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Advances in Perfusion Magnetic Resonance Imaging in Alzheimer's Disease

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ABSTRACT

Recent research has demonstrated that brain circulation abnormalities, either during task-induced neural activity or at rest, are more commonly associated with Alzheimer's disease (AD) than was previously thought. This is consistent with the increasing attention to the early involvement of vascular risk factors in the development of AD, in addition to the dominating neurodegenerative pathology. Early detection of cerebral perfusion changes could help advance diagnosis and intervention therapies. The present paper reviews advances in perfusion MRI in the study of AD. In general, there are consistent accounts of cerebral hypoperfusion in the temporal and parietal lobes, in people with clinically diagnosed AD. In the early stages of the disease, transient hyperperfusion may occur particularly in the prefrontal cortex, possibly as a compensatory effect. Nevertheless, significant variability in the details of perfusion patterns is present in the early phases, making the use of these methods in early diagnosis difficult. Non-invasive perfusion-weighted magnetic resonance imaging methods have advantages over nuclear medicine imaging especially for safe usage in long-term follow-up studies. Optimization of perfusion-weighted imaging techniques is crucial for any future clinical application. Additional studies are needed with optimization likely to come with 3T (and higher) field strength magnets.

Keywords: Alzheimer's disease; cerebral blood flow; cerebral blood volume, magnetic resonance imaging; perfusion; dynamic susceptibility contrast; arterial spin labeling; mild cognitive impairment

Table of Contents

Introduction

Methods

- Search Strategies

- Inclusion and Exclusion Criteria

- Perfusion Imaging Techniques

 - SPECT and PET

 - Perfusion-weighted MRI (PWI)

 - Dynamic Susceptibility Contrast Imaging (DSC)

 - Arterial Spin Labeling (ASL)

Results

- AD Perfusion Studies using PET and SPECT

- AD Perfusion Studies using PWI

 - DSC in the study of AD

 - ASL in the study of AD

 - Hypoperfusion

 - Hyperperfusion

 - Perfusion-based fMRI

- Comparisons on AD Perfusion Studies using Different Techniques

Discussion

- About the Review

- General Perfusion Patterns of AD

- Advantages of PWI in AD

- Challenges and Future Directions of PWI in AD

- Conclusion

Table 1. Perfusion magnetic resonance imaging in AD using dynamic susceptibility contrast

Table 2. Perfusion magnetic resonance imaging in AD using arterial spin labeling

Figure 1. General perfusion deficits in AD

Acknowledgements

Disclosure Statements

References

List of Abbreviations

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by an insidious onset and progressive deterioration and is the most common cause of dementia in late life [1]. Although characteristic neuropathological changes are described (e. g. accumulation of β -amyloid plaques and neurofibrillary tangles that begin in the entorhinal cortex and medial temporal lobe (MTL) and extend gradually to the entire neocortex) [2], the cause is still not clear [3-6]. In recent years, cumulative evidence has called attention to the role of acquired vascular factors in older adults so that many risk factors, such as ischemic stroke, atherosclerosis, hypertension, diabetes, and cardiac disease have been shown to result in cerebrovascular dysfunction and trigger AD pathology [7-10].

Advances in neuroimaging technology have significantly benefited AD research and clinical practice [11-13]. Conventional imaging (*e.g.*, structural computed tomography (CT) and magnetic resonance imaging (MRI) of the MTL) has been recommended to help discriminate probable and possible AD from normal aging and to differentiate AD from other dementias [11-12]. Functional neuroimaging techniques that reflect neural activity and metabolic changes have been developed to detect brain functional changes in preclinical stages [13]. Particularly important to the present review, imaging techniques that are sensitive to hemodynamic properties have revealed new insights into cerebrovascular abnormalities associated with AD. In the past, cerebral perfusion mainly has been imaged by single photon emission computed tomography (SPECT) and positron emission tomography (PET), both of which require radioactive agents. Perfusion weighted MRI (perfusion MRI or PWI) has emerged as a non-invasive alternative. The continued advances in perfusion imaging, especially perfusion MRI, call for a comprehensive review of recent progress. In this paper, we review recent reports on perfusion imaging in AD. Our focus is on the correlation between evidence of brain damage and function. We address the following

questions: 1) Are characteristic perfusion patterns present (both hypoperfusion in clinically diagnosed AD patients and hyperperfusion changes in the early stage)? 2) Does perfusion MRI offer advantages to PET/SPECT in the study of AD? 3) What are the limitations of perfusion MRI and how can they be mitigated in AD research and clinical settings?

METHODS

Search Strategies

We searched MEDLINE for studies published between January 1, 1977 and December 31, 2009. The keywords that we used consisted of combinations of Alzheimer's disease, mild cognitive impairment, perfusion, perfusion MRI, hypoperfusion, cerebral blood flow, dynamic susceptibility contrast, and arterial spin labeling. With "*perfusion*", "*cerebral blood flow*" and "*Alzheimer's disease*" 584 articles were retrieved. With "*perfusion*", "*cerebral blood flow*" and "*mild cognitive impairment*", 79 articles were retrieved. With "*dynamic susceptibility contrast*" and "*Alzheimer's disease*", 14 articles were retrieved. With "*arterial spin labeling*" and "*Alzheimer's disease*" 12 articles were retrieved. A smaller number of articles were found with "*dynamic susceptibility contrast*" and "*mild cognitive impairment*" (3), and with "*arterial spin labeling*" and "*mild cognitive impairment*" (4). These search outcomes were verified with the Canadian Institute for Scientific and Technical Information (CISTI) databases and consistent results were revealed.

Inclusion and Exclusion Criteria

All the retrieved peer-reviewed journal articles studying brain perfusion of patients with AD and/or mild cognitive impairment (MCI) using common perfusion techniques including PET,

SPECT, and PWI were examined. To be considered, a study was required to have at least one type of perfusion MRI, either with or without the use of other neuroimaging techniques. In addition, studies using just PET or SPECT that have provided novel information contributing to the advances of AD perfusion were also considered and the outcomes from those studies were used to compare with those of PWI. Studies that focused on computational methods without acquiring any imaging data, used animal models without having human participants, or applied techniques other than perfusion MRI, PET, or SPECT were excluded.

Perfusion Imaging Techniques

To help readers better understand the result, we will first introduce the basics of perfusion imaging methods used in the studies under review.

Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET)

Imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT) has been the mainstream of perfusion studies for over two decades, while other methods such as dynamic perfusion computed tomography (CT) [14] and transcranial Doppler [15] have also been used by a limited number of AD studies. PET and SPECT were first applied in clinical and preclinical applications in cardiology, oncology, and neurology research in the 1970s. In the neurological domain, they provide information about brain circulation characteristics with parameters such as cerebral blood flow (CBF) and cerebral blood volume (CBV). Both SPECT and PET techniques inevitably rely on radioactive tracers as contrast media [16].

SPECT has been recognized as a reliable technique to measure brain blood flow-based hemodynamics. It uses ^{133}Xe (^{133}Xe), [$^{99\text{m}}\text{Tc}$] hexamethylpropylamine oxime ($^{99\text{m}}\text{Tc}$ -HMPAO), $^{99\text{m}}\text{Tc}$ -Bicisate (ethyl cysteine dimmer [ECD]), or ^{123}I inosine-5'-monophosphate (^{123}I -IMP) as a radiotracer. Although the spatial resolution with SPECT is relatively low (usually on the order of 1 cm), it has had a large number of applications [16-18].

PET has comparatively higher sensitivity and spatial resolution than SPECT, and can be used to obtain data from low perfusion areas. With PET, contrast agents used for the measurement of CBF or CBV are either injected (H_2^{15}O) directly or inhaled via the respiratory system ($^{15}\text{O}_2$ and C^{15}O_2) into the blood. Perfusion maps are acquired through modeling blood sample passing across brain regions of interest (ROI) [16,19]. While both PET and SPECT are important imaging methods for evaluating brain perfusion, non-invasive perfusion MRI technologies with great potential have emerged.

Perfusion-weighted MRI (PWI)

Compared to nuclear medical imaging (e.g., PET, SPECT), perfusion MRI is less expensive and less invasive and can be used repeatedly in the same subjects [16, 20]. Based on the nature of the contrast agent, PWI can be divided into two categories: 1) a dynamic perfusion imaging subcategory (including dynamic contrast enhancement imaging (DCE) and dynamic susceptibility contrast (DSC)) that requires exogenous contrast tracers, and 2) arterial spin labeling (ASL), which does not require exogenous contrast tracers.

Dynamic Susceptibility Contrast Imaging (DSC)

DSC is by far the more common method used to study AD and requires an injection of a paramagnetic contrast agent. Such MRI contrast agents introduce changes in the relaxation rates

(e.g. T1, T2) as a direct function of the local concentration of the paramagnetic species within the blood (as they do not cross the intact blood-brain-barrier). Typically, these agents will lead to a decrease in the relaxation times, thereby changing the MR image contrast. In DSC imaging, the MRI acquisition parameters are chosen to alter the local image contrast as the bolus of paramagnetic tracer passes through the regional capillary beds. Images are acquired rapidly as the contrast flows through the circulatory system. The time-course data of signal change of the tracer is converted to a relative concentration-time curve and is used to quantify the hemodynamic parameters under investigation (*i.e.*, CBF or CBV). This is directly analogous to the time-of-flight methods used in PET.

Arterial Spin Labeling (ASL)

ASL PWI uses inflowing water molecules in blood as an endogenous contrast agent [21,22]. This "magnetic label" is delivered to the slice of interest and alters the image contrast at a rate determined by the local CBF. Typically, two images are acquired and the CBF map is produced by subtracting the magnetic labeling image from the control image. According to the labeling method, ASL can be divided into sub-classes, namely continuous, pulsed, and velocity-selective ASL. Studies have been conducted to enhance ASL labeling optimization with tagging schemas for improved labeling efficiency [23-25]. ASL has also been used to map brain functional activation at cognitive state [26], as has the blood oxygen level-dependent functional MRI (BOLD- fMRI) method. BOLD- fMRI relies on a complex interaction between blood flow changes and the relative concentration of deoxyhemoglobin in the blood, which indirectly reflects neural activity. ASL-fMRI magnetically labels water in the proximal blood supply. The associated signal is proportional to the cerebral blood flow serving neural activity. ASL thus provides more quantitative information than do BOLD signals, but has the same sensitivity for detecting task-

induced changes in local brain function. ASL has been shown to be more robust than BOLD-fMRI with reduced intra- and inter-subject variability [27,28].

RESULTS

AD Perfusion Studies using SPECT and PET

SPECT studies have shown that in people with clinically diagnosed AD, hypoperfusion is robust in several brain regions including the posterior cingulate cortex (PCC), precuneus, temporoparietal and frontal cortices. The pattern of perfusion (and metabolic) deficits in the temporoparietal and association cortices is particularly consistent and is closely correlated with AD progression [29,30]; therefore, this pattern has been accepted to aid in AD diagnosis, although sensitivity/specificity may vary.

Hypoperfusion in the MTL including the hippocampus and parahippocampal cortex has also been repeatedly studied, especially during the early stage. One two-year study of mild AD patients reported a significant rCBF reduction in the hippocampus and surrounding structures, while only a small decrease of rCBF was detected in the PCC and the precuneus [31], suggesting that perfusion changes in MTL are more sensitive than in other regions. In a separate study, the authors suggested that perfusion changes in the MTL occur early in the preclinical stages and may help distinguish people who progress to AD from those who do not [32]. In this study, the amnesic MCI (aMCI) participants who converted to AD (52 of the total 76) showed a significant reduction of rCBF in regions including the bilateral parahippocampal gyri and the PCC and surrounding areas compared to the non-converters [32]. A more recent study also reported that MCI patients who later converted to AD showed significantly lower MTL perfusion than did the people who did not progress to AD [33]. This study also showed that hypoperfusion in the MTL in MCI patients

was accompanied by MTL atrophy, suggesting that MTL volume and perfusion changes may be related [33].

However, other studies have failed to detect a correlation between anatomical and perfusion changes in the structures of MTL. Instead, one showed that PCC perfusion was positively correlated with MTL volume, which was interpreted by compromised connection in the temporo-cingulate network resulted from mediotemporal degeneration [34]. This result has been supported by a second study that showed a close correlation in rCBF between PCC and entorhinal cortex [35].

A higher level of perfusion in the prefrontal cortex (PFC) was also related to greater MTL volume loss [34]. This result suggests that by the time MTL structural changes can be detected, perfusion changes may also be detectable in other regions such as the PFC, which, while affected later than the MTL, compensate for MTL damage [34].

Distinct perfusion patterns of clinically diagnosed AD and non-AD types of dementia have been studied to aid in differential diagnosis of AD [36]. A greater degree of hypoperfusion in the occipital cortex and associated structures has been demonstrated in dementia with Lewy bodies (DLB) than is seen in AD, while lower MTL perfusion was observed in AD compared to DLB [37,38]. No hyperperfusion was reported by these studies, conducted in patients who were in relatively later disease stages. The sensitivity and specificity of SPECT in discriminating AD from DLB have achieved as high as 90% and 80%, respectively [39]. Waragai and colleagues [40] detected more severe perfusion reduction in AD and suggested that “the ratio of the extent of the decrease in rCBF to the decrease in whole-brain blood flow” might be used to differentially diagnose early AD from vascular dementia (VD) or from FTD.

Compared to SPECT, there are relatively few published PET studies on AD perfusion, most of which appeared in the late 1990's. Some of these studies simultaneously examined the

perfusion and metabolic changes (i.e., FDG- PET using fluorodeoxy-glucose as a tracer). Outcomes of PET studies are in agreement with those of SPECT, concerning the general hypoperfusion pattern of the clinical AD, especially in the MTL, PCC, and parietotemporal regions and the close relation between perfusion impairment and cognitive decline [41-43]. These PET studies did not investigate preclinical AD and failed to report a regional hyperperfusion. Tohogi and colleagues reported that in people with dementia of the AD type, greater perfusion was associated with a relatively preserved oxidative metabolism in the frontal, parietal and temporal cortices and the degree of hypoperfusion was significantly correlated with the severity of dementia, suggesting that perfusion changes are highly sensitive to the disease process [44]. A significantly greater rCBF reduction in the PCC in AD also appeared helpful in differentiating AD from frontotemporal dementia (FTD) [45].

AD Perfusion Studies using PWI

DSC in the study of AD

Perfusion MRI with a contrast agent was introduced to AD research in the mid 1990's and has achieved some popularity in clinical applications (Table 1). As with SPECT and PET, hypoperfusion is seen not only in AD patients, but also in MCI/preclinical AD with PWI. For example, compared to controls, significant reductions of rCBF have been reported for both AD and MCI patients in various brain regions including the amygdala and other mesotemporal structures and the anterior cingulate gyrus (ACC) [46]. However, the study did not find a statistically significant difference in the level of regional hypoperfusion between patients with MCI and those with mild AD [46]. This regional perfusion reduction in AD and MCI has been confirmed by other DSC studies, although with regional variability (Table 1).

Perfusion studies based on rCBV have shown changes comparable to rCBF. Harris and colleagues reported a 17% lower rCBV in bilateral temporoparietal regions compared with that in the cerebellar region in patients with clinical AD [47]. In comparison, the healthy control group did not show a significantly reduced rCBV so that AD and cognitively normal (CN) could be distinguished with 88.5% accuracy. This significant reduction in temporoparietal rCBV in AD persisted even after correcting for brain atrophy and lesion loads, suggesting that perfusion impairment may not be solely explained by brain structural changes [48] (Table 1). Other DSC studies have also been able to detect regional cerebral hypoperfusion in AD patients [49].

Meanwhile, hyperperfusion in the frontobasal regions has been found in early AD patients with mild dementia. The extent of hyperperfusion in the frontal lobe appeared to be cognitive performance dependent, indicating a possible neurocompensation mechanism [46].

ASL in the study of AD

The arterial spin labeling method has emerged as a non-invasive way to study brain circulation and brain function. A rich body of ASL studies during the past decade has benefited the understanding of brain circulatory and functional abnormalities associated with the onset and progression of AD (Table 2). A few recent studies have suggested that it is not just low perfusion that is a signal of disease, but compensatory increased perfusion may also be expected in the early stage.

Hypoperfusion

ASL studies have generally demonstrated significant hypoperfusion in various brain regions in clinical AD. These included temporal, parietal, and frontal lobes, as well as the PCC, which may not always match atrophy [20, 50-54] (Figure 1; Table 2). Perfusion insufficiency has been repeatedly proved to be correlated with the severity of the disease. For example, one of the

early ASL studies reported that reductions of the whole brain CBF and the rCBF in the posterior parietal and PCC in AD patients were correlated with their cognitive assessment scores [20]. A recent ASL perfusion study has been able to detect a quantitatively significant decrease of the absolute rCBF in the precuneus and PCC in AD patients compared with matched healthy controls (with a mean rCBF of $27.8 \pm 7.1 \text{ ml/100g/min}$ for AD patients and $36.7 \pm 6.3 \text{ ml/100g/min}$ for healthy controls) [54]. These differences were not accompanied by an equivalent difference in the regional arterial transit time (rATT) or a difference in the arterial brain volume (rABV).

In a study by Johnson and colleagues [50], a perfusion difference was observed among AD, MCI, and cognitive healthy controls groups. MCI patients showed decreased perfusion compared to healthy controls in the right inferior parietal lobe, while AD patients showed greater hypoperfusion compared to MCI patients in the PCC and precuneus regions and within the bilateral inferior parietal lobes [50]. Another study comparing perfusion changes in MCI and AD has also demonstrated decreased rCBF in multiple cortical regions, including the left inferior parietal, lateral frontal, superior temporal, orbitofrontal cortices differed significantly between the two groups [53].

Spatial hypoperfusion patterns were found to be different between AD and FTD by ASL and such differences have been used to improve classification performance [55]. Nonetheless, a recent study reported a reduction in rCBF in both AD and subcortical ischemic VD patients, but the study failed to find a significant difference in the perfusion pattern between the two patient groups [56] (Table 2).

Hyperperfusion

Cerebral hyperperfusion in AD has been suggested by a few recent ASL studies, especially those studying the early progression. For example, a study reported prominent hyperperfusion in

some mild AD patients, but not all, in the hippocampus and other MTL structures even after correction for gray matter loss. A significant temporoparietal hypoperfusion was characterized in most AD patients compared to the matched controls [52]. Increased rCBF was also reported in right ACC in AD patients compared to controls [53]. In addition, increased rCBF in the left hippocampus, right amygdala, and regions of the basal ganglia was identified in MCI compared to healthy subjects [53].

Perfusion-based fMRI

Perfusion-based fMRI mapping brain functions has produced interesting outcomes regarding both resting and cognitive states. One study reported relatively greater perfusion in the MTL at rest in subjects with both family history and high genetic risks for developing AD than in the control subjects who had low risks for AD [57]. A comparatively lower perfusion response in the same area was also observed for the higher risk subjects during memory tasks when inferring to their elevated perfusion during the resting phase [57]. Using perfusion-based fMRI, a study reported hypoperfusion during a control state in the right precuneus and cuneus in the aMCI patients compared to healthy controls. During memory tasks, the spatial distribution of hypoperfusion in the aMCI patients extended to the PCC. A significant increase of the rCBF was detected in the right parahippocampus area in control subjects performing cognitive tasks that was not observed in aMCI [58].

Comparisons of AD Perfusion Studies using Different Techniques

A number of well-designed comparative studies of the imaging properties of various perfusion methods have suggested reasonably robust perfusion patterns in AD. DSC may be more favorable to SPECT mainly for its cost effectiveness and higher sensitivity for perfusion properties in

evaluating AD patients [59-61]. Other studies suggested that SPECT was better to detect greater group differences in perfusion patterns [62]. In one of the earliest studies, Harris and colleagues investigated rCBV in AD patients using DSC and suggested that depending on brain regions studied, the imaging sensitivity and specificity with DSC could be either better than, or similar to, that of visual clinical readings of SPECT [60]. Based on this they proposed that DSC is “promising as a safe, potentially lower-cost alternative” to other perfusion methods for the evaluation of patients with dementia.

For AD diagnosis, the sensitivity and specificity of different perfusion methods appear to be comparable. Maas and colleagues examined AD patients and control subjects using DSC and reported a sensitivity of 81% and specificity of 88% [49]. Other studies with DSC revealed sensitivity and specificity of 87%-95% and 88%-95% respectively, in differentiating patients with mild or moderate AD from healthy controls, superior to SPECT [48]. In recent years, the sensitivity and specificity of DSC in studying temporoparietal rCBV has increased to as high as 93% and 96% respectively, for possible or probable AD [63]. Even so, DSC does not always outperform SPECT. In one comparative study, SPECT sensitivity and specificity were 60% and 94% , whereas those for DSC were 34% and 100% although the thin-section MRI of the hippocampus appeared to be superior [64]. SPECT and PET can each have merits in AD studies in comparison to one another [65,66]. Combining DSC with other neuroimaging methods (e.g. EEG (electroencephalography) power spectra) also appears to improve the characterization of pathological changes in AD [67].

DISCUSSION

About the Review

Direct measurement of brain perfusion is of great significance for *in vivo* evaluation of brain functional changes and the underlying neural process. Perfusion imaging has become important in the study of AD during recent years, allowing evaluation of disease-associated blood supply and activity-motivated circulation changes more conveniently. Perfusion MRI does not involve radioactive media and thus provides a less invasive alternative to enable repeated applications in follow-up studies, which likely accounts for its increasing use.

Our survey result must be interpreted with caution. First, we used a single search engine, the MEDLINE database. Although over 5000 journals are indexed by this most recognized database, publications of non-indexed journals by MEDLINE were not discussed here. Second, as perfusion MRI was our focus, the review was attempted mainly to report PWI findings, whereas important studies applying other methods were discussed mainly for comparison reasons.

General Perfusion Patterns of AD

Early studies often used two diagnostic groups, AD and CN, to investigate perfusion differences in major cerebral lobes with less detailed localization. Most perfusion studies that have used strict clinical criteria (i.e., the NINCDS-ADRDA – the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association and the DSM-III-R/IV – The Diagnostic and Statistical Manual of Mental Disorders Third or Forth Edition) [68] show profound cerebral perfusion defects in AD. This is typically remarkable hypoperfusion in the posterior temporoparietal cortex and the surrounding regions [29,30]. The hypoperfusion can extend to the retrosplenial and lateral parietal cortices and the PFC, whereas the primary sensorimotor and visual cortical areas are usually preserved.

With better spatial and temporal resolution, recent studies have been able to investigate more localized brain regions and more detailed structures. For example, a recent study reported

detailed perfusion differences in various substructures within the MTL and basal ganglia [53].

These studies have also attempted to identify early perfusion alterations by recruiting patients with early AD, preclinical AD (i.e., MCI), and also CN subjects with high genetic risks for AD [46, 57].

The evolution of perfusion abnormalities in the course of AD development holds promise as a means of monitoring the effects of early intervention. In mild AD, hypoperfusion has been identified in the mesiolimbic system, including hippocampal formation and PCC and precuneus and cuneus areas [36,50,52,53]. Most interestingly, changes of cerebral perfusion have also been sensitively detected in the preclinical phase prior to any symptoms being clinically manifested or any brain anatomical changes become evident. These findings suggest that perfusion characteristics may differ depending on disease pathology and hypoperfusion evolves progressively in various brain regions. Nevertheless, preclinical AD represents heterogeneity of disease status that may involve multiple underlying etiologies. For example, without following MCI patients to see who progresses to a clinical diagnosis of dementia, there will be important heterogeneity in any MCI group.

During the preclinical and early AD phase, hyperperfusion has also been reported, typically in the regions that are involved in the memory neural networks such as the MTL, PCC, and PFC before compromised by the disease [35,46,52,53]. These important observations suggest that AD may involve progression-related regional perfusion changes, not only hypo-, but also hyper-perfusion. Hyperperfusion changes have been interpreted by a compensatory neural recruitment. These changes were consistent with those of BOLD-fMRI studies that often showed increased brain fMRI activation in the posterior medial temporal including the posterior hippocampal, parahippocampal and fusiform regions in MCI, but not in AD [69-71]. Other studies investigating early AD have reported increased PFC fMRI activation at memory task states [72,73]. The

transient increase in brain activation has been interpreted as evidence of a brain response to compensate for damage in the anterior medial temporal lobe [71-74].

Having said this, it is during the early process of AD that the literature has suggested considerable perfusion variability. Occurrence of a detectable perfusion change may be variably reported in different studies, making the reliable association between the evolution of perfusion abnormality and the path of AD difficult (e.g, perfusion changes can be detected in variable regions, and can show hypoperfusion or hyperperfusion, depending on the severity of the disease). The inconsistency can be interpreted by the spatial differences in the functional and structural characteristics of the disease at different staging of progression, during which detectable structural changes usually follow subtle functional changes in localized regions. For example, when the MTL and limbic system are first compromised in AD process, other structures such as the PFC that are usually preserved early in the disease progression may not show detectable anatomical damage, but a functional response may be detected.

Some of the differences may also be attributed to different study settings such as demographical variability of the study sample (e.g., disease presentation can vary among MCI patients) and/or properties of the imaging methods applied. Meanwhile, the difference may also be attributed to the heterogeneity of AD neuropathology and/or individual variability of disease expression. In any circumstances, perfusion changes in the early phases of disease formulation and development are not well understood and warrant further investigation. Longitudinal studies of perfusion changes in preclinical AD (e.g., MCI and high risk groups and MCI-AD converters) would help better understand the correlates of clinical disease progression. For this, further improvements in non-invasive perfusion MRI technology would be more readily used repeatedly in longitudinal studies.

Advantages of PWI in AD

While the basic findings about AD perfusion may not differ fundamentally based on perfusion techniques, imaging methods may differ in their relative contributions to AD investigations. Research generally suggests that in evaluating AD patients and cognitively intact older adults, perfusion MRI is very promising with some attractive imaging properties. DSC has advantages chiefly due to its relatively higher sensitivity to the change of perfusion [16,47,61]. Perfusion MRI is also attractive in terms of cost and time effectiveness [16,21]. In addition, detailed anatomical brain imaging (with T1 weighted MRI) can be acquired at imaging acquisition time. PWI is safe (e.g., ASL PWI is completely non-invasive) without the involvement of radiation. This will greatly benefit long-term follow-up studies on AD risk factors, preventive factors, and intervention effect. Quantitative perfusion maps at different stages can also be obtained using PWI. Moreover, compared to BOLD-fMRI that has higher signal-to-noise ratio (SNR) and contrast to noise ratio (CNR) and is therefore more sensitive, but relies on complex coupling to map neural activity, perfusion fMRI provides a more direct alternative to map brain functional activity through measuring blood hemodynamic properties. It can be used to verify BOLD-fMRI outcomes or to better locate neural function and more accurately estimate its magnitude [75].

SPECT and PET are applicable in clinical settings. However, they inevitably rely on the need of radioactive tracers, which typically have a short half-life that restricts the duration of data acquisition and the use in emergent conditions. The sensitivity and specificity of these nuclear medicine imaging methods may be superior to perfusion MRI in areas of very low perfusion (e.g., $<10\text{ml/min, per }100\text{g tissue}$) [16]. Nevertheless, perfusion MRI methods generally have a comparable sensitivity, specificity, and reproducibility compared to SPECT and PET.

Challenges and Future Directions of PWI in AD

Perfusion MRI is technically difficult, especially ASL PWI. An important problem that has limited its clinical application appears to be the relatively low SNR, again especially with ASL. Although labeling efficiency of ASL can actually be quite high (i.e., close to 100%), the small volume fraction available to be labeled limits the SNR. As with all perfusion MRI techniques, higher magnetic fields improve SNR. Therefore acquiring data at higher field strength (e.g. 3 Tesla or higher) can benefit both contrast-enhanced perfusion MRI and ASL. The quality of contrast-enhanced perfusion MRI is improved due to stronger inhomogeneity, whereas that of ASL is improved mainly due to lowered T1 decay rate [76,77]. An ASL study comparing the effect of field strength has shown that compared with 1.5T, 3T shows a significantly higher SNR and a greater number of activated pixels in both gray matter and white matter [78].

Technical limitations of ASL may constrain brain coverage due to acquisition time. Moreover, some important regions like the inferior temporal lobe are often not fully accessible due to susceptibility-related signal loss in the tissue-air boundaries. Some of these problems are difficult to overcome. On the other hand, optimization of various technical aspects, such as using multiple receiver head coils to improve spatial sensitivity [79], has been used to improve image quality. Progress has also been made to improve quantitative efficiency (e.g., with acquisition parameter optimization, partial volume correction, and ROI-based structural adjustment), which will allow higher accuracy and precision of perfusion outcomes [78,80,81]. Taken together, to make perfusion MRI clinically more acceptable compared to current clinical practices in the diagnosis of AD, further improvement of SNR, acquisition speed, and spatial sensitivity will be helpful.

Another challenge arises from the heterogeneity of the aging brain and in the brain of people with AD, some of which may well reflect inherent cognitive dynamics [82]. Damage in brain blood vessels are common in older adults and may vary significantly between AD patients

and healthy older adults. While transit time insensitivity is a prerequisite in quantitative perfusion studies, this measure may differ significantly according to the level of stenosis. Therefore, more accurate quantitative methods are needed for understanding AD perfusion. The new blood velocity-based ASL technique appears to be potentially promising. With this method, the blood water is labeled based on flow velocity rather than spatial location, which may eliminate the problem of transit delays [83,84]. Although velocity based methods have been introduced successfully, most of these studies are at the beginning and their value for AD has yet to be demonstrated.

Conclusion

Perfusion-weighted MRI technology has been developed and used to better understand AD. Diverse cerebral hypoperfusion in the regions compromised by the disease has been well documented in AD patients. Perfusion deficits can present in preclinical AD and are associated with cognitive decline in patients with clinically diagnosed AD. Detection of impaired perfusion has some value to help improve diagnosis of AD from CN and distinguish AD from other dementias. In addition, transient hyperperfusion may occur in the early stages of the disease process, possibly as a compensatory effect. However, it is important to note that significant variability in the details of perfusion patterns is present during the early phase. Such variability can limit the use of these methods in early diagnosis. To promote clinical application of perfusion MRI, longitudinal research for better understanding of perfusion changes during disease progression is needed, along with optimization of PWI techniques.

Table 1. Perfusion MRI in Alzheimer's Disease using Dynamic Susceptibility Contrast Imaging.

Perfusion change	Measure	Imaging method	First author	Year	Subject	Main finding
decrease	rCBV	DSC	Harris GJ [47]	1996	AD=13 CN=13	Comparatively lower rCBV in temporoparietal and sensorimotor regions in AD. Reduced perfusion in temporoparietal even in mild AD. 88.5% classification rate between AD and CN based on temporoparietal CBV.
decrease	rCBV	DSC with principal component analysis method	Maas LC [49]	1997	PrAD=16 CN=16	Global and temporoparietal CBV abnormalities were detected in AD, which could classify AD and CN with a sensitivity of 81% and a specificity of 88%.
decrease	rCBV	Semiquantitative DSC	Harris GJ [60]	1998	moderate AD=19 mild AD=8 CN=18 other patients=5	Reduced rCBV in bilateral temporoparietal region in AD. Based on this, discrimination sensitivity was 95% in moderate AD and 88% in mild AD, and specificity was 96% in CN or other patients, which were comparable with SPECT.
decrease	rCBV	DSC with DWI, with atrophy and lesion as covariates	Bozzao A [48]	2001	Moderate AD=16 Mild AD=18 CN=15	Reduced rCBV in AD, even after the correction for atrophy and lesion load. Sensitivity was about 90% and specificity was 87% in discriminating AD from CN with bilateral temporoparietal rCBV. These values were much lower based on sensorimotor rCBV (50%-73% (mild-moderate), 67%) and hippocampal cortices rCBV (80%, 65%).
decrease	rCBF	DSC	Luckhaus C [46]	2008	Mild AD=20 aMCI=35 CN=13	Decreases of rCBF in MCI vs. CN in MTL by 23%, amygdala by 20%, ACC by 15%. No further reduction in mild AD in these regions, but in PCC.
increase	rCBF	DSC	Luckhaus C [46]	2008	Mild AD=20 aMCI=35 CN=13	Hyperperfusion in frontobasal region in mild dementia stages.
diagnosis	rCBF	DSC SPECT HC MRI	Kubota T [64]	2005	AD=35 non-AD=31	Thin-section hippocampal MRI and 3D-SSP SPECT were equivalent for AD diagnosis; both were superior to transaxial SPECT and DSC.
diagnosis	CBF	DSC SPECT using a 4-grade visual scale	Cavallin L [62]	2006	AD=8 MCI=10 CN=6	DSC could not replace SPECT in AD diagnosis. However, method-related problems of the study should be resolved.

correlation	rCBF	DSC SPECT	Yoshiura T [85]	2002	AD=8	Significant overall correlation in the relative CBF maps between DSC and SPECT in AD, with larger deviations in anterior and posterior cingulate regions.
correlation	rCBV	DSC EEG	Mattia D [67]	2003	PrAD=14 CN=15	Reduced rCBV by DSC in bilateral temporoparietal and sensorimotor areas in AD. A selective correlation between perfusion patterns and EEG power spectra in AD.
correlation	rCBF	DSC SPECT	Olazarán J [59]	2005	AD=14	DSC and SPECT might be concordant in AD at different cerebral lobes regarding rCBF.

Note: PrAD: probable AD; PoAD: possible AD; MCI: mild cognitive impairment; aMCI: amnesic MCI; CN: cognitively normal; HC: hippocampus; DWI: diffusion weighted imaging; PCC: posterior cingulate cortex; 3D-SSP: three-dimensional stereotactic surface projection; EEG: electroencephalographic.

Table 2. Perfusion MRI in Alzheimer's Disease using Arterial Spin Labeling Imaging.

Perfusion change	Measure	Imaging method	First author	Year	Subject	Main finding
decrease	rCBF	PASL	Sandson TA [86]	1996	AD=11 CN=8	Hypoperfusion in the posterior temporoparietal-occipital and parieto-occipital regions. Parieto-occipital perfusion level was correlated with severity of dementia.
decrease	rCBF	PASL	Alsop DC [20]	2000	PrAD=18 CN=11	Reduced perfusion in temporal, parietal, frontal, and PCC in AD. Decrease of perfusion in posterior parietal and PCC but not in temporal regions was related to cognitive performance.
decrease	rCBF	PASL	Johnson NA [50]	2005	AD=20 MCI=18 CN=23	Hypoperfusion in bilateral inferior parietal, PCC, and superior and middle frontal regions in AD compared to CN, even after correction for atrophy and partial volume effect, similar as with PET and SPECT. Hypoperfusion in right inferior parietal lobe in MCI compare to CN, but the reduction was not as great as that in AD.
decrease	rCBF	PASL	Xu G [58]	2007	aMCI=12 CN=14	Hypoperfusion in both control and memory task states in aMCI. Hypoperfusion appeared in right precuneus and cuneus, and PCC during memory task state in aMCI, which was correlated with cognitive test scores. No perfusion changes were observed in parahippocampus in response to the task in aMCI, while an increase was observed in CN.
decrease	rCBF	CASL	Asllani I [51]	2008	mild AD=12 CN=20	Decreased perfusion in multiple locations, especially in superior temporal, cingulate, middle temporal, fusiform gyr, inferior parietal lobule and precuneus in AD. Various analysis methods were applied and the multivariate analysis (e.g., with subject scaling factor as covariate) showed the highest performance (97%) to discriminate AD and CN.
decrease	rCBF GM atrophy	CASL	Alsop DC [52]	2008	AD=22 CN=16	Temporoparietal hypoperfusion in AD. Significant lower CBF was found in extended regions including bilateral precuneus and parietal, and left inferior temporal lobes in AD. Significant mismatch of CBF reduction and GM atrophy.
decrease	rCBF rATT, rABV	PASL	Yoshiura T [54]	2009	AD=19 CN=22	Significant hypoperfusion in AD using rCBF, but not rATT or rABV.
decrease	rCBF	PASL	Schuff N [56]	2009	AD=14	Reduced perfusion in frontal and parietal cortices in both AD and

				SIVD=8 CN=18	SIVD compared to controls.
decrease	rCBF	CASL	Dai W [53]	2009	AD=37 MCI=29 CN=38 Decreased rCBF in the PCC and medial precuneus in both AD and MCI. Decreased rCBF in regions of the left hemisphere, including inferior parietal, lateral frontal, superior temporal, and orbitofrontal cortices in AD compared to MCI.
differentiation by decrease	rCBF	PASL	Du AT [55]	2006	AD=24 FTD=21 CN=25 Lower perfusion in the parietal regions and PCC in AD compared to FTD. Combining frontal and parietal lobe perfusion improved classification of FTD from AD to 87%.
discrimination by decrease	rCBF	PASL	Yoshiura T [87]	2009	AD=23 CN=23 Hypoperfusion in bilateral precuneus and PCC in AD. AUC of ROC for discrimination of AD and CN was 86%-88% for absolute rCBF and 91%-93% for normalized rCBF in different ROIs.
increase	rCBF	CASL	Alsop DC [52]	2008	AD=22 CN=16 MTL hyperperfusion in some mild AD patients. Hippocampal CBF was significantly higher in AD than in CN after correction of atrophy.
increase	rCBF	CASL	Dai W [53]	2009	AD=37 MCI=29 CN=38 Increased rCBF in the ACC in AD compared with controls. Increased rCBF in the left HC, right amygdala, and regions of the basal ganglia in MCI compared with controls.
increase	CBF PWI fMRI BOLD fMRI	PASL	Fleisher AS [57]	2009	high AD risk CN=13 (family history & APOE4 positive) low AD risk CN=10 (no family history & APOE4 negative) The high AD-risk group had elevated MTL rCBF at rest, but no absolutely rCBF difference at memory task. The apparent decrease in both MTL perfusion and BOLD fMRI activation in response to the task was due to the elevated perfusion during the resting phase.
correlation	CBF	pCASL PET	Xu G [88]	2009	AD=1 MCI=2 CN=11 Young=8 Intraclass correlation coefficient for global perfusion >=0.90 using pCASL for each subject group. GM/WM perfusion ratio decreased with advanced age and the lowest ratio was in AD and MCI. pCASL and PET had comparable results.

Note: PrAD: probable AD; PoAD: possible AD; MCI: mild cognitive impairment; aMCI: amnesic MCI; CN: cognitively normal; rATT: regional arterial transit time; rABV: regional arterial volume; FTD: frontotemporal dementia; SIVD: frontotemporal dementia; SIVD: subcortical ischemic vascular dementia; GM: gray matter; WM: white matter; HC: hippocampus; ACC: anterior cingulate cortex; PCC: posterior cingulate cortex; ROI: region of interest. AUC: area under the curve; ROC: receiver operating characteristic; pCASL: pseudo-continuous ASL; BOLD: blood oxygen level dependent.

Figure 1. Significant differences in regional perfusion (rCBF) and atrophy were observed between people with Alzheimer's disease (AD) and matched healthy control (CN) groups. Regions of more decreased perfusion in AD compared to CN are shown in red and those of more profound atrophy are shown in green. Images were adapted from Alsop et al [52] with permission from publisher (Elsevier License Number: 2390771118895).

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LIST OF ABBREVIATIONS

ACC: anterior cingulate cortex
AD: Alzheimer's disease
aMCI: amnesic mild cognitive impairment
ASL: arterial spin labeling
AUC: area under the curve
BOLD: blood oxygen level dependent
CASL: continuous ASL
CBF: cerebral blood flow
CBV: cerebral blood volume
CISTI: Canadian Institute for Scientific and Technical Information
CN: cognitively normal
CNR: contrast-to-noise ratio
CT: computed tomography
DCE: dynamic contrast enhancement imaging
DLB: dementia with Lewy bodies
DSC: dynamic susceptibility contrast
DSM III-R/IV: the Diagnostic and Statistical Manual of Mental Disorders Third or Fourth Edition
DWI: diffusion weighted imaging
EEG: electroencephalographic
FTD: frontotemporal dementia
fMRI: functional MRI
GM: gray matter
HC: hippocampus
MCI: mild cognitive impairment
MRI: magnetic resonance imaging
MTL: medial temporal lobe
NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PASL: pulsed ASL
pCASL: pseudo-continuous ASL
PCC: posterior cingulate cortex
PET: positron emission tomography
PFC: prefrontal cortex
PoAD: possible AD
PrAD: probable AD
PWI: perfusion-weighted MRI
rABV: regional arterial volume
rATT: regional arterial transit time
rCBF: regional cerebral blood flow
Rcbv: regional cerebral blood volume
ROC: receiver operating characteristic
ROI: region of interest
SIVD: subcortical ischemic vascular dementia
SNR: signal-to-noise ratio
SPECT: single photon emission computed tomography
VD: vascular dementia

WM: white matter