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Cerebral Blood Flow Measured by Arterial Spin Labeling MRI as a Preclinical Marker of Alzheimer's Disease

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Abstract

There is growing recognition that cerebral hypoperfusion is related to the pathogenesis of Alzheimer's disease (AD), implicating the measurement of cerebral blood flow (CBF) as a possible biomarker of AD. The ability to identify the earliest and most reliable markers of incipient cognitive decline and clinical symptoms is critical to develop effective preventive strategies and interventions for AD. Arterial spin labeling (ASL) magnetic resonance imaging (MRI) measures CBF by magnetically labeling arterial water and using it as an endogenous tracer. Studies using ASL MRI in humans indicate that CBF changes are present several years before the development of the clinical symptoms of AD. Moreover, ASL-measured CBF has been shown to distinguish between cognitively normal individuals, adults at risk for AD, and persons diagnosed with AD. Some studies indicate that CBF may even be sensitive for predicting cognitive decline and conversion to mild cognitive impairment and AD over time. Taken together, evidence suggests that the current staging models of AD biomarker pathology should incorporate early changes in CBF as a useful biomarker, possibly present even earlier than amyloid β accumulation. Though still a research tool, ASL imaging is a promising non-invasive and reliable method with the potential to serve as a future clinical tool for the measurement of CBF in preclinical AD.

Keywords

Alzheimer's disease; arterial spin labeling; cerebral blood flow; cerebrovascular disorders; cognition; mild cognitive impairment; neuroimaging; neurovascular dysfunction; perfusion

1. Introduction

Alzheimer's disease (AD) is the third leading cause of death in the United States, with approximately 500,000 AD-related deaths each year [1]. The identification of biomarkers of AD is critical since a latent phase of the disease exists [2], with significant neuropathologic changes beginning years before the clinical features of AD are apparent. This long preclinical phase provides a prime opportunity for potential intervention with disease-modifying therapy, but depends on the ability to identify the earliest, and most reliable and

non-invasive markers of incipient cognitive decline and clinical symptoms. Given that the number of people with AD is expected to triple by 2050 [1], biomarker identification is arguably among the most important research objectives of the next decade.

The pathogenesis of AD remains unclear, though prevailing theories attribute AD etiology to either the overproduction and deposition of beta amyloid (e.g., the amyloid cascade hypothesis) or cerebral hypoperfusion resulting from vascular disease and aging (e.g., the vascular hypothesis), which lead to neuronal death and cognitive decline. The amyloid cascade model of AD progression [2] describes a sequence of biomarker changes that occur along a continuum from normal aging to mild cognitive impairment (MCI) to AD. Amyloid biomarkers become abnormal well ahead of tau-related markers of neural injury and neurodegeneration, which then leads to structural brain changes, subtle cognitive declines, MCI, and finally—when functional deficits are apparent—dementia.

In favor of the vascular hypothesis, accumulating evidence suggests vascular pathology and hypoperfusion contribute to AD. This includes impaired structure and function of cerebral blood vessels and the neurovascular unit, which is comprised of endothelial, glial, and neuronal cells. There is growing support for a synergistic relationship between vascular dysfunction and accumulation of amyloid- β and neurofibrillary tangles (NFT), whereby amyloid- β and NFTs result from inadequate cerebral perfusion, and the neurotoxic effects of amyloid- β in turn impair vascular function, such as endothelial function and neurovascular coupling, and induce hypoperfusion (see [3–5] for reviews of vascular dysfunction in AD). For example, according to the two-hit vascular hypothesis of AD, [6] damage to the brain's microcirculation (hit one), which may result from aging or vascular risk factors such as hypertension, cerebrovascular disease, diabetes, or hyperlipidemia [4], initiates a cascade of vascular-related neuronal dysfunction. This causes changes in blood brain barrier function and mild hypoperfusion, defined as the disruption of normal regulation of cerebral perfusion by arterioles. Together, these vascular changes contribute to the second hit (hit 2), which arises from increased amyloid- β accumulation and impaired clearance, which exerts neurotoxic effects on the brain leading to degeneration and dementia. In support of this hypothesis, clinical studies show that cerebral blood flow (CBF) dysregulation occurs in at-risk elderly even before amyloid- β accumulation or brain atrophy are demonstrated [7–9]. Altered cerebral autoregulation and vasoreactivity have been shown in animal models of AD [10,11] and patients with mild to moderate AD [12]. And mouse models implicate capillary disturbances as the precursors to the neurodegenerative changes associated with AD [13,14]. These disturbances have been shown to not only cause diminished perfusion, but to cause a breakdown in the blood brain barrier, eventually impairing cerebral clearance mechanisms and leading to amyloid- β accumulation in mice [15].

In vivo assessment of CBF via arterial spin labelling (ASL) magnetic resonance imaging (MRI) may be promising as a potential tool for early detection and characterization of AD progression. CBF refers to the *rate* of delivery of arterial blood to the capillary bed in brain tissue and is typically quantified in milliliters of blood per 100 grams of tissue per minute [16]. ASL is a noninvasive and reliable MRI technique [17] that magnetically labels arterial water in the brain and uses it as an endogenous tracer to measure CBF. Because ASL MRI provides a quantitative measure of CBF in the capillary bed, rather than a relative measure

such as the venous blood oxygenation level dependent (BOLD) fMRI signal, it has the potential to more accurately estimate the magnitude and location of neural function [16], which is an advantage over peripheral measures of vascular pathology.

This review aims to provide a thorough analysis of evidence of resting CBF dysfunction in clinical studies of AD and AD risk measured by ASL MRI, rather than a full systematic review. To this end, a search of the published literature (PubMed) was conducted using the following terms: ‘Alzheimer’s disease’, ‘mild cognitive impairment’, and ‘APOE’, using the Boolean ‘OR’. The Boolean operator ‘AND’ was used to link these to the terms: ‘arterial spin labeling’, ‘cerebral blood flow’, and ‘perfusion’. Papers published until May 2014 were included. Preference was given to papers including original data on human subjects. The references in the selected articles were scanned for other relevant articles. Given the critical need for early diagnosis and intervention, we examine evidence for the utility of CBF to differentiate individuals at risk for AD from cognitively normal peers, as well as to predict cognitive decline and disease conversion.

2. Resting CBF in Alzheimer’s Disease

Compared to age-matched cognitively normal adults, individuals with AD show an approximately 40% global decrease in CBF [18]. Regional decreases in CBF tend to be most prominent in the precuneus, posterior cingulate and superior parietal cortex [19], though additional areas of hypoperfusion have been reported in the lateral frontal lobe, orbitofrontal cortex, and temporal lobe including the parahippocampal gyrus and hippocampus [19–23]. Notably, these reductions in CBF appear largely independent of gray matter atrophy [24]. However, a few studies have also found increases in CBF in the hippocampus and medial temporal lobe (MTL)—which only reached significance after controlling for gray matter atrophy [25]—and the anterior cingulate [20,24,25] and dorsolateral prefrontal cortex [24]. Taken together, AD patients tend to demonstrate a distinct pattern of posterior hypoperfusion in the MTL, precuneus, and lateral parietal cortex, consistent with the regional concentration of neurofibrillary pathology and plaque formation in AD [26], and that can be distinguished from other forms of dementias such as frontotemporal dementia [24] and Parkinson’s disease dementia [27]. Increased CBF in frontal regions has been hypothesized to reflect compensatory or pathological elevation of neural activity, inflammation, or elevated production of vasodilators [25,28], reflecting the dynamic pathological process in early AD. This is supported by evidence that parieto-occipital CBF in AD patients correlated with dementia severity [29]. Classification methods demonstrate CBF quantified with ASL has good diagnostic accuracy in differentiating early AD from normal controls, but whether CBF contributes added value over structural MRI measures is debated [30].

3. Resting CBF in Alzheimer’s Disease Risk

3.1. Apolipoprotein E & Family History

The utility of CBF as a prognostic indicator of AD depends on its ability to differentiate adults at risk for AD from healthy peers and to predict cognitive decline or AD conversion. First-degree familial history (FH) of AD may increase risk of developing AD up to 10 fold [31]. Possessing the apolipoprotein E (APOE) epsilon4 ($\epsilon 4$) allele has been shown to

increase AD risk by 3–8 fold and to considerably lower the age of disease onset [32]. Alterations in resting CBF are associated with both risk factors. The APOE ϵ 4 allele plays a role in cerebrovascular integrity and is associated with small vessel arteriosclerosis, higher LDL-cholesterol levels, ischemic strokes, microinfarcts of the deep nuclei, neuritic plaque density and amyloid angiopathy [33,34]. Against the backdrop of widespread reduction in CBF, ranging from 18–28% in older adults compared to young adults [5], cognitively normal APOE ϵ 4 carriers demonstrate both increased and decreased CBF compared to non-carriers. Areas of hyperperfusion in older ϵ 4 carriers have been shown in the MTL [35], left lingual gyrus, precuneus [36], and insula [37]. Hypoperfusion is mainly evident in the middle temporal gyrus, inferior parietal lobe, and insula [38], with greater rate of CBF decline over time in ϵ 4 carriers in frontal, temporal and superior parietal regions [37]. The effect of APOE on CBF appears to be mediated by age, with evidence that older ϵ 4 adults display greater hypoperfusion and younger ϵ 4 adults show greater hyperperfusion in the anterior cingulate cortex [36]. The hyperperfusion observed in younger ϵ 4 carriers was correlated with better executive functioning, suggesting compensatory mechanisms may be engaged many years prior to symptom onset [36].

Cognitively intact middle age adults with a parental history of AD showed decreased CBF in the right superior and middle frontal cortices compared to individuals without a family history [39]. Notably, a maternal history of AD conferred a greater risk of altered CBF, evidenced by reduced CBF in the hippocampus and frontoparietal regions [39]. Studies that have examined the combination of familial and genetic risk support an additive effect of these risk factors on CBF revealed by exaggerated posterior hypoperfusion and hippocampal hyperperfusion. For example, cognitively intact FH+/APOE ϵ 4+ adults had reduced CBF in lateral frontal and superior parietal regions, hippocampus, precuneus and posterior cingulate [39], although a slightly younger group showed increased hippocampal CBF [40] compared to adults with no known risk factors for AD.

Taken together, the regionally elevated CBF in asymptomatic individuals at risk for AD suggests a possible vascular regulatory mechanism to compensate for altered brain metabolism and/or an increased need for glucose and oxygen in order to achieve a similar level of cognitive performance. Similarly, lower CBF seen in older asymptomatic adults at higher risk (e.g., FH+/APOE ϵ 4+) suggests a breakdown in this early compensatory mechanism that may precipitate a decrease in neural activity and later degeneration and cognitive decline. This is consistent with a recent finding that higher amyloid- β load is related to lower CBF independent of diagnostic group (e.g., cognitively normal, early or late MCI, AD) [41].

3.2. Mild Cognitive Impairment

MCI is considered to be a distinct construct representing a risk factor for AD and other dementias, characterized by cognitive decline in the absence of pronounced functional impairment that would otherwise warrant a dementia diagnosis [42]. MCI is arguably the most well-characterized risk factor for AD, although the lack of a universal operational definition of MCI among research practices contributes to widely varying results across studies. Relative to age-matched controls, adults with MCI have shown both increases and

decreases in CBF across studies. Decreased CBF has been consistently reported in a lateral temporo-parietal-frontal pattern, extending to the MTL, posterior cingulate, and precuneus [20,21,35,43,44]. Areas of increased CBF in adults with MCI have also been reported in some overlapping regions including the MTL, anterior cingulate, insula, hippocampus, putamen, amygdala, and ventral striatum [20,43]. Bangen et al [35] found increased MTL CBF was correlated with better memory performance, whereas decreased CBF has been linked to visuospatial and general cognitive dysfunction in MCI [35,45]. Individuals with amnesic MCI (aMCI), a subtype of MCI characterized by a primary memory impairment, demonstrate hypoperfusion in the left occipital lobe, bilateral inferior temporal cortex, and right middle temporal cortex, with hyperperfusion in the bilateral frontal lobes [46]. Discrepant findings may be due to use of different MCI diagnostic schemes, as some studies include only amnesic MCI (aMCI) [44] whereas others include amnesic and non-amnesic (naMCI) subtypes [20]. For example, Xu et al [44] found decreased CBF in the precuneus/cuneus in aMCI compared to cognitively normal older adults, which correlated with verbal learning performance and scores on the Mini-Mental State Examination (MMSE). When compared to aMCI, individuals with non-amnesic single-domain MCI, characterized by predominantly executive function impairments, showed lower CBF in the left middle frontal gyrus, left posterior cingulate, and left precuneus, and both groups demonstrated increased CBF in the posterior cingulate compared to controls [47]. This supports the existence of distinct subgroups of MCI that correspond to distinct neurovascular underpinnings.

Studies of APOE genotype in adults with MCI suggest that MCI APOE ϵ 4 carriers have increased CBF in the posterior cingulate, anterior cingulate, and parahippocampal gyrus [38] compared to MCI non-carriers. Evidence that disease severity may mediate the relationship between APOE genotype and CBF comes from studies showing an interaction of genotype and cognitive status, whereby MCI APOE ϵ 4 carriers showed decreased CBF in the parahippocampal gyrus and increased CBF in the anterior cingulate, and cognitively normal non-carriers showed the opposite pattern [23]. We found that improved verbal memory was correlated with an upsurge in resting CBF in the anterior cingulate in MCI APOE ϵ 4 carriers and elevated CBF in the parahippocampal gyrus in APOE ϵ 4 cognitively normal adults. This is consistent with suggestions of a differential neurovascular compensatory increase in CBF in posterior and anterior cortices that may correspond to cognitive decline and encroaching neuropathology [23]. Taken together, evidence of both hypoperfusion as well as hyperperfusion in individuals with MCI is consistent with a continuum of CBF alterations from normal aging to AD and suggestive of early neurodegeneration resulting in compensatory CBF increases, as a possible attempt to maintain cognitive function via increased metabolic demands [48], in the context of encroaching neuropathology and impairment.

4. Resting CBF as a Predictive Tool

4.1. Conversion to MCI

Although cross-sectional studies provide promising evidence that CBF is sensitive to early changes associated with AD and may differentiate high and low risk, not all cases with vascular change will lead to AD and these studies are inherently limited by their inability to

follow participants longitudinally or to autopsy in order to determine cognitive decline, AD conversion, etiology of impairment, and association between CBF and neuropathology. Beason-Held and colleagues recently demonstrated that resting CBF is sensitive to predict conversion to MCI [49]. Compared to individuals who remained cognitively normal, adults who later developed MCI showed hyperperfusion in orbitofrontal, medial frontal and anterior cingulate regions over time, with decreased CBF in parietal, temporal and thalamic regions. This suggests that increases and decreases in CBF take place years before the onset of cognitive symptoms in individuals who eventually develop cognitive impairment. Most of these changes were seen in areas that reflect early AD pathology and are thought to be associated with maintaining cognitive function, suggesting a connection between early changes in CBF and AD pathology [49].

4.2. Conversion to AD

Recent research also implicates CBF as a sensitive marker to predict who will likely decline from MCI to AD. In one of the only prospective longitudinal ASL studies in AD, Chao and colleagues found that in adults with MCI, hypoperfusion in the precuneus, inferior parietal and middle frontal cortices predicted conversion to AD within approximately 3 years [50]. Similarly, patients with MCI who converted to AD after 2 years of follow-up demonstrated decreased CBF in the parietal lobes (e.g., precuneus, cuneus, inferior parietal lobe) and increased CBF in the MTL compared to controls. No change in cerebral blood volume (CBV) was detected, suggesting CBF is a more sensitive measure than CBV to detect vascular changes in preclinical AD [22]. This is consistent with studies reporting that CBF differentiates individuals with MCI who convert to AD from adults who do not convert using single photon emission computed tomography (SPECT) imaging [51,52]. Specifically, decreased perfusion in the parahippocampal gyrus [52,53], right precuneus [51,52], cingulate gyrus [52], and posterior cingulate [51] has been implicated in MCI patients who converted to AD. Taken together, these results suggest that for adults with MCI, lower brain perfusion at baseline in regions such as the hippocampus and precuneus increases risk for further decline and possible conversion to AD.

5. Resolving Inconsistent Findings of Hypoperfusion and Hyperperfusion

Inconsistencies remain across studies which are difficult to resolve. The studies reviewed above tend to suggest hyperperfusion precedes hypoperfusion in earlier phases of disease development and progression (Figure 1) [23,36,37,40]. Some differences across studies may be attributable to methodological differences, such as CBF collection methods, patient demographics such as age and vascular risk burden [54], diagnostic criteria for MCI, disease severity, or misclassifying preclinical AD as normal controls. It is also possible that differences in the way CBF is coupled with local metabolic needs during different phases of disease development and progression may explain this paradoxical, biphasic early hyperperfusion followed by later hypoperfusion CBF response. The capillary dysfunction hypothesis of AD developed by Ostergaard [48] may offer a possible explanation for this biphasic response. It posits that increases in the heterogeneity of capillary blood flow patterns occurs early in the preclinical stage of AD and requires increases in CBF to maintain adequate brain oxygenation. Progressive increases in heterogeneity with disease

course result in low tissue oxygen that requires suppression of CBF to maintain tissue metabolism. Thus early compensatory hyperperfusion, which has been observed in AD risk, and later hypoperfusion (which reflects neurovascular adjustments in an attempt to maintain oxygen availability in the tissue) seen in the progression from normal cognitive aging to MCI and AD, is therefore consistent with early disturbances in capillary flow patterns and fits well into established models of AD neuropathology. However, this model needs further testing and validation in human studies.

6. Limitations

The evidence suggesting CBF measures can differentiate individuals diagnosed with AD and adults at risk for developing AD from cognitively normal peers is compelling [55]. Recent comparison studies indicate equivalent diagnostic performance between ASL and positron emission tomography (PET) and SPECT methods, but ASL offers the advantage of being non-invasive, cost-effective, and easily repeatable [56,57]. Hence ASL MRI is the most promising tool to non-invasively study changes in CBF as they relate to AD risk and progression. However, several methodological issues limit its widespread use. For example, there is a current lack of standardization for ASL MRI in multi-center studies. Also, there are limitations in many of the existing pulse sequences (e.g., sensitivity to transit time effects, limited brain coverage, low spatial resolution, less sensitivity to white matter CBF) which may account for some of the apparent conflicting data in AD and AD risk. Moreover, the specificity of ASL-measured CBF to distinguish between AD pathology and other vascular etiologies has not been firmly established, as reduced CBF has also been reported in vascular dementia [58] and a post-stroke non-demented group [59], and may mimic changes found in AD. This cautions against the use of CBF measures in isolation, without considering other clinical information (e.g., neuropsychological performance, neuropathology measures). Despite the advantage of providing quantitative measurement of CBF, making standard reference values for CBF has been difficult due to variability of findings across studies. Taken together, while ASL MRI holds promise, it has not been clearly demonstrated to be ready for routine use in clinical trials and clinical practice (i.e., it remains a research tool).

7. Conclusions and Future Directions

With the recently revised criteria put forth by the NIA-AA workgroup for the diagnosis of preclinical AD [60], it is clear that we are entering a new era of research and clinical activity that will increasingly focus on the role of biomarkers in disease detection, diagnosis, and clinical outcome. A biomarker, by definition, is a characteristic that is objectively measured and evaluated as an indicator of pathologic processes, and can be used as a diagnostic tool to identify patients, for staging a disease, as an indicator of disease prognosis, or for prediction and monitoring of clinical response to an intervention [61]. As reviewed here, emerging evidence supports the potential of CBF as a biomarker of AD. For example, CBF changes have been shown to differentiate patients at risk for or diagnosed with AD from normal controls, and to predict cognitive decline and conversion to MCI and AD [50]. This not only implicates CBF as a useful biomarker for tracking disease severity and progression, but also suggests that CBF measures may be useful for identifying candidates for future AD

treatment trials, especially in the preclinical phases of the disease. Given the substantial evidence implicating CBF changes as one of the earliest signs of AD, it is warranted that early CBF dysregulation be incorporated into current staging frameworks of AD biomarker pathology (Figure 2).

Revealing the vascular mechanisms underlying cognitive decline, and identifying pathogenic vascular changes pre-clinically as treatment targets holds great potential to delay or prevent the onset of the clinical symptoms of AD. We expect findings will further elucidate the role of vascular dysregulation in AD and support further development of vasoprotective treatments. Given recent findings associating regulatory elevations of CBF in the MTL with sedentary behavior in APOE ϵ 4 carriers [62], and increased CBF in the anterior cingulate following an exercise intervention in older adults [63], future research must exploit the potential disease-modifying role that pharmacological [4] and behavioral lifestyle factors, such as exercise, diet, and cognitive engagement may play in the regulation of CBF and prevention of AD.

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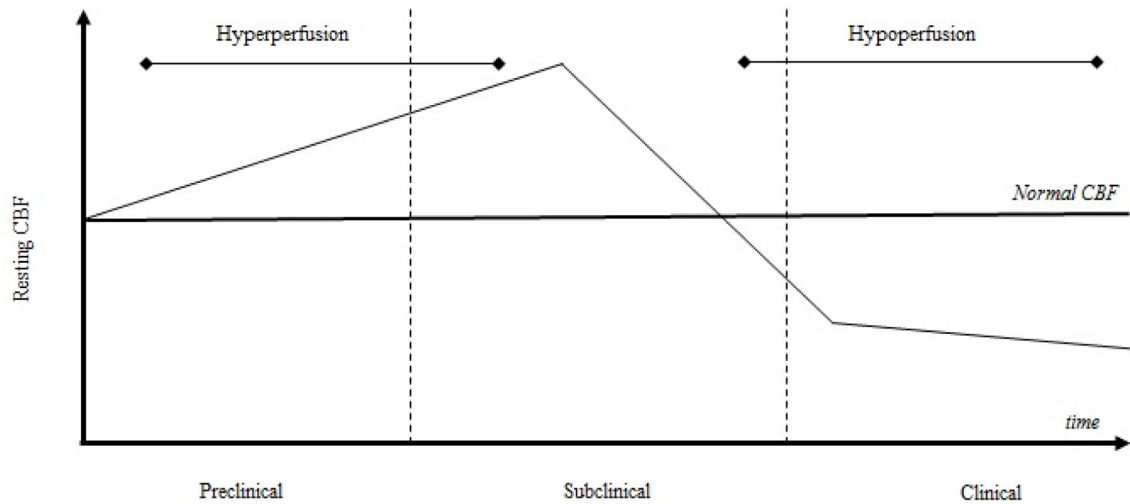


Figure 1.

Summary of ASL studies showing CBF alterations in the preclinical, subclinical and clinical phases of AD. In the preclinical phase, which includes asymptomatic APOE ϵ 4 carriers with or without a familial history of AD, there is evidence of hyperperfusion, especially in younger individuals [35–37,40]. In the subclinical phase, which includes MCI, studies show both hyperperfusion and hypoperfusion, with some evidence of early CBF increases and later decreases [41]. The clinical phase includes AD, with most studies showing widespread decreases in CBF [18,19].

** This figure has been adapted from [48].

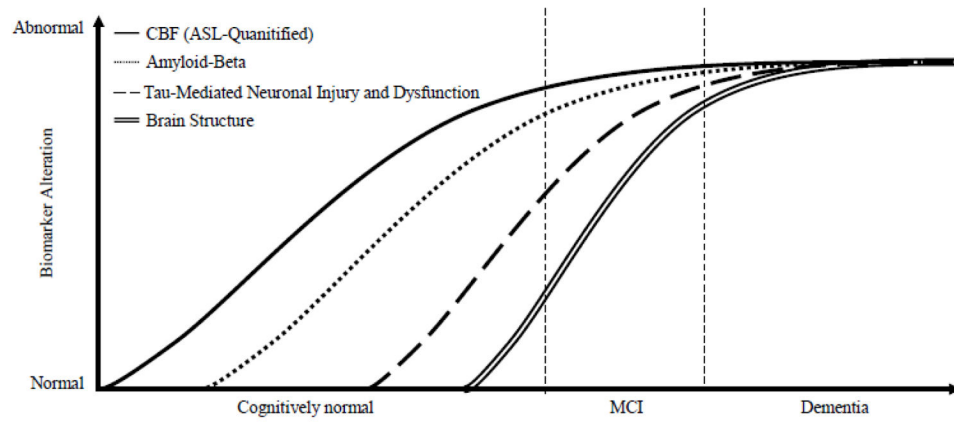


Figure 2. Hypothetical model of the temporal ordering of physiological biomarkers of AD. This figure is adapted from [2] to include early alterations in CBF in the sequence of biomarkers across the continuum from normal aging to MCI to AD. Direction of CBF alteration is not specified because, as reviewed here, both hyper and hypoperfusion reflect abnormality in different stages of cognitive decline.