowered uncorrected CBF (p=0.06) and PVC cortical CBF (p=0.05) compared to subjects with subjective complaints. Additional correction for WMH did not change the differences between groups.

Table 2. Total region-of-interest based CBF values.

<table>
<thead>
<tr>
<th></th>
<th>Subjective complaints</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected CBF</td>
<td>33±5</td>
<td>30±5c</td>
<td>27±5aaa,bb</td>
</tr>
<tr>
<td>PVC cortical CBF</td>
<td>49±7</td>
<td>44±8d</td>
<td>41±8aaa</td>
</tr>
<tr>
<td>PVC white matter CBF</td>
<td>26±4</td>
<td>24±4</td>
<td>22±4aaa,bb</td>
</tr>
</tbody>
</table>

Cerebral blood flow (CBF) values in ml/100g/min. Results demonstrated in means and standard deviations. Shown results are corrected for age and sex. PVC: partial volume corrected. aaa p<0.001 compared to subjects with subjective complaints, bb p<0.01 compared to MCI patients, c p=0.06 compared to subjects with subjective complaints, d p=0.05 compared to subjects with subjective complaints.
Post-hoc tests of regional CBF values showed similar patterns as aforementioned total brain findings (Table 3), with an additional difference between MCI and AD patients in parietal, PPC and temporal PVC cortical CBF. Furthermore, MCI patients showed lowered uncorrected CBF compared to subjects with subjective complaints in the parietal and PPC regions, and lowered PVC cortical CBF in the parietal, PPC, frontal and occipital regions. The hippocampus only differed in uncorrected CBF values between AD patients and subjects with subjective complaints. The cerebellum showed no differences between diagnostic groups. Additional correction for WMH did not change the group differences.

Voxel-wise CBF differences

AD patients showed lower uncorrected CBF compared to subjects with subjective complaints throughout the brain, and most prominently in the posterior cingulate, precuneus and bilateral parietal cortical regions (Figure 3). A less pronounced, but similar pattern was found for uncorrected CBF in AD patients compared to MCI patients. Compared to subjects with subjective complaints, MCI patients showed regions of significantly lower uncorrected CBF in the precuneus and posterior cingulate. Similar results were found when comparing the PVC cortical CBF maps (Figure 3). There were no regions of higher CBF found in AD patients compared to MCI patients or subjects with subjective complaints, nor in MCI patients compared to subjects with subjective complaints. Percentual changes of CBF in AD and MCI compared to subjects with subjective complaints are displayed in Figure 4.
Figure 3. Differences in cerebral blood flow (CBF) displayed for uncorrected CBF maps and partial volume corrected (PVC) cortical CBF maps. Results of voxel-wise permutation tests, with correction for age and sex. Data are presented as T-maps (T>2.3, corresponding to FWE-corrected p<0.05). SC: subjective complaints.

Association between CBF and cognition

Across diagnostic groups both total and regional CBF were associated with MMSE (Table 4). This association was mainly driven by the strong association between CBF and cognition within the AD group, most markedly in the parietal and PPC regions (Figure 5). PVC cortical CBF showed a similar association pattern as uncorrected CBF, except for the hippocampus. In the hippocampus the association between CBF and MMSE disappeared, most likely due to the correction for hippocampal atrophy. The association between CBF and cognition within the AD group remained significant after additional adjustment for severity of WMH.
Table 3. Region-of-interest based CBF values.

<table>
<thead>
<tr>
<th></th>
<th>Subjective complaints</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncorrected CBF (ml/100g/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>30±5</td>
<td>27±5(a)</td>
<td>22±6(aaa,bbb)</td>
</tr>
<tr>
<td>PPC</td>
<td>38±6</td>
<td>34±7(a)</td>
<td>29±7(aaa,bbb)</td>
</tr>
<tr>
<td>Frontal</td>
<td>22±5</td>
<td>20±5</td>
<td>19±5(aaa)</td>
</tr>
<tr>
<td>Temporal</td>
<td>26±5</td>
<td>24±4</td>
<td>21±5(aaa,bbb)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>32±6</td>
<td>32±6</td>
<td>30±5(c)</td>
</tr>
<tr>
<td>Occipital</td>
<td>34±7</td>
<td>31±7(c)</td>
<td>26±7(aaa,bbb)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>25±5</td>
<td>25±6</td>
<td>23±6</td>
</tr>
<tr>
<td><strong>Partial volume corrected cortical CBF (ml/100g/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>56±9</td>
<td>51±9(a)</td>
<td>45±10(aaa,b)</td>
</tr>
<tr>
<td>PPC</td>
<td>64±10</td>
<td>57±11(a)</td>
<td>52±11(aaa,b)</td>
</tr>
<tr>
<td>Frontal</td>
<td>50±9</td>
<td>45±9(a)</td>
<td>42±9(aaa)</td>
</tr>
<tr>
<td>Temporal</td>
<td>45±7</td>
<td>42±6</td>
<td>37±7(aaa,bb)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>39±6</td>
<td>40±7</td>
<td>38±7</td>
</tr>
<tr>
<td>Occipital</td>
<td>55±9</td>
<td>50±11(a)</td>
<td>46±10(aaa)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>42±9</td>
<td>39±9</td>
<td>39±9</td>
</tr>
</tbody>
</table>

Results demonstrated in means and standard deviations. Shown results are corrected for age and sex. CBF: cerebral blood flow, PPC: precuneus and posterior cingulate. \(a\) \(p<0.05\) compared to subjects with subjective complaints, \(aa\) \(p<0.01\) compared to subjects with subjective complaints, \(aaa\) \(p\leq0.001\) compared to subjects with subjective complaints, \(b\) \(p<0.05\) compared to MCI patients, \(bb\) \(p<0.01\) compared to MCI patients, \(bbb\) \(p\leq0.001\) compared to MCI patients, \(c\) \(p=0.06\) compared to subjects with subjective complaints.
Figure 4. Voxel-wise percentual cerebral blood flow (CBF) changes in AD and MCI patients compared to subjects with subjective complaints. Maps were created by dividing the difference in mean CBF between groups by the mean CBF of the subjective complaints (SC) group within the regions of significantly decreased CBF between AD patients and subjects with subjective complaints according to voxel-wise comparison (FWE-corrected p<0.05). PVC: partial volume corrected.

Figure 5. Scatterplot of uncorrected cerebral blood flow (CBF) in the precuneus and posterior cingulate cortex (PPC) plotted against mini mental state examination (MMSE) scores.
Table 4. Associations between region-of-interest based CBF and cognition (MMSE).

<table>
<thead>
<tr>
<th></th>
<th>Across groups</th>
<th>Subjective complaints</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncorrected CBF (ml/100g/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.46***</td>
<td>-.11</td>
<td>-.17</td>
<td>.41***</td>
</tr>
<tr>
<td>Parietal</td>
<td>.53***</td>
<td>-.10</td>
<td>-.25</td>
<td>.47***</td>
</tr>
<tr>
<td>PPC</td>
<td>.52***</td>
<td>-.08</td>
<td>-.10</td>
<td>.44***</td>
</tr>
<tr>
<td>Frontal</td>
<td>.37***</td>
<td>-.04</td>
<td>.10</td>
<td>.42***</td>
</tr>
<tr>
<td>Temporal</td>
<td>.51***</td>
<td>.09</td>
<td>.13</td>
<td>.37**</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>.29***</td>
<td>.02</td>
<td>.08</td>
<td>.32**</td>
</tr>
<tr>
<td>Occipital</td>
<td>.45***</td>
<td>-.09</td>
<td>-.34</td>
<td>.34**</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>.21**</td>
<td>-.02</td>
<td>-.02</td>
<td>.19</td>
</tr>
<tr>
<td><strong>Partial volume corrected cortical CBF (ml/100g/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.42***</td>
<td>-.10</td>
<td>-.12</td>
<td>.42***</td>
</tr>
<tr>
<td>Parietal</td>
<td>.49***</td>
<td>-.06</td>
<td>-.10</td>
<td>.48***</td>
</tr>
<tr>
<td>PPC</td>
<td>.48***</td>
<td>-.04</td>
<td>-.17</td>
<td>.48***</td>
</tr>
<tr>
<td>Frontal</td>
<td>.39***</td>
<td>-.14</td>
<td>-.13</td>
<td>.44***</td>
</tr>
<tr>
<td>Temporal</td>
<td>.43***</td>
<td>-.05</td>
<td>-.07</td>
<td>.35**</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>.20**</td>
<td>-.09</td>
<td>.12</td>
<td>.21</td>
</tr>
<tr>
<td>Occipital</td>
<td>.39***</td>
<td>-.08</td>
<td>-.19</td>
<td>.35**</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>.19*</td>
<td>-.08</td>
<td>.02</td>
<td>.25*</td>
</tr>
</tbody>
</table>

Results demonstrated in standardized β's. Shown results are adjusted for the effect of age and sex. MMSE: Mini Mental State Examination, CBF: cerebral blood flow, PPC: precuneus and posterior cingulate. *p<0.05, **p<0.01, ***p<0.001.

Figure 6. Receiver operating characteristic (ROC) curve for uncorrected cerebral blood flow (CBF) in the precuneus and posterior cingulate cortex (PPC) of AD patients and subjects with subjective complaints. The optimal CBF cut-off value of 32.9 ml/100g/min was determined at a sensitivity of 80% and a specificity of 69%.
An ROC-curve was generated for uncorrected CBF in the PPC region of AD patients and subjects with subjective complaints, to determine the optimal cut-off value at a sensitivity of 80% (Figure 6). The area under the curve (AUC) was 0.83 (95% CI 0.76 to 0.89). A sensitivity of 80% resulted in a specificity of 69% and an optimal cut-off value for uncorrected CBF in the PPC of 32.9 ml/100g/min. At this cut-off value, positive predictive value was 0.74 (49 true positives and 17 false positives) and negative predictive value was 0.71 (55 true negatives and 22 false negatives).

**DISCUSSION**

In this study we used a whole brain 3D PCASL technique at 3T to investigate quantitative CBF in a ROI-based and voxel-wise fashion. AD patients showed lower uncorrected and PVC CBF values compared to subjective complaints subjects in all brain regions except the cerebellum. In MCI patients CBF was significantly decreased in the precuneus and the parietal and occipital lobes. Additional voxel-wise analyses confirmed these results, showing largest decreases of CBF in AD and MCI patients in the posterior cingulate, precuneus and in more extended bilateral parietal areas. Correlation analyses showed a strong relation between CBF and cognitive function in the group of AD patients.

To date, several smaller studies have used a variety of ASL techniques (i.e. pulsed and continuous, mainly non-whole brain sequences) to study CBF in patients with MCI and AD, all demonstrating patterns of decreased CBF mainly located in the posterior cingulate cortex, precuneus and bilateral parietal areas. Only two of these studies directly compared CBF of AD patients, MCI patients and controls, both by using voxel-wise analyses on 1.5T non-whole brain data. Johnson et al. used relative CBF measures to compare AD and MCI patients with a control group, and found regions of relative hypoperfusion in AD patients in the bilateral posterior cingulate and precuneus and in the right inferior parietal lobe. In MCI patients an overlapping, but weaker pattern was found. Dai et al. found AD and MCI patients to have decreased CBF in the posterior cingulate, precuneus and inferior parietal cortex as well, with the regions of hypoperfusion in AD being more extensive than in MCI. Our results endorse those results, showing quantitative CBF values of MCI patients to be intermediate between AD patients and subjects with subjective complaints, with largest perfusion differences being found in the PPC region.

The pattern of decreased CBF that we found using a voxel-wise comparison overlaps with the commonly described pattern of FDG-PET hypometabolism in AD. Currently,
FDG-PET is the standard clinical imaging tool to assess functional changes in terms of hypometabolism in AD and forms as such part of the diagnostic process of memory clinic patients. Although the exact relation between both processes is not completely clear, glucose metabolism and CBF are described to be closely coupled.\(^7,27\) ASL might therefore become an important alternative for the visualization of cerebral (and neuronal) function, especially when considering the advantages of ASL compared to FDG-PET imaging, such as its non-invasive nature, short acquisition time and widespread accessibility. With the development of new labeling techniques such as pseudo-continuous labeling, which uses a multitude of millisecond-long pulses to achieve a high labeling efficiency and effective compensation of magnetization transfer effects, and possibilities to improve image quality by scanning at higher field strength and using 3D imaging with whole brain coverage, this MR imaging technique has become a serious alternative for FDG-PET imaging in the diagnostic workup of dementia. Although our results indicate that ASL is a suitable technique for differentiating both MCI and AD patients from subjects with subjective complaints on a group level, future studies are needed to clarify whether PCASL measured CBF is a distinctive marker on the individual level, and comparable to other modalities for predicting the correct diagnosis.

Our results showed that uncorrected CBF was decreased in the hippocampus in AD patients compared to subjects with subjective complaints. This effect disappeared after partial volume correction. Previous groups have described CBF increases in the hippocampal region in AD and MCI patients,\(^26,28\) suggesting a compensatory mechanism of hyperperfusion in the hippocampus. However, these groups reported regional CBF results normalized by subject-specific CBF values (visual cortex \(^28\) and whole brain,\(^26\) CBF) which most likely contributed to finding a relative hippocampal hyperperfusion, and therefore a discrepancy with our absolute CBF results.

In this study, we investigated CBF both with and without correction for partial volume effects. The disappearance of a decrease in CBF and the association between CBF and cognition in the hippocampus in AD patients after partial volume correction (Table 3 and 4), confirms the use of applying this correction to filter out the effect of cortical atrophy. However, in clinical practice CBF maps are presented to radiologists as uncorrected images. Our results show that partial volume correction of CBF maps is not necessary to improve the radiological differentiation between AD patients and subjects with subjective complaints, most likely due to the additive discriminatory effect of cortical atrophy and decreased CBF.

This study has some limitations. First of all, the group of MCI patients lacked clinical follow-up. Secondly, our control group consisted of subjects with subjective complaints instead of healthy controls. However, this is a good reflection of a normal clinical
situation. Furthermore, based on our results no conclusions can be drawn on the individual subject level, since analyses were performed on a group level. Subsequently, some image-related limitations should be mentioned: ASL scan quality could not be assured completely. All images except for those of one subjective complaints subject were visually of good quality. However, the labeling efficiency was not assessed formally. Furthermore, we did not scan with several delay times to account for differences in travel times between groups. However, to take into account several factors that might cause a delayed blood water arrival in the brain of our study group (e.g. age, cerebrovascular co-morbidity, delayed transit time due to AD pathology), we used an age-adjusted delay time of 2.0s instead of the commonly used 1.5s.29 Finally, no correction for possible confounders such as history of diabetes, stage of digestion, smoking habits and recent caffeine intake were applied. Future studies are needed to clarify the effect of these factors on CBF, and their contribution to between-subject variability.

We conclude that quantitative CBF measured by 3D PCASL detects functional brain injury caused by AD pathology both in the prodromal and more advanced stages of the disease; its relation to cognition indicates the clinical relevance of this functional marker. Being a non-invasive and easily accessible alternative for FDG-PET imaging, 3D PCASL could become of important additional value in the workup of dementia.

ACKNOWLEDGEMENTS

The authors thank Ajit Shankaranarayanan of GE Healthcare for providing the 3D pseudo-continuous ASL sequence that was used to obtain data for this paper. The study was supported by the Alzheimercenter and the Imaging Analysis Center of the VU University Medical Center Amsterdam, The Netherlands.
REFERENCES


