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Arterial Spin Labeling MRI: An Emerging Biomarker for Alzheimer's Disease and Other Neurodegenerative Conditions

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Abstract

Purpose of the Review—The search for biomarkers that detect and track disease progression in early Alzheimer's Disease (AD) has been a major pursuit for two decades. Functional measures reflecting alterations of synaptic activity associated with neuronal dysfunction have displayed promise for following disease course in early stages. While fluorodeoxyglucose positron emission tomography (FDG PET) and blood oxygen level dependent functional MRI (BOLD fMRI) have been studied extensively for this purpose, this review will discuss the emergence and potential role of arterial spin labeling (ASL) MRI, which measures cerebral blood flow (CBF), in neurodegeneration.

Recent Findings—Several recent studies have explored ASL MRI in early and prodromal AD and have reported areas of hypoperfusion that overlap considerably with hypo-metabolism frequently reported with FDG PET. However, some studies have also noted increased regional CBF of patients with prodromal and early stage clinical AD, which may have implications for pathophysiology and/or the role of compensatory responses to neurodegeneration. Additionally, a few recent studies have begun to use this modality to explore the role of cerebrovascular factors in cognitive decline and its relationship to AD.

Summary—SL MRI is just beginning to be applied more widely to various neurodegenerative conditions. Initial data suggest that this methodology may provide similar information to FDG PET, but with several advantages in the ease of acquisition and expense. Additional applications of this modality, including task-related studies and testing of pharmacological effects, are underexplored, but potentially of significant value in understanding disease related functional changes and treatment effects.

Keywords

Arterial spin labeling; cerebral blood flow; cerebral perfusion; Alzheimer's Disease; Mild Cognitive Impairment

Introduction

The biomarker landscape for Alzheimer's Disease (AD) and other neurodegenerative conditions has expanded dramatically in the last decade (1). This development has been

driven by the desire for markers that allow for earlier disease detection and more sensitive monitoring of progression. In addition to their potential role in clinical practice, such tools are invaluable to clinical trial endeavors. Indeed, it has become a general belief in the field that therapeutic interventions are likely to be most effective and desirable at early disease stages, including, perhaps, before the onset of clinical symptoms (i.e. preclinical disease) (2). In this context, a greater reliance on biomarkers is necessary given the relative paucity of clinical or cognitive measures sensitive to changes in these early stages.

In particular, the development of molecular biomarkers that are sensitive to the pathologic species of AD have been a major achievement in the field. Positron emission tomography (PET) imaging with ligands that bind to the fibrillar amyloid plaques of AD, such as Pittsburgh Compound-B (PiB), and cerebrospinal fluid measures of A β ₁₋₄₂ and tau protein have displayed significant sensitivity to early disease and even histologic measures of pathology (3–8). However, these measures appear to be limited in their sensitivity to clinical status and capacity to track disease progression (1, 9–15), potentially rendering them less desirable as outcome measures in clinical trials.

More tightly linked to clinical state are measures of brain structure and function, so-called “neurodegenerative” biomarkers, which reflect the downstream injury of the AD-related pathological process (1, 10, 11, 13). These measures appear to provide complementary information to the more disease-specific molecular biomarkers. Measures of function [i.e. fluorodeoxyglucose (FDG) PET and fMRI], which reflect alterations in synaptic activity, may be particularly sensitive to the earliest consequences of AD pathology prior to the neuropil and neuronal degeneration that is required for detection by structural approaches (2).

FDG PET is the most well-studied functional measure that has been applied to neurodegenerative conditions. This modality measures glucose metabolism (CMRGlu), which is generally thought to largely reflect synaptic activity (16, 17). Numerous studies have supported the potential role of FDG PET for early detection and disease monitoring in AD, as well as other neurodegenerative conditions (18–26).

Cerebral blood flow (CBF) is generally tightly coupled to brain metabolism and measures of CBF appear to overlap with CMRGlu (27, 28). Arterial spin labeling MRI (ASL MRI) provides a non-invasive, quantitative measure of CBF. While potentially producing redundant information with FDG PET, ASL MRI has a number of potential advantages: 1. It does not involve exposure to radioactivity or injection of a contrast agent. 2. It can be acquired in conjunction with the structural MRI typically obtained during routine evaluation, reducing burden and expense, as well as allowing for direct assessment of important structure-function relationships (e.g. volumetric, white matter abnormalities, etc). 3. Short task-related sequences may more easily be implemented, potentially adding to functional assessment. 4. MRI is generally more accessible and relatively less expensive than PET.

Given the considerable success and utility of FDG PET in neurodegenerative populations, ASL MRI has begun to be more rigorously explored for similar applications. While the literature remains somewhat limited, a number of studies with this modality have been published in the last decade and will be reviewed here.

ASL MRI methodology

A full discussion of ASL MRI methodology is beyond the scope of this review and has been summarized elsewhere (29, 30). Briefly, ASL MRI utilizes magnetically labeled blood water as an endogenous tracer for quantification of brain perfusion. Unlike other measures of CBF, such as ¹⁵O-PET, there is no requirement for an exogenous tracer or exposure to ionizing

radiation. After a region of flowing blood is magnetized, the resulting tissue perfusion produces local change to tissue magnetization, which can be measured with a standard MRI imaging sequence and compared to an unlabelled “control” image. Similar to PET ligands, such as ^{15}O , the tracer decays at a fixed rate, but in ASL the decay is determined by T1 relaxation. Accordingly, CBF can be calculated from a knowledge of the brain magnetization with and without arterial labeling and assumptions about the labeling efficiency and T1 relaxation time (31). In human ASL, the transit time from the labeling location to the imaging location must also be considered in the data acquisition and modeling (32).

There are various strategies for carrying out arterial labeling and for sampling and modeling the resulting changes in brain magnetization. All of these methods ultimately allow CBF quantification in MRI independent physiologic units (e.g. mL/100 g/min), facilitating comparisons across sites and scanning sessions (33). This particular feature offers an advantage over the more commonly applied blood oxygen level dependent (BOLD) fMRI, which is susceptible to baseline drift across longer time scales (34) and produces increased intersubject variability (35). Further, this capability makes ASL MRI particularly suitable for measuring drug effects over varying intervals.

Although ASL-MRI technology has been available for human use for over a decade, numerous advances in data acquisition and analysis, as well as the greater availability of 3T MRI, have resulted in improvements in signal-to-noise (SNR) and reliability of the methodology. Currently, several different variants of ASL MRI are widely used and have been applied to neurodegenerative populations. Continuous ASL (CASL) involves the continuous labeling of blood water as it passes through a labeling plane while pulsed ASL (PASL) uses short RF pulses to selectively label blood and tissue (36–38).

Pseudocontinuous ASL (pCASL) represents a hybrid of these approaches in which many short pulses simulate the continuous labeling of CASL (39, 40). Continuous inversion allows labeling throughout the cardiac cycle, greatly reducing cardiac noise (41). This difference results in a significant SNR and test-retest reliability advantage for pCASL relative to PASL; the latter being commercially available on a number of scanner platforms [(41, 42)]. This reproducibility advantage for pCASL occurs at a whole grey matter level, but also includes regions of interest (ROIs) that may be particularly relevant to AD, including the posterior cingulate and hippocampus (42). More recent developments with 3D sequences such as fast spin echo, as opposed to the echoplanar imaging most frequently employed, allow for background suppression of static tissue water, increasing the sensitivity to CBF (43, 44). This sequence is now also available commercially on some platforms.

ASL MRI in Patients with AD

A number of groups have now reported findings using ASL MRI in patients with clinical AD. Relative to healthy controls, these studies have frequently reported hypoperfusion to posterior cingulate, precuneus, inferior parietal, and lateral prefrontal cortices (33, 45–49). Importantly, as grey matter loss could account for the reduced perfusion signal, several of these studies applied an atrophy correction (46, 49, 50), which did not appear to significantly alter the findings of regional hypoperfusion. For example, Alsop and colleagues studied 22 patients with mild-to-moderate AD relative to age-matched controls and reported relative hypoperfusion in a broad set of regions inclusive of bilateral midline and lateral parietal cortices and left inferior temporal cortex (50). In general, these regions displayed greater group level CBF reductions than loss of grey matter tissue consistent with the notion that the functional change reflected by this measure exceeds volume loss.

The above findings are in keeping with regional hypometabolism reported in numerous studies of AD using FDG PET (14, 51). To more directly compare these modalities, we recently reported on 15 patients with mild-to-moderate AD and a group of age-matched controls who underwent “simultaneous” ASL MRI and FDG PET (52). Injection of FDG occurred during the pCASL scan which was immediately followed by the PET study. A high degree of overlap was observed between the two modalities most evident in the posterior cingulate and lateral parietal regions (Figure 1). We also applied a composite ROI composed of five individual ROIs that have consistently discriminated AD patients from HC with FDG-PET based on a prior meta-analysis (51). With this composite measure, we observed very high group discrimination for both modalities as reflected by receiver operating characteristic (ROC) curves; area under the curve (AUC's) were 0.94 (95% CI: 0.77, 0.99) and 0.92 (95% CI: 0.76, 0.99) for ASL-MRI and FDG-PET, respectively.

Although quantitative ASL MRI studies have revealed significant capacity to discriminate patients with AD from healthy controls, most assessments of imaging in clinical practice are still based upon visual reads by radiologists. A couple of studies have begun to explore such qualitative reads of perfusion maps (53, 54). For example, in a relatively small cohort, Raji and colleagues found a modest accuracy (70%) for visual reads of CASL scans that exceeded that of structural T1 MRI scans (53). In the same cohort as described above, we compared visual reads for pCASL scans with FDG PET in discrimination of AD from age-matched controls (54). As can be observed in Figure 2, the two modalities produced quite similar appearing images. Blinded visual reads by two expert nuclear medicine physicians yielded moderate and moderate-to-strong Cohen κ statistic for inter-modality agreement (reader 1: 0.45; reader 2: 0.61) although the interobserver κ was higher for FDG PET (0.74) than ASL MRI (0.48). Comparable sensitivity (66.7% versus 63.4%) and specificity (97.4% versus 92.1%) for FDG PET and ASL MRI, respectively, were observed for the two modalities.

While the above data argue for a strong correlation between measures of hypoperfusion by ASL MRI and hypometabolism by FDG PET, there do appear to be some regions of discordance. In particular, the medial temporal lobe (MTL) has been reported to be relatively hyperperfused in at-risk controls and patients at relatively early stages of AD (46, 50, 55). For example, in the study by Alsop and colleagues noted above, despite the regions of hypoperfusion, hippocampal and parahippocampal regions were associated with increased CBF in AD patients relative to age-matched controls. This finding is in contrast to a number of FDG-PET studies that have reported MTL hypometabolism (19, 23, 56–60), or, at most, preserved metabolism (61–63). Increased CBF in a few other regions not typically associated with increased CMRGlu, such as the anterior cingulate (48, 50), have also been reported. While decoupling of CBF from CMRGlu can occur with vascular compromise, the explanation is unclear for these areas of hyperperfusion; possibilities include local inflammation or attempts at plastic remodeling, as well as compensatory responses (48, 50).

ASL MRI in Patients with Prodromal AD

Patients with Mild Cognitive Impairment (MCI) are often conceptualized as representing a group enriched in individuals who are transitioning from being cognitively normal to developing the symptoms of early AD (64). This group is frequently referred to as having “prodromal” AD and given their early symptomatic stage, has been thought to be a potentially important target for disease modifying therapeutics. As such, numerous biomarker studies have investigated this group with a frequent goal being prediction of conversion to clinical AD, as well as enhanced ability to monitor disease progression in this more mild stage.

A limited, but growing, number of studies have applied ASL MRI to this population (46, 49, 65–67). Consistent with work in AD and the FDG PET literature, these investigations have generally reported decreased CBF to posterior cingulate/precuneus and parietal regions that tend to be to a lesser extent than in AD when directly compared. However, as alluded to above, some studies have also reported regions of increased perfusion in MCI relative to age-matched controls (46, 67). For example, Dai et al. scanned 29 MCI patients and 28 controls with CASL and found that in addition to regional hypoperfusion in the posterior cingulate and precuneus, MCI patients displayed hyperperfusion to the left hippocampus, right amygdala, and ventral striatum (46). AD patients from the same cohort differed from MCI with greater hypoperfusion in inferior parietal, superior temporal, and orbital frontal cortices, but also increased anterior cingulate CBF relative to control participants. The authors for this study invoked the notion of compensatory activity in the face of neurodegeneration to explain these dissociations.

To our knowledge, there has been only one study that has applied ASL MRI to an MCI population that was followed longitudinally (68). Similar to findings using FDG PET, Chao and colleagues reported that patients who converted to clinical AD displayed greater hypoperfusion in the precuneus, middle cingulum, inferior parietal and middle frontal cortices. Furthermore, the parietal and frontal measures of CBF provided additional predictive power when combined with a measure of hippocampal volume at baseline. Measures of perfusion also predicted additional measures of cognitive and functional decline.

Task-Related ASL MRI in Early AD

In addition to measuring CBF when subjects are at “rest”, ASL MRI can also be acquired when participants are actively engaged in a task similar to as with BOLD fMRI. While the latter methodology is generally associated with larger signal changes and the capacity for event-related designs, ASL MRI offers some advantages, including 1. quantification in MRI independent physiologic units (e.g. mL/100 g/min), facilitating comparisons across sites and scanning sessions; 2. potentially less intersubject variability, critical for interpretation in the clinical setting (35); 3. less susceptibility to baseline drift allowing for easier comparison across longer time scales (34); and 4. as a result of measurement in absolute units, no need for comparison with a reference state. Importantly, this baseline, or reference, state may be altered by neurological disorders, which, in turn, limit interpretation of activation given a non-linear and significant influence of baseline oxygen extraction on task-related activation (69)

Despite these potential advantages, only two studies have examined the potential value of task-related ASL MRI in neurodegenerative populations (55, 65). In a study of 12 patients with MCI and 14 age-matched controls, Xu and colleagues measured CBF at rest and during performance of a visual scene memory encoding task (65). Consistent with the above data, MCI patients displayed relative hypoperfusion in the precuneus at rest relative to the cognitively normal group. However, during performance of the memory encoding task, this regional difference increased in extent and included posterior cingulate cortex. Further, at rest there was no significant difference detected with the MTL, but with task only the cognitively normal adults displayed increased CBF to the right parahippocampus (22.7% increase) while patients with MCI, if anything, displayed decreased perfusion during task (-5.2%). Thus, task performance appeared to accentuate group differences.

Fleisher and colleagues (2009) also examined rest and task-related ASL MRI in cognitively normal older adults, but divided the groups based on family history and ApoE carrier status to define “high” and “low” risk groups (55). At rest, they found increased CBF in the MTL

of the high risk group, but a blunted increase within this region during performance of a face-name memory encoding task relative to the low risk group. Amongst other implications, this study suggests that ASL MRI may be sensitive to preclinical functional changes and could be a useful biomarker in such populations.

ASL MRI in Non-AD Dementias

Much less work has utilized ASL MRI methodology in non-AD neurodegenerative conditions. However, at least two studies have examined CBF with this approach in patients with frontotemporal dementia [FTD; (70, 71)]. Consistent with expectations, these studies reported variable regions of hypoperfusion within the prefrontal cortex and insula. For example, Hu and colleagues studied 42 patients with FTD, 18 patients with AD, and 23 control participants (70). They reported that patients with FTD had significantly reduced CBF to bilateral regions of the frontal cortex and insula relative to control participants while patients with AD displayed hypoperfusion to posterior regions, including the precuneus and lateral parietal cortices. Interestingly, both populations also displayed reciprocal regions of hyperperfusion, such that the FTD patients had increased CBF to the precuneus/posterior cingulate while patients with AD had increased CBF to the anterior cingulate, dorsolateral prefrontal cortex and insula. Amongst other possibilities, the authors suggested that the hyperperfusion in each case may reflect compensation by networks that are largely spared in early stages of the respective disease states. As this study included mostly AD patients with atypical presentations more consistent with FTD, but considered AD based on CSF biomarkers or autopsy, it is remarkable that such distinct patterns of perfusion were found and encouraging with regard to the potential utility of ASL MRI in differential diagnosis of such populations. The potential role of ASL MRI in this clinical context is further accentuated by data supporting the value of FDG PET in discrimination of AD and FTD (72, 73).

While almost all work with biomarkers in MCI have been in the study of the amnesic variant (a-MCI), which is assumed to most likely develop into clinical AD, a few studies have examined imaging biomarkers in non-amnesic MCI, thought to more frequently represent the prodromal state for non-AD dementias. One study that utilized ASL MRI compared 12 MCI patients with isolated executive impairment, or dysexecutive MCI (dMCI), to 12 patients with a-MCI (66). While both groups displayed hypoperfusion to posterior cingulate/precuneus, the dMCI patients demonstrated additional hypoperfusion to prefrontal regions. Of note, the underlying pathology of these patients was unknown and could be due to either non-AD dementia or the frontal variant of AD.

Despite the fact that ASL MRI measures CBF, its use for vascular dementia has been underexplored. However, one small study did compare 8 patients with subcortical ischemic vascular dementia (SIVD) to 14 patients with AD (74). In this study, cortical CBF appeared to be generally lower in patients with SIVD compared to AD. Furthermore, subcortical white matter lesion burden inversely correlated with cortical CBF, most saliently in the frontal cortex. These data are broadly consistent with other work measuring frontal cortical metabolism or CBF with PET (75, 76). In another study attempting to better understand the link between vascular risk and AD, Glodzik and colleagues examined vasoreactivity to hypercapnia in older controls and MCI patients (77). Using a rebreathing protocol, they found that changes of CBF in the hippocampus measured by ASL MRI were inversely correlated with the Framingham cardiovascular risk profile (FCRP). This relationship was strongest in the MCI patients, who also more generally exhibited decreased vasoreactivity compared to controls regardless of FCRP, suggesting that there may be independent effects of early neurodegeneration and vascular risk on vessel function.

Conclusion

ASL MRI has displayed considerable promise as a biomarker in neurodegenerative conditions. However, most of the above described work involved relative small samples and there is great variability in the methodology and processing applied across these studies. Larger studies in MCI and preclinical AD with more direct comparison to existing molecular and neurodegenerative biomarkers will be necessary to determine the value of this approach. In particular, while there appears to be significant overlap with FDG PET findings, the relative sensitivity and specificity of these modalities has not been directly compared in prodromal and preclinical populations. Furthermore, there does appear to be regions of relative “mismatch” between findings with ASL MRI measures of CBF and FDG PET measures of glucose metabolism, most notably in the MTL. The significance of these dissociations may have important implications for the pathophysiology and course of the AD process. Additionally, differential changes in metabolism and CBF may offer insight into findings with BOLD fMRI of hyper- or hypo-activation of MTL structures during memory encoding as patients progress in early disease stages (78).

As the ASL MRI technology has experienced significant advances over the last two decades, a number of different approaches have been developed and there is need to directly compare the relative value of various data acquisition and image processing methods. Higher field strengths, such as with 7T scanners, may offer additional SNR and spatial resolution in the future. Task-related approaches are relatively easy to implement and also deserve further exploration as both a biomarker and to better understand the mechanisms underlying cognitive change with neurodegeneration. ASL MRI also offers great potential as a tool to better understand the vascular changes that appear to occur in conjunction with AD-related pathology and that may be intimately linked to the pathoetiology and progression of the condition (79). Finally, given the temporal stability and absolute units of CBF measurements, this methodology may also be particularly valuable as a measure of response to pharmacologic interventions, particularly those that have potential symptomatic benefit (80). Thus, we believe ASL MRI will likely be implemented more widely in the future and contribute significantly to our understanding and treatment of neurodegenerative conditions.

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References

1. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010; 9:119–128. [PubMed: 20083042]
2. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7:280–292. [PubMed: 21514248]
3. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol*. 2009; 65:403–413. [PubMed: 19296504]
4. De Meyer G, Shapiro F, Vanderstichele H, et al. Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. *Arch Neurol*. 2010; 67:949–956. [PubMed: 20697045]
5. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004; 55:306–319. [PubMed: 14991808]

6. Wolk DA, Klunk W. Update on amyloid imaging: from healthy aging to Alzheimer's disease. *Curr Neurol Neurosci Rep.* 2009; 9:345–352. [PubMed: 19664363]
7. Wolk DA, Grachev ID, Buckley C, et al. Association between in vivo fluorine 18-labeled flutemetamol amyloid positron emission tomography imaging and in vivo cerebral cortical histopathology. *Arch Neurol.* 2011; 68:1398–1403. [PubMed: 21747004]
8. Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA.* 2011; 305:275–283. [PubMed: 21245183]
9. Vemuri P, Wiste HJ, Weigand SD, et al. MRI and CSF biomarkers in normal, MCI, and AD subjects: predicting future clinical change. *Neurology.* 2009; 73:294–301. [PubMed: 19636049]
10. Vemuri P, Wiste HJ, Weigand SD, et al. MRI and CSF biomarkers in normal, MCI, and AD subjects: diagnostic discrimination and cognitive correlations. *Neurology.* 2009; 73:287–293. [PubMed: 19636048]
11. Jack CR Jr, Lowe VJ, Weigand SD, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain.* 2009; 132:1355–1365. [PubMed: 19339253]
12. Jack CR Jr, Lowe VJ, Senjem ML, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain.* 2008; 131:665–680. [PubMed: 18263627]
13. Jagust WJ, Landau SM, Shaw LM, et al. Relationships between biomarkers in aging and dementia. *Neurology.* 2009; 73:1193–1199. [PubMed: 19822868]
14. Jagust WJ, Bandy D, Chen K, et al. The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. *Alzheimers Dement.* 2010; 6:221–229. [PubMed: 20451870]
15. Engler H, Forsberg A, Almkvist O, et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. *Brain.* 2006; 129:2856–2866. [PubMed: 16854944]
16. Schwartz WJ, Smith CB, Davidsen L, et al. Metabolic mapping of functional activity in the hypothalamo-neurohypophyseal system of the rat. *Science.* 1979; 205:723–725. [PubMed: 462184]
17. Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. *J Cereb Blood Flow Metab.* 2001; 21:1133–1145. [PubMed: 11598490]
18. Jagust W, Gitcho A, Sun F, Kuczynski B, Mungas D, Haan M. Brain imaging evidence of preclinical Alzheimer's disease in normal aging. *Ann Neurol.* 2006; 59:673–681. [PubMed: 16470518]
19. Mosconi L, De Santi S, Li J, et al. Hippocampal hypometabolism predicts cognitive decline from normal aging. *Neurobiol Aging.* 2008; 29:676–692. [PubMed: 17222480]
20. Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med.* 1996; 334:752–758. [PubMed: 8592548]
21. Small GW, Ercoli LM, Silverman DH, et al. Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proc Natl Acad Sci U S A.* 2000; 97:6037–6042. [PubMed: 10811879]
22. Mosconi L, Sorbi S, de Leon MJ, et al. Hypometabolism exceeds atrophy in presymptomatic early-onset familial Alzheimer's disease. *J Nucl Med.* 2006; 47:1778–1786. [PubMed: 17079810]
23. Mosconi L, Perani D, Sorbi S, et al. MCI conversion to dementia and the APOE genotype: a prediction study with FDG-PET. *Neurology.* 2004; 63:2332–2340. [PubMed: 15623696]
24. Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology.* 2003; 60:1374–1377. [PubMed: 12707450]
25. Arnaiz E, Jelic V, Almkvist O, et al. Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. *Neuroreport.* 2001; 12:851–855. [PubMed: 11277595]
26. Drzezga A, Lautenschlager N, Siebner H, et al. Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. *Eur J Nucl Med Mol Imaging.* 2003; 30:1104–1113. [PubMed: 12764551]
27. Baron JC, Lebrun-Grandie P, Collard P, Crouzel C, Mestelan G, Bousser MG. Noninvasive measurement of blood flow, oxygen consumption, and glucose utilization in the same brain

- regions in man by positron emission tomography: concise communication. *J Nucl Med.* 1982; 23:391–399. [PubMed: 6978932]
28. Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci U S A.* 1986; 83:1140–1144. [PubMed: 3485282]
 29. Detre JA, Rao H, Wang DJ, Chen YF, Wang Z. Applications of arterial spin labeled MRI in the brain. *J Magn Reson Imaging.* 2012. • Review of the ASL MRI technique and potential applications in clinical research and neuroscience.
 30. Detre JA, Wang J, Wang Z, Rao H. Arterial spin-labeled perfusion MRI in basic and clinical neuroscience. *Curr Opin Neurol.* 2009; 22:348–355. [PubMed: 19491678]
 31. Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. *Magn Reson Med.* 1992; 23:37–45. [PubMed: 1734182]
 32. Alsop DC, Detre JA. Reduced transit-time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow. *J Cereb Blood Flow Metab.* 1996; 16:1236–1249. [PubMed: 8898697]
 33. Alsop DC, Dai W, Grossman M, Detre JA. Arterial spin labeling blood flow MRI: its role in the early characterization of Alzheimer's disease. *J Alzheimers Dis.* 2010; 20:871–880. [PubMed: 20413865]
 34. Borogovac A, Habeck C, Small SA, Asllani I. Mapping brain function using a 30-day interval between baseline and activation: a novel arterial spin labeling fMRI approach. *J Cereb Blood Flow Metab.* 2010
 35. Detre JA, Wang J. Technical aspects and utility of fMRI using BOLD and ASL. *Clin Neurophysiol.* 2002; 113:621–634. [PubMed: 11976042]
 36. Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. *Proc Natl Acad Sci U S A.* 1992; 89:212–216. [PubMed: 1729691]
 37. Luh WM, Wong EC, Bandettini PA, Hyde JS. QUIPSS II with thin-slice TI1 periodic saturation: a method for improving accuracy of quantitative perfusion imaging using pulsed arterial spin labeling. *Magn Reson Med.* 1999; 41:1246–1254. [PubMed: 10371458]
 38. Wong EC, Buxton RB, Frank LR. Implementation of quantitative perfusion imaging techniques for functional brain mapping using pulsed arterial spin labeling. *NMR Biomed.* 1997; 10:237–249. [PubMed: 9430354]
 39. Wu WC, Fernandez-Seara M, Detre JA, Wehrli FW, Wang J. A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. *Magn Reson Med.* 2007; 58:1020–1027. [PubMed: 17969096]
 40. Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. *Magn Reson Med.* 2008; 60:1488–1497. [PubMed: 19025913]
 41. Wu WC, Edlow BL, Elliot MA, Wang J, Detre JA. Physiological modulations in arterial spin labeling perfusion magnetic resonance imaging. *IEEE Trans Med Imaging.* 2009; 28:703–709. [PubMed: 19150788]
 42. Chen Y, Wang DJ, Detre JA. Test-retest reliability of arterial spin labeling with common labeling strategies. *J Magn Reson Imaging.* 2011; 33:940–949. [PubMed: 21448961] . •Important manuscript comparing the reliability of different ASL variants.
 43. Garcia DM, Duhamel G, Alsop DC. Efficiency of inversion pulses for background suppressed arterial spin labeling. *Magn Reson Med.* 2005; 54:366–372. [PubMed: 16032674]
 44. Fernandez-Seara MA, Edlow BL, Hoang A, Wang J, Feinberg DA, Detre JA. Minimizing acquisition time of arterial spin labeling at 3T. *Magn Reson Med.* 2008; 59:1467–1471. [PubMed: 18506806]
 45. Alsop DC, Detre JA, Grossman M. Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging. *Ann Neurol.* 2000; 47:93–100. [PubMed: 10632106]
 46. Dai W, Lopez OL, Carmichael OT, Becker JT, Kuller LH, Gach HM. Mild cognitive impairment and alzheimer disease: patterns of altered cerebral blood flow at MR imaging. *Radiology.* 2009; 250:856–866. [PubMed: 19164119]

47. Yoshiura T, Hiwatashi A, Yamashita K, et al. Simultaneous measurement of arterial transit time, arterial blood volume, and cerebral blood flow using arterial spinlabeling in patients with Alzheimer disease. *AJNR Am J Neuroradiol*. 2009; 30:1388–1393. [PubMed: 19342545]
48. Hu WT, Wang Z, Lee VM, Trojanowski JQ, Detre JA, Grossman M. Distinct cerebral perfusion patterns in FTLN and AD. *Neurology*. 75:881–888. [PubMed: 20819999]
49. Johnson NA, Jahng GH, Weiner MW, et al. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. *Radiology*. 2005; 234:851–859. [PubMed: 15734937]
50. Alsop DC, Casement M, de Bazelaire C, Fong T, Press DZ. Hippocampal hyperperfusion in Alzheimer's disease. *Neuroimage*. 2008; 42:1267–1274. [PubMed: 18602481]
51. Landau SM, Harvey D, Madison CM, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging*. 2009
52. Chen Y, Wolk DA, Reddin JS, et al. Voxel-level comparison of arterial spinlabeled perfusion MRI and FDG-PET in Alzheimer disease. *Neurology*. 2011; 77:1977–1985. [PubMed: 22094481] . • Study directly comparing ASL MRI with FDG PET acquired in the same patients at the same time. High correlation and very similar overall sensitivity and specificity reported for the two modalities.
53. Raji CA, Lee C, Lopez OL, et al. Initial experience in using continuous arterial spin-labeled MR imaging for early detection of Alzheimer disease. *AJNR Am J Neuroradiol*. 2010; 31:847–855. [PubMed: 20075093]
54. Musiek ES, Chen Y, Korczykowski M, et al. Direct comparison of fluorodeoxyglucose positron emission tomography and arterial spin labeling magnetic resonance imaging in Alzheimer's disease. *Alzheimers Dement*. 2011
55. Fleisher AS, Podraza KM, Bangen KJ, et al. Cerebral perfusion and oxygenation differences in Alzheimer's disease risk. *Neurobiol Aging*. 2009; 30:1737–1748. [PubMed: 18325636]
56. Mevel K, Desgranges B, Baron JC, et al. Detecting hippocampal hypometabolism in Mild Cognitive Impairment using automatic voxel-based approaches. *Neuroimage*. 2007; 37:18–25. [PubMed: 17566762]
57. Walhovd KB, Fjell AM, Brewer J, et al. Combining MR imaging, positron-emission tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer disease. *AJNR Am J Neuroradiol*. 31:347–354. [PubMed: 20075088]
58. De Santi S, de Leon MJ, Rusinek H, et al. Hippocampal formation glucose metabolism and volume losses in MCI and AD. *Neurobiol Aging*. 2001; 22:529–539. [PubMed: 11445252]
59. Anchisi D, Borroni B, Franceschi M, et al. Heterogeneity of brain glucose metabolism in mild cognitive impairment and clinical progression to Alzheimer disease. *Arch Neurol*. 2005; 62:1728–1733. [PubMed: 16286547]
60. Nestor PJ, Fryer TD, Smielewski P, Hodges JR. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Ann Neurol*. 2003; 54:343–351. [PubMed: 12953266]
61. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol*. 1997; 42:85–94. [PubMed: 9225689]
62. Ishii K, Sasaki M, Yamaji S, Sakamoto S, Kitagaki H, Mori E. Relatively preserved hippocampal glucose metabolism in mild Alzheimer's disease. *Dement Geriatr Cogn Disord*. 1998; 9:317–322. [PubMed: 9769444]
63. Chetelat G, Desgranges B, Landeau B, et al. Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. *Brain*. 2008; 131:60–71. [PubMed: 18063588]
64. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. *Arch Neurol*. 2009; 66:1447–1455. [PubMed: 20008648]
65. Xu G, Antuono PG, Jones J, et al. Perfusion fMRI detects deficits in regional CBF during memory-encoding tasks in MCI subjects. *Neurology*. 2007; 69:1650–1656. [PubMed: 17954780]
66. Chao LL, Pa J, Duarte A, et al. Patterns of cerebral hypoperfusion in amnesic and dysexecutive MCI. *Alzheimer Dis Assoc Disord*. 2009; 23:245–252. [PubMed: 19812467]

67. Alexopoulos P, Sorg C, Forschler A, et al. Perfusion abnormalities in mild cognitive impairment and mild dementia in Alzheimer's disease measured by pulsed arterial spin labeling MRI. *Eur Arch Psychiatry Clin Neurosci*. 2012; 262:69–77. [PubMed: 21786091]
68. Chao LL, Buckley ST, Kornak J, et al. ASL perfusion MRI predicts cognitive decline and conversion from MCI to dementia. *Alzheimer Dis Assoc Disord*. 2010; 24:19–27. [PubMed: 20220321]
69. Cohen ER, Ugurbil K, Kim SG. Effect of basal conditions on the magnitude and dynamics of the blood oxygenation level-dependent fMRI response. *J Cereb Blood Flow Metab*. 2002; 22:1042–1053. [PubMed: 12218410]
70. Hu WT, Wang Z, Lee VM, Trojanowski JQ, Detre JA, Grossman M. Distinct cerebral perfusion patterns in FTLN and AD. *Neurology*. 2010; 75:881–888. [PubMed: 20819999]
71. Du AT, Jahng GH, Hayasaka S, et al. Hypoperfusion in frontotemporal dementia and Alzheimer disease by arterial spin labeling MRI. *Neurology*. 2006; 67:1215–1220. [PubMed: 17030755]
72. Rabinovici GD, Rosen HJ, Alkalay A, et al. Amyloid vs FDG-PET in the differential diagnosis of AD and FTLN. *Neurology*. 2011; 77:2034–2042. [PubMed: 22131541]
73. Foster NL, Heidebrink JL, Clark CM, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain*. 2007; 130:2616–2635. [PubMed: 17704526]
74. Schuff N, Matsumoto S, Kmiecik J, et al. Cerebral blood flow in ischemic vascular dementia and Alzheimer's disease, measured by arterial spin-labeling magnetic resonance imaging. *Alzheimers Dement*. 2009; 5:454–462. [PubMed: 19896584]
75. Tullberg M, Fletcher E, DeCarli C, et al. White matter lesions impair frontal lobe function regardless of their location. *Neurology*. 2004; 63:246–253. [PubMed: 15277616]
76. Kraut MA, Beason-Held LL, Elkins WD, Resnick SM. The impact of magnetic resonance imaging-detected white matter hyperintensities on longitudinal changes in regional cerebral blood flow. *J Cereb Blood Flow Metab*. 2008; 28:190–197. [PubMed: 17534385]
77. Glodzik L, Rusinek H, Brys M, et al. Framingham cardiovascular risk profile correlates with impaired hippocampal and cortical vasoreactivity to hypercapnia. *J Cereb Blood Flow Metab*. 2011; 31:671–679. [PubMed: 20842159] . • Study exploring the role of cardiovascular risk in the functional response of the vascular supply to the hippocampus in mild cognitive impairment to mild hypercapnia.
78. Dickerson BC, Sperling RA. Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging. *Behav Neurol*. 2009; 21:63–75. [PubMed: 19847046]
79. Austin BP, Nair VA, Meier TB, et al. Effects of hypoperfusion in Alzheimer's disease. *J Alzheimers Dis*. 2011; 26(Suppl 3):123–133. [PubMed: 21971457]
80. Chen Y, Wan HI, O'Reardon JP, et al. Quantification of cerebral blood flow as biomarker of drug effect: arterial spin labeling phMRI after a single dose of oral citalopram. *Clin Pharmacol Ther*. 2011; 89:251–258. [PubMed: 21191380]

Key Points

1. Arterial spin labeling (ASL) MRI is an emerging biomarker for measuring functional change associated with neurodegenerative conditions.
2. Changes in cerebral blood flow (CBF) measured by ASL MRI appear to overlap considerably with alterations of brain metabolism measured by FDG PET.
3. Patients with Mild Cognitive Impairment (MCI) and Alzheimer's Disease display regional hypoperfusion, but also areas of hyperperfusion which may provide clues to the brain's response to neurodegeneration.
4. ASL MRI has great potential for the investigation of vascular factors that contribute to cognitive decline and neurodegeneration which is just beginning to be exploited.

Figure 1.

Areas of (A) hypoperfusion (CBF) measured by ASL MRI and (B) hypometabolism (CMRGlu) measured by FDG PET in patients with AD relative to healthy controls rendered onto 3-dimensional brains, with color intensity representing depth from brain surface. Red represents Alzheimer disease–related decreases. (C) Results of conjunction analysis showing areas of overlap between hypoperfusion and hypometabolism. All images were statistically thresholded at $p < 0.05$, false discovery rate correction for multiple comparisons, cluster > 50 . Figure adapted from (52).

Figure 2.
Representative images from two patients with AD comparison of ASL MRI and FDG PET. White arrows highlight areas of concordant hypoperfusion on ASL MRI and hypometabolism. Figure adapted from (54).