Neurovascular unit impairment in early Alzheimer's disease measured with magnetic resonance imaging

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1. Introduction

The pathogenesis of Alzheimer’s Disease (AD) is still unknown, despite decades of research. A popular hypothesis states that the accumulation of insoluble proteins is a central part of the pathological cascade that leads to AD (Jack et al., 2010). However, there is also very strong evidence that cerebrovascular damage is a key element in this cascade (De La Torre, 2004). The notion that cerebrovascular pathology contributes to AD has recently gained more popularity, as the amyloid hypothesis does not satisfactorily represent the cause of the disease (Drachman, 2014). Therefore, the neurovascular unit hypothesis states that any damage to the neurovascular unit can start a complicated cascade involving a reduction in cerebral blood flow (CBF) and BBB disruption (Iadecola, 2010). Another important function of the neurovascular unit is the regulation of blood flow.

A general hypothesis is that impairment of the neurovascular unit is a central feature in the pathophysiology that leads to AD. In short, the neurovascular unit impairment hypothesis states that any damage to the neurovascular unit can start a complicated cascade involving a reduced cerebral blood flow (CBF) and BBB disruption (Jackson, 2008; Zlokovic, 2011). This hypothesis is centered around the neurovascular unit, a collection of capillary endothelial cells and smooth muscle cells, neuronal cells, neurons and subcellular structures in the brain (Lecrux and Hamel, 2011). Different parts of the neurovascular unit form functional elements, which work together to perform necessary functions. One of these functions is that the BBB protects the brain from circulating neurotoxins while allowing molecules essential to the parenchyma to pass (Abbott et al., 2010; Hawkins and Davis, 2005). Another important function of the neurovascular unit is the regulation of blood flow.
time, the neurovascular unit impairment increases and chronic damage results in neurodegeneration and cognitive decline. The neurovascular unit has been found to be impaired in dementia, mainly due to inflammation, oxidative stress, and a nitric oxide deficit, leading to reduced CBF and increased BBB permeability (Iadecola, 2013; Lyros et al., 2014; Montagne et al., 2015). Given the gradual progression of AD, this impairment is expected to start early in the disease process. Furthermore, under the assumption that this loop is an integral part of the pathophysiology of early AD, the impairment of the different functional elements of the neurovascular unit are expected to co-occur, and thus may be correlated. Thus far, these mechanisms are, to a large extent, deduced from animal and in vitro studies (Sagare et al., 2012). However, in vivo human studies are scarce.

If there is widespread damage to the neurovascular unit, global deterioration of measures that should be strictly regulated by the neurovascular unit can be expected. Advanced MRI techniques allow for spatially resolved measurement of some of these measures that are relevant to AD, namely the CBF, BBB leakage, and local blood volume. In this study, we measured CBF with arterial spin labeling (ASL), which magnetically labels protons of the arterial blood and subsequently follows their distribution throughout the brain (Alsop et al., 2015). These CBF measurements were combined with a dedicated dynamic contrast-enhanced (DCE) MRI protocol, which allows for the measurement of subtle BBB leakage. With DCE-MRI, the spatiotemporal distribution of a contrast agent over brain vasculature and parenchyma is measured. It is a suitable method to examine local cerebral blood plasma volume ($v_p$) and the leakage rate ($K_L$, in minute$^{-1}$) of a contrast agent from the blood space into the parenchyma (Sourbron, 2010; Tofts et al., 1999).

Our aim was to investigate the functioning of neurovascular unit in terms of blood flow regulation and BBB function in AD by examining the possible link between cerebral (microvascular) perfusion and BBB leakage in the gray matter (GM) of patients with early AD and healthy controls.

2. Materials and methods

2.1. Participants

Patients were recruited at the memory clinics from the Maastricht University Medical Center and Leiden University Medical Center (LUMC). All patients were clinically diagnosed with either mild cognitive impairment (MCI) due to AD or mild dementia of the Alzheimer type, which we combined into 1 group and termed early AD. Diagnosis was made by consensus of a multidisciplinary team according to the Dubois criteria for MCI and the criteria of the National Institute on Aging and the Alzheimer’s Association for AD (Dubois et al., 2007; McKhann et al., 2011). None of the patients had an evident cerebrovascular origin for the dementia such as a history of stroke. In addition, participants were excluded in case of contraindications for MRI, renal dysfunction, major structural brain abnormalities such as tumors, alcohol and/or drug abuse, cerebrovascular pathology, or other major psychiatric or neurological disorders. The controls were recruited through advertisements in local newspapers. All participants underwent the mini mental state examination test before MRI (Folstein et al., 1975). This study was approved by both the Medical Ethical Committee AZM/UM and the Committee for Medical Ethics LUMC. Written informed consent was obtained from all participants. We included 16 patients and 18 healthy controls (4 and 3 at the LUMC, respectively). Two patients were excluded because of incomplete MRI examinations, and 2 controls were excluded because of severe motion-induced artifacts and a lowered renal function. Therefore, the data of 14 patients (7 AD, 7 MCI, mean age 75.3 years, range 65–85 years, 8 males) and 16 healthy controls (mean age 76.4 years, range 65–85 years, 11 males) were used for final analysis.

2.2. Image acquisition

CBF was measured using a pseudo-continuous ASL (PC) 2D multislice sequence with a repetition time (TR) of 3847 ms, an echo time (TE) of 14 ms, voxel size of $3 \times 3 \times 7 \text{ mm}^3$, matrix size of $80 \times 80 \times 17$, a 1525 ms postlabeling delay of the most inferior slice, and a label duration of 1650 ms. Slices were obtained in the inferior-superior direction (35 ms per slice), and 50 control-label pairs were acquired. The labeling slice was positioned perpendicular to the internal carotid arteries, with the help of coronally and sagittally oriented phase-contrast angiograms. A single proton density (PD) sequence was acquired with the same geometric properties as the PCASL sequence and a TR of 10 seconds to scale the PCASL signal intensity to absolute CBF in mL/min/100 g of brain tissue.

Blood–brain barrier leakage and local blood plasma volume were measured using a dual-time resolution DCE-MRI sequence, which was developed to increase sensitivity to the subtle leakage expected in early AD. This protocol utilizes a high temporal resolution during contrast agent arrival and initial distribution to properly sample the initial arrival peak (the fast sequence), and a lower temporal but higher signal-to-noise during the longer washout (the slow sequence), (Jelescu et al., 2011). The dual-time resolution sequence was also found to be relatively insensitive to perfusion differences (Jelescu et al., 2011). The acquisition protocol and analysis method are analogous to a previously described procedure (van de Haar et al., 2016). The fast sequence was a 3D saturation recovery gradient recalled sequence with a TR/TE 5.2/2.5 ms, flip angle 30°, voxel size $1 \times 1 \times 5 \text{ mm}^3$, matrix size 256 x 200 x 10, SENSE factor 2 (direction RL), with a saturation prepulse given at a delay time (TD) of 120 ms, 29 volumes total, dynamic scan interval of 3.2 seconds resulting in a scan time of 1.55 minutes. The contrast agent was injected at the fourth dynamic scan (gadobutrol, 0.1 mmol/kg, injected using a power injector with a flow of 3 mL/s, followed by a 20-mL saline flush). The slow sequence was a saturation recovery gradient recalled sequence (TR/TE 5.6/2.5 ms, flip angle 30°, voxel size $1 \times 1 \times 2 \text{ mm}^3$, matrix size 256 x 256 x 50 matrix, SENSE factor 2 (direction RL), dynamic scan interval 31.8 seconds, 45 volumes (including 3 precontrast volumes), with the same prepulse. The slow sequence started immediately after the fast sequence, for a total scan time of 25 minutes. The field-of-view (FOV) was centered on the corpus callosum, ensuring optimal coverage of the brain surrounding the lateral ventricles, which is the most common location of white matter (WM) hyperintensities. Because the WM hyperintensities are presumed to be of vascular origin, we expected the periventricular region to show the most microvascular pathology (Prins and Scheltens, 2015). The 2 sequences were combined by upsampling the volumes of the fast sequence using linear interpolation to match the slow sequence FOV and voxel size. It should be noted that in this way the final spatial resolution is limited by the lowest of these sequences. A T1-weighted structural scan (TR of 8.4 ms, inversion time [TI] of 706 ms, TE of 4.0 ms, flip angle of 8°, cubic voxel size of 1 mm, matrix size $256 \times 155 \times 256$) was used for structural reference and to perform image registration between the various contrasts. All imaging was performed on a dual-transmit 3 Tesla system (Phillips Achieva, Best, The Netherlands), with a 32-channel receiver head coil.

2.3. Image analysis

Motion correction for all sequences was performed using FMRIB’s linear image registration tool [FLIRT (Jenkinson et al., 2002)] using a mutual-information algorithm. Further analysis
was performed by a researcher blinded to the using in-house
developed software implemented in Matlab (version 2012B, The
Mathworks Inc, MA, USA).

2.3.1. Arterial spin labeling MRI

Motion correction was performed relative to the mean of the
control images. Next, the label images were subtracted from the
control images. Control-label pairs were removed when visual
inspection of the subtraction result showed artefacts. CBF calculation
was based on an adaptation of the formula proposed in the ASL
whitepaper presented by the ISMRM Perfusion Study Group and
the European Consortium for ASL in Dementia (Alsop et al., 2015)
to correct for the 2D multislice readout scheme and by including a
correction factor for background suppression (Van Osch et al.,
2009):

\[
CBF = \frac{6000 \cdot \lambda \cdot (S_{\text{control}} - S_{\text{label}}) \cdot e^{T_{\text{delay}} \cdot T_{\text{RPA}} / (T_{\text{RPA}} - T_{\text{b}})}}{2 \cdot \alpha \cdot \delta_{\text{SI}} \cdot T_{\text{blood}} \cdot S_{\text{Pd}} \cdot (1 - e^{-T_{\text{b}} / T_{\text{blood}}})}
\]

Here \( \lambda \) is the blood–brain partition coefficient [set at 0.9 mL/g
(Herscovitch and Raichle, 1985)], \( S_{\text{control}} \) and \( S_{\text{label}} \) are the means
over time of the control and label images, respectively. \( T_{\text{delay}} \) is the
post label delay (1525 ms), \( T_{\text{RPA}} \) is the acquisition time for a single
slice (35 ms), \( z \) is the slice number, \( T_{\text{b}} \) is the longitudinal
relaxation time of blood [set at 1650 ms for 3T (Lu et al.,
2004)], \( \alpha \) is the labeling efficiency [set at 0.85 (Alsop et al.,
2015)], \( \delta_{\text{SI}} \) is a correction factor for the background suppression [set at 0.83 (Van
Osch et al., 2009)]. \( S_{\text{Pd}} \) is the signal intensity of the PD image, and \( t \) is the label duration (1650 ms). This study will focus on
effects in the GM, as ASL in the WM remains challenging (Van
Osch et al., 2009).

2.3.2. Dynamic contrast–enhanced MRI

Motion correction was performed relative to the mean of the
precontrast images. Individual vascular input functions (VIFs) were
extracted from the superior sagittal sinus, which was chosen as this
was the largest cerebral blood vessel in the FOV and has been used
successfully in other studies (Haroon et al., 2004; Jelescu et al.,
2011; Lavini and Verhoeff, 2010; Li et al., 2000). Conversion of
signal enhancement to contrast agent concentration was performed
differently for the VIF and for tissue. The conversion of signal of the
VIF to contrast agent concentration was implemented using an
in vitro-diluted MnCl2 stock solution with different gadobutrol
concentrations (range 0–40 mM, baseline T1 relaxation time of
1650 ms, comparable to human blood). For tissue, we observed
much lower signal changes. Therefore, a linear relationship
between signal change and contrast agent concentration (\( C_{\text{t}} \)) was
assumed for tissue (Schabel and Parker, 2008). The range of contrast
agent concentration found in brain tissue was approximately
0–0.2 mM. At 0.2 mM, the linear approximation showed an error
margin of at most 2% in tissue, compared with the nonlinear
conversion. For this calculation, baseline T10 values were used,
based on measurements using a pulse sequence comparable to the
slow sequence but with different TD values (120–4000 ms) using
\( S = M_0 \cdot (1 - e^{-T_{\text{b}} / T_{\text{b}}}) \), where \( S \) is the measured signal and \( M_0 \) is a
fit parameter in which the magnetization and scanner-specific
properties are combined (Larsson et al., 2009). The mean T10
values for the tissue of the participants was calculated, and the T1
structural scans were used to assign voxelwise T10 values. These
T10 maps were smoothed with a 2 × 2 × 2 mm kernel. We also
measured signal drift by using the total DCE-MRI sequence on
phantoms with 2 different gadobutrol concentrations (1 and
5 mM). Further information on the signal drift and its effect on the
DCE-MRI measures can be found in the Appendix. After calculation
of the concentration-time courses, the BBB leakage rate \( K_l \) (in
minute \(^{-1}\) ) and local blood plasma volume \( v_p \) (fraction of total voxel
volume) were determined using the Patlak graphical approach using
(Patlak et al., 1983):

\[
C_t(t) = v_p C_p(t) + K_l (1 - Hct) \int_0^t C_p(\tau) d\tau
\]

Where Hct is the hematocrit, which was set to 45% and \( C_p \) and \( C_t \)
are the contrast agent concentration in blood plasma and tissue,
respectively. Next, the mean \( K_l \) and \( v_p \) were calculated per partici-
and used for statistical analysis.

The noise on the concentration curves sometimes caused negative
slope values in the Patlak plot. To further increase the sensitivity of this leakage detection for the lowest possible \( K_l \) values close to the noise level, a histogram approach was used. The
histograms were normalized, and noise was estimated by assuming
that negative slope values can only be attributed to noise and that a
similar distribution of noise is also present in positive slope values.
The data were then corrected by subtracting the estimated noise
from the measured histogram. The cumulative remaining sum of the bins was defined as the BBB leakage volume fraction \( v_L \). For
further details on this procedure, we refer to our previous work
(van de Haar et al., 2016). Note that the noise suppression method
was only used to calculate \( v_L \), and when the \( K_l \) is reported, the mean
of the entire histogram is meant without applying the noise
suppression method.

2.3.3. Structural reference

The T1-weighted structural scan was processed using the Free-
Surfer software package to automatically define the GM (Fischl,
2002). This software was also used to calculate an atrophy score per participant (atrophy score = 1 – [GM volume + WM
volume]/intracranial volume). Next, the mean values of CBF, \( K_l \), and \( v_p \) of the total GM were calculated per participant. As the ASL
images had the lowest spatial resolution, it was chosen as a refer-
ence, and the T1-weighted image and the DCE-MRI images were
linearly transformed to the ASL images to calculate the correlation
between CBF and the DCE measures.

2.3.4. Statistics

All statistical tests were performed using SPSS (IBM SPSS Sta-
tistics for Windows, version 20.0, NY, USA). The difference in CBF, \( K_l \),
\( v_L \), and \( v_p \) in the GM between the patients and controls, corrected
for age and gender, was first tested using linear regression. Next, the
Pearson correlation coefficient was calculated between the GM CBF
and the DCE measures in the patient and control groups. Because
the effect of age and atrophy may influence these correlations, they
were subsequently added as covariates in a multivariable regres-
sion analysis. To find any regional differences, the group compar-
ison analysis was repeated for different GM regions, the frontal,
temporal, parietal and occipital cortex, and the deep (subcortical)
GM. To correct for the increasing number of statistical tests in the
regional analyses, a false discovery rate procedure for multiple
comparisons \((q = 0.05)\) was applied. Statistical significance was
inferred when \( p < 0.05 \).

3. Results

The patients had a score ≤2 on the modified Hachinski scale,
indicating that the dementia did not have a vascular origin
(Moroney et al., 1997). All patients diagnosed with AD had a Clinical
Dementia Rating of 1, indicating a mild stage of dementia (Hughes
et al., 1982; Morris, 1993). MRI revealed that the patients had a
mean medial temporal lobe atrophy score of 1.6 (standard deviation
The incidence of other vascular risk factors, including atherosclerosis, cardiac arrhythmia, and coronary disease, was not significantly different between the groups (patients: 5, controls: 2, p = 0.14). On neuropsychological tests, the patients had a mean digit span Wechsler adult intelligence scale test score of 11.9 (s.d. 2.0) (Wechsler, 1997), and a mean letter digit substitution test (correct items after 90 seconds) score of 29.5 (s.d. 12.7) correct and 0.1 (s.d. 0.3) incorrect (van der Elst et al., 2006).

Example maps of the CBF, \(K_v\), and \(v_p\) measures can be seen in Fig. 1. To demonstrate the quality of the data, example concentration–time curves and a Patlak plot are shown in Fig. 2. An overview of the results of the CBF, \(K_v\), \(v_p\), and \(v_L\) values in the GM is displayed in Fig. 3. The mean CBF in the GM was significantly lower in the patients (32.1 s.d. 7.0 mL/min/100g) compared with the controls (39.3 s.d. 6.4 mL/min/100g, \(p < 0.001\)). The mean \(K_v\) value in the GM showed a trend of a higher \(K_v\) in the patients (2.7 \(\times\) 10\(^{-4}\) s.d. 1.3 \(\times\) 10\(^{-4}\) minute\(^{-1}\)) compared with controls (1.8 \(\times\) 10\(^{-4}\) s.d., 1.3 \(\times\) 10\(^{-4}\) minute\(^{-1}\), \(p = 0.055\)). The \(v_p\) was significantly higher in patients (0.38 s.d. 0.29) compared with controls (0.12 s.d. 0.10, \(p = 0.001\)). The \(v_p\) in the GM was significantly lower in the patients (0.015 s.d. 0.005) compared with controls (0.020 s.d. 0.003, \(p < 0.001\)). The atrophy score was not significantly different between the patients (34.4% s.d. 7.3%) and controls (32.7% s.d. 3.4%, \(p = 0.4\)). Linear regression revealed a significant negative correlation between CBF and \(K_v\) in the GM of the patients (Pearson’s \(r = -0.69\), \(p = 0.007\), also see Fig. 4). There was no significant correlation between CBF and \(K_v\) in the controls (\(p = 0.6\)). Between CBF and \(v_p\), a significant correlation was found in the GM of the patients (Pearson’s \(r = -0.54\), \(p < 0.05\), Fig. 4) but not for the controls (\(p = 0.6\)). There were no significant correlations between CBF and \(v_p\) for the patients (\(p = 0.4\)) or the controls (\(p = 0.9\)). Adding age and atrophy as potential confounders to these correlations had a minor effect on the correlation between CBF and \(K_v\) (Pearson’s \(r = -0.73\), \(p = 0.011\)), and for the correlation between CBF and \(v_p\) it raised the \(p\) value to 0.07 (Pearson’s \(r = -0.57\)), making it a trend. The results of the regional CBF are listed in Table 1. In short, all regions exhibit significant hypoperfusion in the patients compared with the controls, which remains after false discovery rate correction. The drift measurements showed a signal decrease of 0.07% per minute in the low concentration (1 mM) phantom and a decrease of 0.04% per minute in the high concentration (5 mM) phantom. This causes a decrease in \(K_v\) (5% in patients and 9% in controls) and no change in \(v_p\). More information can be found in the Appendix.

**4. Discussion**

In the GM of patients with early AD, we have found evidence of global hypoperfusion, a trend for a higher leakage rate and a significant increase in leakage extent and decrease of blood volume. Most interestingly, we observed that a global reduction in CBF is correlated with an increase in BBB leakage in these patients.

The CBF values of this study (roughly 30–50 mL/min/100g) are in the range of commonly reported values in healthy elderly controls and patients with AD (roughly 20–60 mL/min/100g) (Alsop et al., 2015; Binnewijzend et al., 2014; Dai et al., 2009). Widespread hypoperfusion in MCI and AD has been found by numerous other studies using ASL and other modalities (Alsop et al., 2010; Austin, 2011; Chen et al., 2011). The most common finding is hypoperfusion in the frontal and temporoparietal regions, which mostly covers the region investigated in the present study (Kehoe et al., 2014). The relative difference in CBF between the groups is roughly the same in all lobes and in the deep GM (Table 1), indicating that the hypoperfusion is global, instead of regional, as was found in some other studies (Alsop et al., 2010; Mattsson et al., 2014). Given that the atrophy between in patients did not significantly differ from healthy controls, the observed results are unlikely to be affected by differences in cortical thickness and inherent partial volume effects of the cortex voxels. We found \(K_v\) values of...
1–3 \times 10^{-4} \text{ minute}^{-1}, which are comparable to previously reported values in patients with vascular cognitive impairment (0–6 \times 10^{-4} \text{ minute}^{-1}) (Taheri et al., 2011). The cerebral blood volume in AD has usually been studied using Dynamic Susceptibility Contrast MRI, where a lower blood volume is usually found in the temporoparietal regions, which are known to be impaired in AD (Chen et al., 2011). Furthermore, it is frequently mentioned that blood volume differences are smaller and harder to detect compared with blood flow (Lacalle-Aurioles et al., 2014; Uh et al., 2010).

The subtle contrast agent leakage found in this study is often considered to be limited by the permeability surface-area product (Larsson and Tofts, 1992; Sourbron and Buckley, 2013; Tofts et al., 1999). This means that, for more contrast agent to leak out of the blood space, the blood vessels have to become more permeable to the contrast agent. An alternative would be that the leakage is flow-limited, meaning that the leakage is limited by the amount of contrast agent supplied by the blood during a certain period. For the current expected low-permeability regime, the leakage should be more or less independent of the blood flow (Larsson and Tofts, 1992; Sourbron and Buckley, 2013; Tofts et al., 1999). However, the observed correlation between CBF and BBB leakage indicates that either the leakage rate is not purely limited by the permeability surface-area product or a common pathophysiological pathway involves both BBB breakdown and hypoperfusion. Given the very low leakage values and modest reductions in CBF found in this study, we consider it unlikely that the leakage rate is limited by the amount of contrast agent supplied by the blood. Therefore, it is more likely that a physiological process involving the neurovascular unit is responsible for this link, especially because the BBB and local compensatory mechanisms for hypoperfusion are essential functional elements of the neurovascular unit.

**Table 1**

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Patients (mean ± s.d. CBF)</th>
<th>Controls (mean ± s.d. CBF)</th>
<th>Difference relative to controls (%)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cortex</td>
<td>32.8 ± 7.2</td>
<td>40.2 ± 6.7</td>
<td>−22.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>33.3 ± 7.6</td>
<td>38.9 ± 7.2</td>
<td>−16.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>32.4 ± 7.4</td>
<td>39.6 ± 6.7</td>
<td>−22.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>31.1 ± 5.5</td>
<td>36.8 ± 6.2</td>
<td>−18.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Deep gray matter</td>
<td>30.7 ± 9.1</td>
<td>37.9 ± 8.3</td>
<td>−23.5</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Key: s.d., standard deviation.  
* Corrected for age and gender.  
† Remains significant after correction for multiple comparisons.
The link between hypoperfusion and BBB leakage extent and strength complements the previous finding that hypoperfusion is correlated with cognitive decline and hippocampal volume decrease (Roher et al., 2012). Atrophy is one of the hallmarks of AD, but adding atrophy as a confounder did not change the (qualitative) results. Adding age as a confounder also did not change the correlation, which shows that increased BBB leakage due to age or partial volume effects caused by atrophy cannot explain the observed link between hypoperfusion and BBB leakage. Together, this all points toward a complicated progressive cascade of events that involve decreased CBF, BBB leakage, and inflammation (Janota et al., 2015). Although the precise pathways remain to be elucidated, the correlation between hypoperfusion and increased BBB leakage does fit to the hypothesized positive feedback loop linking the BBB and perfusion management. Such a feedback loop would cause an increase in BBB leakage when the CBF decreases and, vice versa, a decrease of CBF when BBB leakage increases. BBB leakage can be caused by ischemia-triggered inflammation, whereas the hypoperfusion is caused by upregulation of vasoconstrictors, oxidative stress, and insufficient clearance of amyloid β (Iadecola, 2010). The recent finding that amyloid β can passively pass the BBB in a rat model of AD further supports the neurovascular hypothesis (Keaney et al., 2015). Furthermore, upregulation of vasoconstrictors would by definition decreases local blood volume as was found in this study. The lower blood volume may be further explained by a lower vascular density which has also been found in AD (Janota et al., 2015).

Measuring very low BBB leakage using DCE-MRI is very challenging, and it requires a modified acquisition and analysis scheme compared with DCE-MRI in high-leakage scenarios such as (high-grade) tumors (Armitage et al., 2011). Several studies have investigated the effect of temporal resolution, the choice of the pharmacokinetic model, the effect of signal drift, and the total scan time on the ability to detect subtle BBB leakage (Barnes et al., 2016; Cramer and Larsson, 2014; Cramer et al., 2014; Heye et al., 2016). Although the effect of drift on the DCE-MRI measures in the present study was relatively small compared with other studies (Barnes et al., 2016; Heye et al., 2016), future studies may have to correct for effects of drift. It is also important to use a modified acquisition sequence to detect subtle BBB leakage. For this, we decided to combine the dual-time resolution DCE-MRI protocol used by Jelescu et al. with the sequence described by Larsson et al. (Jellescu et al., 2011; Larsson et al., 2009). The dual-time resolution protocol allows for accurate sampling of the rapid signal changes during the initial arrival of the contrast agent, whereas the slower scan has a higher signal-to-noise during the slow washout, when it is more important to have a higher sensitivity to small signal changes. The sequence described by Larsson et al. allows for measurement of the T10 with slight adaptations to the scan parameters, and it also provides an analytical formula to convert the signal changes to the contrast agent concentration. However, further improvements of DCE-MRI protocols to increase sensitivity to subtle BBB leakage and decrease the influence of noise are necessary. This is especially relevant when voxelwise mapping of the leakage is desired, such as in neurodegenerative diseases where the leakage may not be localized to hotspots or clear anatomically defined regions.

In this study, the neurovascular unit was found to be impaired in patients with early AD, resulting in a lower cerebral hypoperfusion and local blood volume, and a larger fraction of leaking voxels and a trend for increased BB leakage. This, combined with our finding that hypoperfusion and increased BB leakage are correlated, provides further evidence for the hypothesis that vascular damage, and neurovascular impairment in particular, plays a key role in the pathophysiology of AD.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2016.06.006.

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