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Regional Cerebral Blood Flow Changes in Healthy Ageing and Alzheimer's Disease: A Narrative Review

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Abstract
Background: Cerebral blood flow is known to decline with increasing age and is a potential biomarker to distinguish between healthy and unhealthy ageing, where healthy ageing is defined as an absence of comorbidities in senescence. This review aims to synthesize evidence of cerebral blood flow changes over multiple brain regions, for use as a clinical reference or for in silico modelling. ***Summary:*** The search identified 1,087 studies, of which 33 met the inclusion criteria to map the difference in cerebral blood flow reduction between healthy ageing and Alzheimer's disease. Analysis was also performed on the effect of imaging modality and brain region functionality as potential confounding factors. ***Key Messages:*** No significant difference was found between the specific functionality of a brain region and cerebral blood flow in healthy ageing ($p = 0.65$) or Alzheimer's disease ($p = 0.42$). Arterial spin labelling MRI imaging was shown to measure statistically larger decreases in flow in both healthy ageing ($p = 0.0001$) and Alzheimer's disease ($p = 0.0465$). Cerebral blood flow was shown to decrease 0.3–0.5% per year in healthy ageing, which increased to a decline of 2–5% per year in Alzheimer's disease. There was large variability both between and within individual brain regions, and this variability increased greatly in Alzheimer's disease. Future studies would add value by taking more cerebral blood flow measurements during Alzheimer's disease progression and by investigating ageing with comorbidities such as hypertension.

Introduction

Cerebral blood flow (CBF) is the primary method of oxygen and glucose delivery to the human brain. The inability of the brain to store these key resources in significant quantities leads to a tightly controlled autoregulation system which is critical to maintaining brain functionality and overall health [1]. The brain consumes 20% of the total oxygen in the body and 25% of the total glucose despite representing just 2% of the body's mass [2]. Even a brief disruption to this system can result in cell death and longer term cognitive disability [3].

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As the average age of the global population continues to rise, more and more people thus live with impaired brain functionality. Over 32% of people over the age of 85 years live with dementia [4], and the number of people living with dementia is expected to double in the UK to 3.2 million people by 2040 [5]. Dementia is the leading cause of death in the UK, and the cost of care continues to rise both as a percentage of the health service's budget and in terms of unpaid care given by family members and friends. In 2019, dementia was estimated to cost over GBP 4.9 billion to the UK economy [6].The vascular hypothesis for Alzheimer's disease (AD), the most common cause of dementia, is now well documented [7]. Therefore, understanding how CBF changes with age in both healthy ageing (defined as an absence of comorbidities in senescence) and AD is critical in understanding the development of this disease to both identify early onset and potentially to develop new biomarkers to target treatments.

The decrease in CBF with ageing is already well documented in the literature. A variety of imaging methods using nuclear medicine, X-ray computed tomography, and magnetic resonance imaging (MRI) document this decrease across various regions of the brain [8]. However, there is large variability in results, and there are many ways of presenting data which makes comparisons difficult. These methods of presentation include raw CBF measurements, regression scores, and highlighting of the brain regions with the largest CBF change. The regions with the greatest CBF decrease are generally the frontal and parietal lobes [9]. However, this does not give an overall picture of CBF change region by region, or an acceptable magnitude range for healthy ageing and AD.

As CBF is a property that can be easily measured in vivo, it is important to have accurate numerical values for as much of the brain volume as possible. This is due to the potential of CBF as an input for in silico models [10] at scales which cannot currently be imaged easily, or as a biomarker for early onset of neurodegenerative disease [11]. Therefore, the aim of this review was to address three research questions:

1. How does CBF vary regionally with ageing within the brain?
2. Do the confounding factors of functionality of brain region and imaging modality have an effect on CBF decrease in ageing?
3. Does the change in CBF with ageing vary between healthy ageing and AD?

By quantifying the answers to these questions based on the available literature, the use of CBF as a biomarker for ageing and neurodegenerative disease can be better assessed. It will also give further understanding to the variability seen in the literature between patients, imaging modalities, and individual studies.

Methods

Study Selection

This review was performed from a PubMed search of "regional cerebral blood flow ageing" from 1 January 1965 to 15 September 2020. Additional studies were identified through hand search of references cited in relevant reviews which appeared in the PubMed search. Only English language studies were sought. One researcher identified potentially relevant articles by initial screening of the titles and abstracts. Full texts were then retrieved and screened by the same researcher to identify articles for inclusion for the review. Any uncertainties were discussed with other members of the research team (flowchart of literature search can be found in online suppl. Fig. 1; see www.karger.com/doi/10.1159/000524797 for all online suppl. material).

Eligibility Criteria

The focus for this review was entirely on healthy ageing and AD in humans. Studies were included if they measured regional CBF (rCBF) in multiple brain regions across a range of ages to calculate the effect of ageing on rCBF. Studies were only included that mapped the ageing process of individuals reaching >60 years. Both longitudinal and cross-sectional studies were included.

Studies which modified the patient state through ingestion of substances or external stimuli were not considered. Studies focussed on non-human species as well as those human patients with other underlying comorbidities (such as diabetes) were also excluded. In addition, studies were not considered where the data were not presented in a way that allowed for extraction of a percentage change in rCBF per year figure.

The neuropsychological tests used to determine patients were also recorded (see online suppl. Table 2). These were not considered as exclusion criteria due to limited available relevant studies for inclusion. The similarity of tests performed and clinical standards used across separate studies to determine healthy ageing and AD diagnosis suggest comparison between the data from these studies is valid.

Data Extraction

Data were found to be presented in the selected studies in one of two ways: a linear regression coefficient specifying the percentage change in rCBF per year or two discrete data points at different average ages. The latter can be converted to a percentage change and then directly compared to the regression coefficients. The use of a fractional change in CBF per year was intended to remove uncertainty around the baseline measurements, due to variability between individuals and through other confounding factors.

There are many different imaging techniques used to measure the rCBF in vivo, and all of these were considered with the method for each selected study noted. For methods where brain diagrams were used to show the locations of sensors on the surface of the scalp, these were compared to a clinical brain diagram and the subsequent regions labelled [12]. All data points from all studies were

included with the name of the brain region measured taken from the source study.

Patient characteristics were also screened for in this review. Only studies with representative gender balances and no abnormal characteristics on initial scans were chosen. The number of patients in each study was noted. The difference in age between the two sets of patients was also recorded in the case of discrete rCBF measurements.

Data Analysis

The data from the study selection contained many different designations for the same spatial location in the brain. These were then compared across studies, and identical regions with different nomenclature were combined. We took regions identified in each study as stated, and the final regional classification is shown in the results. In order to maximize the number of measurements, measurements from regions which were found to be a subset of a final brain region were included as part of the final brain region measurement. The results with these subsets excluded are not shown here as they were found to cause minimal difference in overall region mean and variance. For each individual brain region, a mean weighted by the number of patients in each study and a 95% confidence interval (CI) for the measurements was calculated using the bootstrap method, resampling 500 times.

The purpose of this review is also to group brain regions by functionality. The classification is made to divide the cerebral structure into association regions responsible for complex processing tasks, sensory regions that receive information, and motor regions which control and execute movement [13]. For each region found in a selected study, a definition is found from the study where the measurement was taken and an assessment made into which of these three primary groups its functionality falls. Measurements of whole brain, white matter, and grey matter CBF are kept separate for comparison. These were checked with specific brain maps from Gray's Anatomy and the clustering of functionality can be assumed to be roughly based on regions within the brain [14].

Statistical testing was performed to assess the difference in CBF decrease in different brain region functionalities and with different imaging modalities, as well as the interactions between these two factors. These were performed on the dataset for brain regions where at least three measurements in the literature were found. This was done in order to understand if

1. the difference in the CBF decrease per year in association, sensory, and motor regions was statistically significant
2. the difference in the CBF decrease per year measured with Xe-133 inhalation, positron emission tomography (PET), single photon emission computed tomography (SPECT), and arterial spin labelling magnetic resonance imaging (ASL MRI) was statistically significant
3. the confounding factors of imaging modality and region functionality have interaction effects
4. the difference in the CBF decrease per year between healthy ageing and AD was significant

Simple one-way and two-way ANOVA was suggested, but the CBF decreases per year data do not satisfy the assumptions of normality or homogeneity of variance (AD set). Instead, the non-parametric Kruskal-Wallis test was used to assess the individual effects of functionality and imaging modality. This is considered invalid to assess the interaction effects as the test functions using data ranks. Therefore, two-way ANOVA was also carried out on the data as there is evidence in the literature of robustness of this test to violations of the normality assumption [15].

The data were also normalized, and then one-way and two-way ANOVA were carried out. As the data are all negative, a constant of 1 was added to all the data and the natural logarithm then taken. After this transform, the data still did not satisfy assumptions of normality. The data were then normalized by z-score to satisfy normality assumption and one-way and two-way ANOVA was performed, with results compared to those from the non-parametric tests.

To assess significant differences between groups, the Tukey HSD post hoc test was used. All calculations were performed using MATLAB.

Results

In total, there were 1,087 publications identified through the PubMed search and additional screening process. A total of 114 studies were selected for full-text review and 33 met all the criteria to be included in the study.

Of these studies, 21 researched healthy ageing and 11 researched AD, with one study containing measurements for both AD and healthy patients. These studies included a total of 1,452 patients. In terms of study structure, 13 were longitudinal and 20 were cross-sectional.

Characteristics of the Included Studies

The 33 included studies are shown in Table 1. The methods of CBF measurement in the included studies are as follows: Xe-133, PET, SPECT, and ASL MRI. The final studies comprise 5 Xe-133, 10 PET, 9 SPECT, and 9 ASL MRI studies. In Table 1, the difference between the mean values of each cohort (if there are multiple cohorts) is recorded, and longitudinal studies are denoted without an age difference with the mean age of longitudinal cohort in brackets.

Summary of rCBF with Ageing

Forty brain regions were identified as key areas of interest and each of these are plotted in groups sorted by functionality, with an individual point representing a study measurement. Forty regions were found to be the number of regions which were present in the selected studies to cover the entire brain volume with minimal overlap. Within each functional section, the regions are listed in order of brain regions matching the entire brain regions list in online supplementary Table 1. Online supplementary Table 1 also contains a summary of the classification of each brain region with a clinical definition.

Table 1. Characteristics of included studies

H/AD	Study	Year	Sample	Imaging modality	Age difference (mean age)
H	Naritomi et al. [42]	1979	46	Xe-133 inhalation	– (52)
H	Melamed et al. [43]	1980	44	Xe-133 inhalation	– (42)
H	Zemcov et al. [44]	1984	33	Xe-133 inhalation	– (45)
H	Pantano et al. [45]	1984	27	PET	25
H	Tachibana et al. [46]	1984	20	SPECT	– (56)
H	Tsuda and Hartmann [47]	1989	30	Xe-133 inhalation	37
H	Hagstadius and Risberg [48]	1989	97	Xe-133 inhalation	– (42)
H	Leenders et al. [49]	1990	34	PET	– (45)
H	Martin et al. [50]	1991	30	PET	– (62)
H	Waldemar et al. [51]	1991	21	SPECT	33
H	Claus et al. [52]	1998	35	SPECT	15
H	Krausz et al. [53]	1998	27	SPECT	– (49)
H	Meltzer et al. [54]	2000	27	PET	– (56)
H	Larsson et al. [55]	2001	24	SPECT	48
H	Giovacchini et al. [14]	2004	15	PET	38
H	Chen et al. [56]	2011	75	ASL MRI	21
H	Santos-Galduróz et al. [57]	2012	77	SPECT	39
H	Aanerud et al. [58]	2012	40	PET	20
H	Zimmerman et al. [59]	2014	55	ASL MRI	– (69)
H	De-Vis et al. [60]	2015	46	ASL MRI	38
H	Zhang et al. [61]	2018	30	ASL MRI	– (46)
H & AD	Beason-Held et al. [62]	2013	99 & 22	PET	– (69)
AD	Amano et al. [63]	1982	15	SPECT	4
AD	Eberling et al. [64]	1992	52	SPECT	5
AD	Ishii et al. [65]	1997	28	PET	3
AD	Ishii et al. [66]	1998	26	PET	3
AD	Huang et al. [67]	2007	39	SPECT	– (62)
AD	Firbank et al. [68]	2011	46	ASL MRI	3
AD	Mak et al. [69]	2012	28	ASL MRI	5
AD	Alexopoulos et al. [70]	2012	43	ASL MRI	3
AD	Codispoti et al. [71]	2012	6	PET	7
AD	Binnewijzend et al. [72]	2016	144	ASL MRI	8
AD	Lajoie et al. [73]	2017	71	ASL MRI	3

Studies without an age difference are longitudinal, with the mean age in brackets. H, healthy; AD, Alzheimer's disease; Sample, number of patients in a study; Age diff., difference between the mean ages of cohorts in a study.

As is consistent with the literature, in Figure 1 a significant decrease in CBF with healthy ageing was seen throughout the brain with large variability between regions and within individual region measurements. As shown in Figure 2, this decrease is much larger in AD than in healthy ageing, although data on fewer regions are available for the AD dataset.

In order to summarize the data, these measurements are grouped by functionality as individual mean values and 95% CIs in Figures 3 and 4. The mean values (weighted by number of patients per study) and CIs of percentage CBF change per year are −0.37% (95% CI: −0.42, −0.32), −0.40% (95% CI: −0.46, −0.34), −0.40% (95% CI: −0.49, −0.31), and −0.34% (95% CI: −0.41, −0.27) for the entire regions, association regions, sensory regions, and motor regions, respectively, for healthy ageing and −3.2% (95% CI: −4.1, −2.3), −5.0% (95% CI: −6.2, −3.8), −2.1% (95% CI: −3.2, −1.0), and −2.2% (95% CI: −3.8, −0.6) for the entire regions, association regions, sensory regions, and motor regions, respectively, for ageing with AD.

Graphs summarizing the weighted mean and 95% CIs in each individual region can be found in online supplementary Figures 2 and 3. These illustrate the degree of variability found in the data for each individual brain region, even when summarized and weighted by patient number.

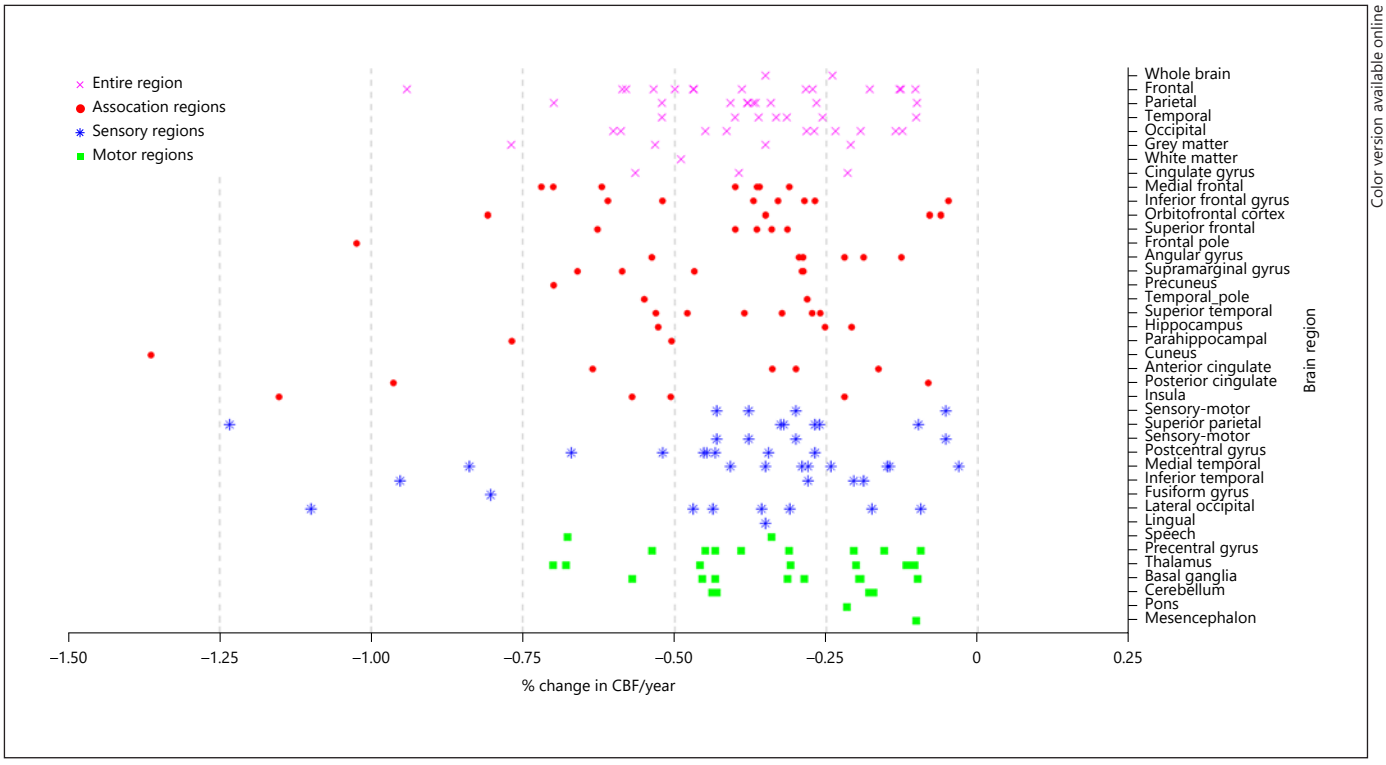

Fig. 1. Individual study results for each brain region in healthy ageing.

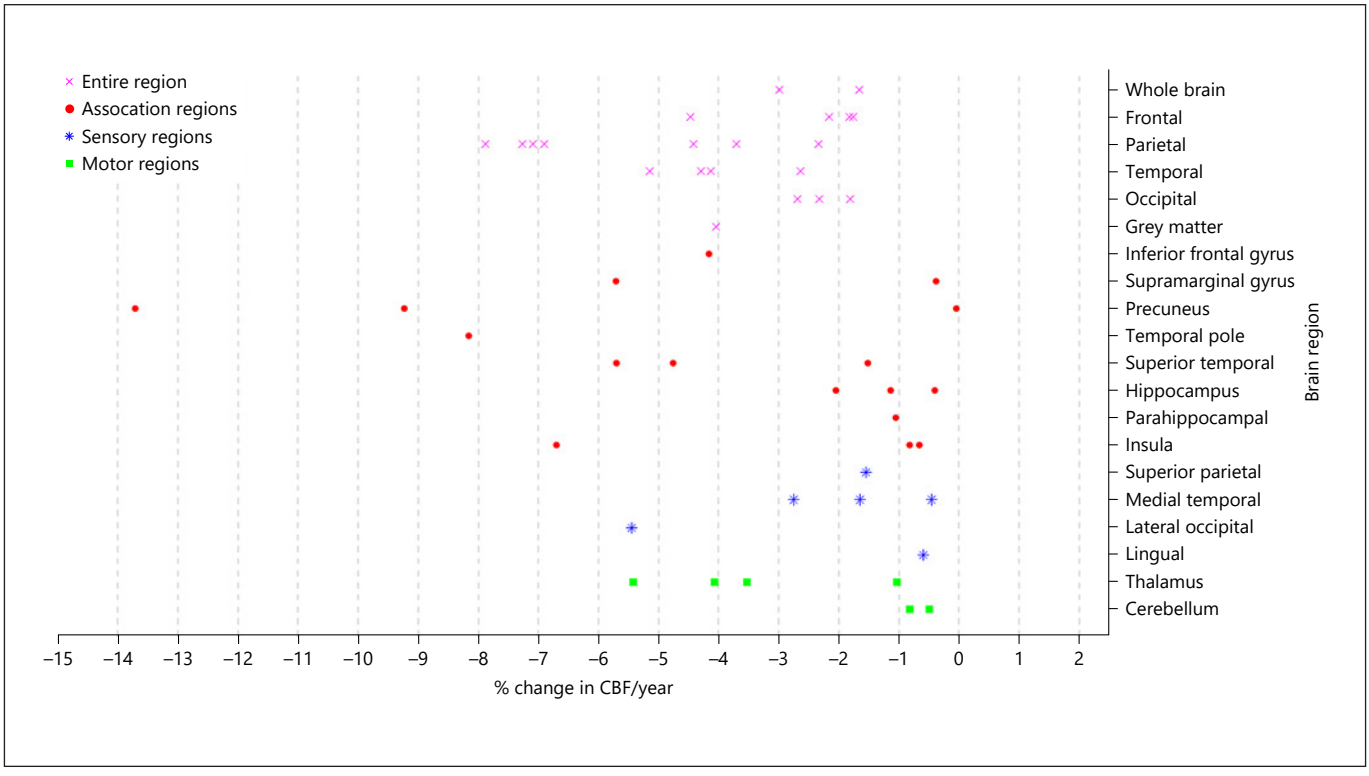

Fig. 2. Individual study results for each brain region in AD.

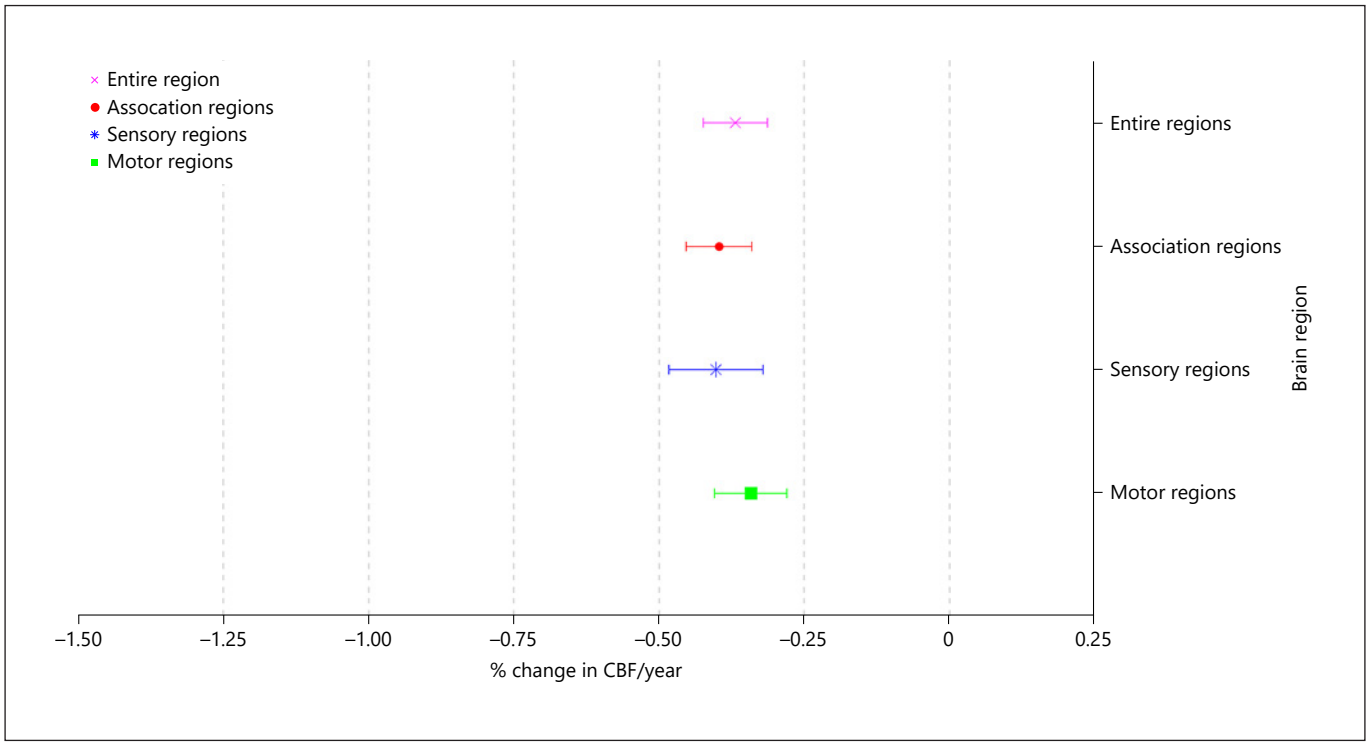

Fig. 3. Weighted summary mean and 95% CI values of CBF with healthy ageing.

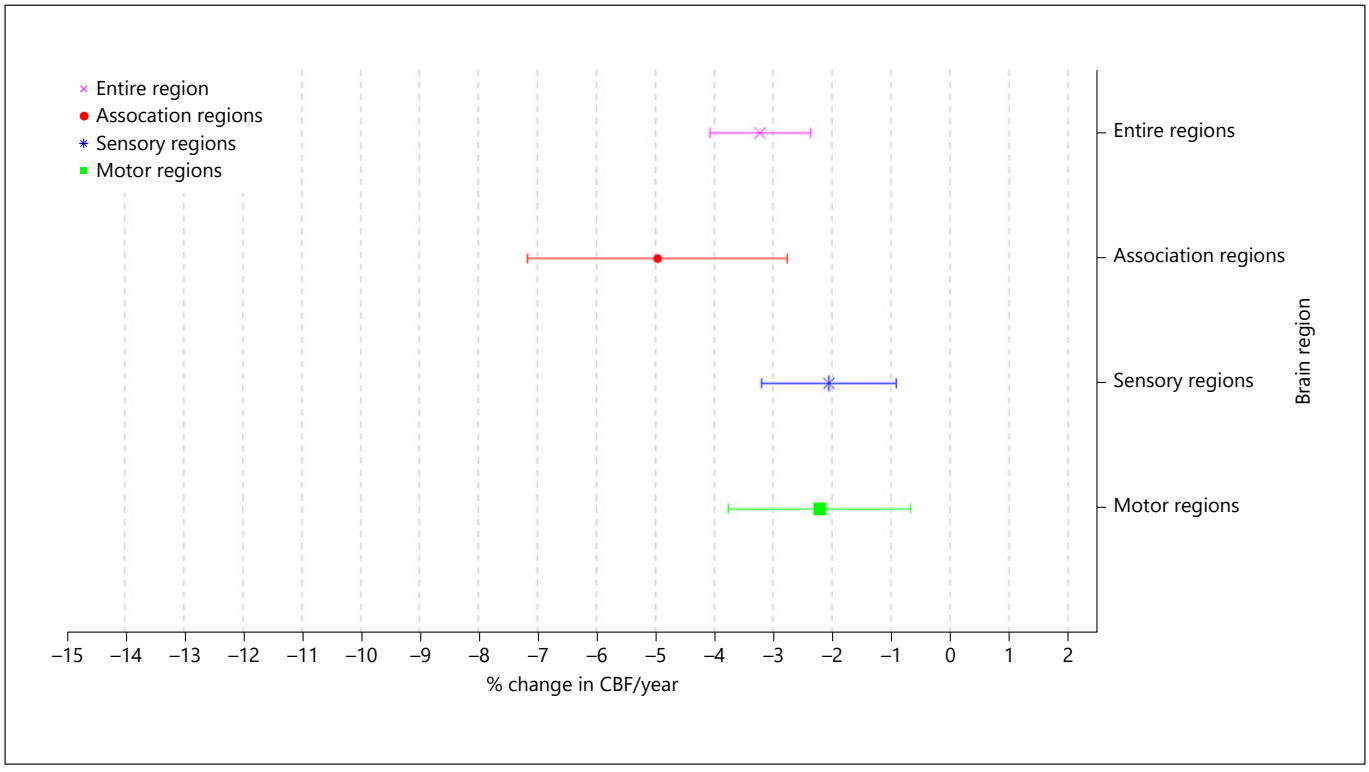

Fig. 4. Weighted summary mean and 95% CI values of CBF in AD.

Statistical Testing Results

Statistical tests were performed on this dataset without weighting by number of patients (i.e., average reduction in CBF of studies without adjusting for study cohort size). The mean values of the raw data without weighting were −0.38%, −0.39%, −0.36%, and −0.31% for the entire regions, association regions, sensory regions, and motor regions, respectively, for healthy ageing and −4.0%, −4.6%, −1.6%, and −2.2% for the entire regions, association regions, sensory regions, and motor regions, respectively, for ageing with AD. This corresponds to small differences between weighted and unweighted results for included studies.

The results for the statistical tests were consistent between the parametric and non-parametric equivalent tests that we carried out. The tests performed on the raw data using the Kruskal-Wallis test showed no significant difference in CBF decrease per year between regions with different functionality (in healthy ageing [$p = 0.65$] or AD [$p = 0.42$]); in healthy ageing, measuring CBF using ASL MRI produces significantly larger CBF decreases per year than using Xe-133 inhalation (p value = 0.0001), PET ($p = 0.0016$), SPECT ($p < 0.0001$); in AD, the decrease measured using ASL MRI is significantly larger than using PET ($p = 0.0465$) but not SPECT ($p = 0.6684$); 2-way ANOVA shows no significant interaction effects between the two confounding factors of imaging and functionality in healthy ageing ($p = 0.3101$) and AD ($p = 0.3166$); there was a significant difference ($p = <0.0001$) between CBF decrease per year in healthy ageing and AD.

The parametric tests on normalized data lead to the same conclusions of significance with moderately different p values. There is no evidence to suggest that there is a difference in CBF decrease with regional functionality, but there is evidence to suggest that imaging using ASL MRI leads to a larger measured decrease in CBF per year. There are no significant interaction effects between these two factors. The results suggest that the decrease in CBF with ageing is significantly larger in AD than in healthy ageing.

Discussion

There have been many reviews on CBF and ageing within the human brain, although none quantifies the number of regions that this work attempts to summarize. The aim of this review was to identify studies with measurements of rCBF across an age range to assess the effect of ageing on this property. This review also investigates if the brain region functionality affects CBF in ageing. The reviews available in this area generally include CBF as a subsection of their overall scope, most commonly in conjunction with cerebral vessel structure and metabolism [2, 16, 17]. Many others also summarize the effect of factors such as exercise [18–20], carbon dioxide [21], or depression [22, 23] on CBF with age. There are also reviews discussing the benefits and limitations of specific imaging methodologies such as Functional Near-Infrared Spectroscopy [24], SPECT [25, 26], PET [27–29], transcranial Doppler ultrasound [30], and both MRI and ASL MRI [19, 31]. A previous review of CBF in small vessel disease should be viewed as complementary to this work [32]. Taken together, these reviews allow for a differentiation between disease of the vascular structure (small vessel disease) and those with regional bias (AD) [33]. We focus on AD as it is the most common cause of dementia in the elderly [7].

The reduction of CBF with ageing is widely described in the literature, but there has previously been no review to summarize these results. This review attempts to synthesize the available data and analyse CBF by brain region for healthy ageing and AD. The added variable of brain region functionality yields no statistically significant results, despite the mean reduction in CBF in AD being over twice as large in association regions than in the other regions of the brain. This does suggest a possible trend, which will need to be investigated further as more data become available. However, the imaging modality used to collect the data has been shown to have an effect when ASL MRI is used, with ASL MRI consistently measuring larger CBF decreases with ageing. AD significantly exacerbates the loss in CBF per year by approximately a factor of ten compared to healthy ageing. The variability is also shown to be very large within individual region measurements and between brain regions of similar functional type.

The limitations of this review derive from the relatively small quantity of data available which were presented in a format which could be extracted as a percentage change in CBF per year. Therefore, it could not be determined whether the variability is a function of the ageing process itself, or other confounding factors. There was also variability in the age of the included participants and therefore the results captured individuals at different stages of senescence.

The studies chosen for this review also only consider "healthy" ageing populations. The idea of "healthy" ageing is complex as many older individuals have comorbidities such as hypertension and diabetes, which have a significant effect on cerebrovascular health. There is also complexity added in how healthy ageing has been defined over time, especially as AD onset has become further understood, but this is not expected to have a large effect on

measurements [34]. Furthermore, the stage of disease has not been quantified in the studies reviewed which makes it difficult to assess the difference between mild AD and progressed AD. It is also difficult to quantify what a healthy brain is due to large inter-subject variability and the effect of senescence, although here we use a specific definition of an absence of comorbidities in senescence.

The main interacting factors on CBF drop identified in this study were the imaging modality, the functional region of the brain, and variability within individuals due to relative health of patients involved in the selected studies. Investigating the first two of these showed that functionality of brain region had no significant effect on CBF decrease per year, although a non-significant trend was found for AD and association regions. By imaging method, ASL MRI was shown to have a greater measured decrease than other methods in both healthy ageing and AD. Several previous studies have shown that ASL MRI overestimates CBF magnitude versus other imaging techniques, such as PET [34–36]. However, the method in this review deliberately converts the CBF values to a fractional change to avoid this effect. It is thus surprising that this uncertainty between imaging methods persists, indicating that a degree of caution is needed when choosing an imaging modality for future experimentation or when interpreting measurements of CBF in the literature.

We decided, due to the small number of studies, to include all studies referring to AD patients, taking the latest stage measurement possible for an individual cohort. However, since AD patients have a broad continuum of health this will naturally add uncertainty in comparing measurements in AD. By comparing the neuropsychological tests used for each study, we were able to determine a relatively uniform standard applied to diagnose AD (using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria [37] and other associated tests [e.g., Mini-Mental State Examination [38], Wechsler Adult Intelligence Scale [39]]). However, many of the studies do not specify specific thresholds applied when using these tests, so some discrepancy between stages of AD will remain.

The timescale for the AD reviews spans an average of 4.6 years versus 31.4 years for cross-sectional studies in the healthy ageing reviews. The shorter timescale in analysis of AD CBF decrease per year may contribute to some of the extreme decreases seen in this case when calculating the percentage change. There was considerably less available data for the AD brain than in healthy ageing (46 measurements in regions with at least 3 data points vs. 160 measurements in healthy ageing), and therefore, we decided to include all these studies to maximize the robustness of the statistical results.

The resting CBF measured in these studies could also be considered in conjunction with the known atrophy of the brain in ageing as the smaller volume might simply require a lower glucose metabolism and supply of oxygen [40, 41]. We do not correct for atrophy in this review as this was not consistently performed through the available studies, and therefore we used non-corrected data for consistency. In addition, the resting CBF value does not capture the ability of the brain to respond to everyday events such as exercise, change in blood oxygen levels, and other physiological changes. Further explanation of the similarities and difference between how these quantities change with ageing in comparison to resting CBF will further clarify the use of CBF measurements in both clinical practice and in in silico modelling.

This review clearly shows a strong negative correlation between ageing and reduction in CBF. The gradient of the CBF decrease increases greatly with the onset of AD. Future work should identify how early this increased gradient is noticeable and whether the trend is linear through the ageing process. As more data become available to map the reduction of CBF with AD, reinvestigating the correlation with functional region and imaging modality will provide more nuanced findings. Overall, however, we found that altered CBF has the potential to be a biomarker for early neurodegeneration, with the promise of identifying "unhealthy" brain ageing before the cognitive function of the individual is affected.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Barnaby J. Graff conducted the review of the material, collation of evidence, analysis, and writing; Wahbi K. El-Bouri and Stephen J. Payne designed and supervised the research and revised the manuscript; Stephanie L. Harrison contributed to the revision and modification of the manuscript.

References

1 Payne SJ. Cerebral blood flow and metabolism: a quantitative approach; 2017. Epub ahead of print 2017.
2 Nagata K, Yamazaki T, Takano D, Maeda T, Fujimaki Y, Nakase T, et al. Cerebral circulation in aging. Ageing Res Rev. 2016 Sep;30:49–60.
3 Gale SD, Hopkins RO. Effects of hypoxia on the rain: neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. J Int Neuropsychol Soc. 2004 Jan;10(1):60–71.
4 Hebert LE, Weuve J, Scherr PA, Evans DA . Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology. 2013 May 7;80(19):1778–83.
5 Storey A. Living longer: how our population is changing and why it matters. Office for National Statistics. 2018 Aug.
6 Wittenberg R, Hu B, Barraza-Araiza LF, Rehill A. Projections of older people with dementia and costs of dementia care in the United Kingdom, 2019–2040. Care Policy and Evaluation Centre. 2019 Nov.
7 Tublin JM, Adelstein JM, del Monte F, Combs CK, Wold LE. Getting to the heart of Alzheimer disease. Circ Res. 2019 Jan 4;124(1):142–9.
8 Griffiths PD, Hoggard N, Dannels WR, Wilkinson ID. In vivo measurement of cerebral blood flow: a review of methods and applications. Vasc Med. 2001;6(1):51–60.
9 Simons J, Collerton D. Dementia and the brain. Alzheimer's Society; 2014.
10 Graff BJ, El-Bouri WK, Payne SJ. The ageing brain: investigating the role of age in changes to the human cerebral microvasculature with an in-silico model. Front Aging Neurosci. 2021 Aug 5;13:632521. VPH2020 Conference.
11 Kantarci K, Jack CR. Neuroimaging in Alzheimer disease: an evidence-based review. Neuroimaging Clin N Am. 2003 May;13(2):197–209.
12 Gray H, Lewis WH. Gray's anatomy of the human body. New York, NY; 2000.
13 Friston KJ, Frith C, Dolan RJ, Price C, Zeki S, Ashburner J, et al. Human brain function. 2nd ed. Burlington: Elsevier Science; 2004.
14 Giovacchini G, Lerner A, Toczek MT, Fraser C, Ma K, DeMar JC, et al. Brain incorporation of 11C-arachidonic acid, blood volume, and blood flow in healthy aging: a study with partial-volume correction. J Nucl Med. 2004 Sep;45(9):1471–9.
15 Schmider E, Ziegler M, Danay E, Beyer L. Is it really robust?: reinvestigating the robustness of ANOVA against violations of the normal distribution assumption. Methodology. 2010 Jan;6(4):15–147.
16 Deture MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener. 2019 Aug 2;14(1):32.
17 Riddle DR, Sonntag WE, Lichtenwalner RJ. Microvascular plasticity in aging. Ageing Res Rev. 2003 Apr;2(2):149–68.
18 Tarumi T, Zhang R. Cerebral blood flow in normal aging adults: cardiovascular determinants, clinical implications, and aerobic fitness. J Neurochem. 2018 Mar;144(5):595–608.
19 Haeger A, Costa AS, Schulz JB, Reetz K. Cerebral changes improved by physical activity during cognitive decline: a systematic review on MRI studies. Neuroimage Clin. 2019;23:101933.
20 Veronese N, Solmi M, Basso C, Smith L, Soysal P. Role of physical activity in ameliorating neuropsychiatric symptoms in Alzheimer disease: a narrative review. Int J Geriatr Psychiatry. 2019 Sep;34(9):1316–25.
21 Reich T, Rusinek H. Cerebral cortical and white matter reactivity to carbon dioxide. Stroke. 1989 Apr;20(4):453–7.
22 Chen ZQ, Du MY, Zhao YJ, Huang XQ, Li J, Lui S, et al. Voxel-wise meta-analyses of brain blood flow and local synchrony abnormalities in medication-free patients with major depressive disorder. J Psychiatry Neurosci. 2015 Nov;40(6):401–11.
23 Li W, Chen Z, Wu M, Zhu H, Gu L, Zhao Y, et al. Characterization of brain blood flow and the amplitude of low-frequency fluctuations in major depressive disorder: a multimodal meta-analysis. J Affect Disord. 2017 Mar 1;210:303–11.
24 Yeung MK, Chan AS. A systematic review of the application of functional near-infrared spectroscopy to the study of cerebral hemodynamics in healthy aging. Neuropsychol Rev. 2021 Mar;31(1):139–66.
25 Waldemar G. Functional brain imaging with SPECT in normal aging and dementia: methodological, pathophysiological, and diagnostic aspects. Cerebrovasc Brain Metab Rev. 1995 Summer;7(2):89–130.
26 Pagani M, Salmaso D, Borbely K. Optimisation of statistical methodologies for a better diagnosis of neurological and psychiatric disorders by means of SPECT. Nucl Med Rev Cent East Eur. 2005;8(2):140–9.
27 Ito H, Kanno I, Fukuda H. Human cerebral circulation: positron emission tomography studies. Ann Nucl Med. 2005 Apr;19(2):65–74.
28 Gerasimou G, Bostantjopoulou S, Gotzamani-Psarrakou A. Molecular imaging of cerebral blood flow and metabolism with SPET and PET in principal dementias. Hell J Nucl Med. 2009 Jan–Apr;12(1):79–83.
29 Pakrasi S, O'Brien JT. Emission tomography in dementia. Nucl Med Commun. 2005 Mar;26(3):189–96.
30 Sabayan B, Jansen S, Oleksik AM, van Osch MJ, van Buchem MA, van Vliet P, et al. Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: a meta-analysis of transcranial Doppler studies. Ageing Res Rev. 2012 Apr;11(2):271–7.
31 Veldsman M, Cumming T, Brodtmann A. Beyond BOLD: optimizing functional imaging in stroke populations. Hum Brain Mapp. 2015 Apr;36(4):1620–36.
32 Shi Y, Thrippleton MJ, Makin SD, Marshall I, Geerlings MI, de Craen AJM, et al. Cerebral blood flow in small vessel disease: a systematic review and meta-analysis. J Cereb Blood Flow Metab. 2016 Oct;36(10):1653–67.
33 Haroutunian V, Katsel P, Schmeidler J. Transcriptional vulnerability of brain regions in Alzheimer's disease and dementia. Neurobiol Aging. 2009 Apr;30(4):561–73.
34 Bokkers RPH, Bremmer JP, van Berckel BNM, Lammertsma AA, Hendrikse J, Pluim JP, et al. Arterial spin labeling perfusion MRI at multiple delay times: a correlative study with H(2)15(O) positron emission tomography in patients with symptomatic carotid artery occlusion. J Cereb Blood Flow Metab. 2010 Jan;30(1):222–9.
35 Kimura H, Kado H, Koshimoto Y, Tsuchida T, Yonekura Y, Itoh H. Multislice continuous arterial spin-labeled perfusion MRI in patients with chronic occlusive cerebrovascular disease: a correlative study with CO 2 PET validation. J Magn Reson Imaging. 2005 Aug;22(2):189–98.
36 Ye FQ, Berman KF, Ellmore T, Esposito G, van Horn JD, Yang Y, et al. H215O PET validation of steady-state arterial spin tagging cerebral blood flow measurements in humans. Magn Reson Med. 2000 Sep;44(3):450–6.
37 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology. 1984 Jul;34(7):939–44.
38 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189–98.
39 Wechsler D. Manual for the Wechsler adult intelligence scale: revised. Psychological Corporation; 1981.
40 Ibáñez V, Pietrini P, Furey ML, Alexander GE, Millet P, Bokde AL, et al. Resting state brain glucose metabolism is not reduced in normotensive healthy men during aging, after correction for brain atrophy. Brain Res Bull. 2004 Mar 15;63(2):147–54.
41 Yoshii F, Barker WW, Chang JY, Loewenstein D, Apicella A, Smith D, et al. Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy, and cerebrovascular risk factors. J Cereb Blood Flow Metab. 1988 Oct;8(5):654–61.

42 Naritomi H, Meyer JS, Sakai F, Yamaguchi F, Shaw T. Effects of advancing age on regional cerebral blood flow: studies in normal subjects and subjects with risk factors for atherothrombotic stroke. Arch Neurol. 1979 Jul; 36(7):410–6.
43 Melamed E, Lavy S, Bentin S, Cooper G, Rinot Y. Reduction in regional cerebral blood flow during normal aging in man. Stroke. 1980 Jan–Feb;11(1):31–5.
44 Zemcov A, Barclay L, Blass JP. Regional decline of cerebral blood flow with age in cognitively intact subjects. Neurobiol Aging. 1984 Spring;5(1):1–6.
45 Pantano P, Baron JC, Lebrun-Grandié P, Duquesnoy N, Bousser MG, Comar D. Regional cerebral blood flow and oxygen consumption in human aging. Stroke. 1984 Jul–Aug;15(4):635–41.
46 Tachibana H, Meyer JS, Okayasu H, Kandula P. Changing topographic patterns of human cerebral blood flow with age measured by xenon CT. AJR Am J Roentgenol. 1984 May; 142(5):1027–34.
47 Tsuda Y, Hartmann A. Changes in hyperfrontality of cerebral blood flow and carbon dioxide reactivity with age. Stroke. 1989 Dec; 20(12):1667–73.
48 Hagstadius S, Risberg J. Regional cerebral blood flow characteristics and variations with age in resting normal subjects. Brain Cogn. 1989 May;10(1):28–43.
49 Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJ, et al. Cerebral blood flow, blood volume and oxygen utilization: normal values and effect of age. Brain. 1990 Feb;113(Pt 1):27–47.
50 Martin AJ, Friston KJ, Colebatch JG, Frackowiak RS. Decreases in regional cerebral blood flow with normal aging. J Cereb Blood Flow Metab. 1991 Jul;11(4):684–9.
51 Waldemar G, Hasselbalch SG, Andersen AR, Delecluse F, Petersen P, Johnsen A, et al. 99mTc-d,l-HMPAO and SPECT of the brain in normal aging. J Cereb Blood Flow Metab. 1991 May;11(3):508–21.
52 Claus JJ, Breteler MMB, Hasan D, Krenning EP, Bots ML, Grobbee DE, et al. Regional cerebral blood flow and cerebrovascular risk factors in the elderly population. Neurobiol Aging. 1998 Jan–Feb;19(1):57–64.
53 Krausz Y, Bonne O, Gorfine M, Karger H, Lerer B, Chisin R, et al. Age-related changes in brain perfusion of normal subjects detected by 99mTc-HMPAO SPECT. Neuroradiology. 1998 Jul;40(7):428–34.
54 Meltzer CC, Cantwell MN, Greer PJ, Ben-Eliezer D, Smith G, Frank G, et al. Does cerebral blood flow decline in healthy aging? A PET study with partial-volume correction. J Nucl Med. 2000 Nov;41(11):1842–8.
55 Larsson A, Skoog I, Aevarsson O, Arlig A, Jacobsson L, Larsson L, et al. Regional cerebral blood flow in normal individuals aged 40, 75 and 88 years studied by 99tcm-d, l-hmpao spet. Nucl Med Commun. 2001 Jul;22(7): 741–6.
56 Chen JJ, Rosas HD, Salat DH. Age-associated reductions in cerebral blood flow are independent from regional atrophy. Neuroimage. 2011 Mar 15;55(2):468–78.
57 Santos-Galduróz RF, Bueno OFA, Yamaga LI, Armani F, Galduróz JC. Influence of blood viscosity to cerebral blood flow in older humans compared to young subjects. Clin Neurophysiol. 2012 Jan;123(1):117–20.
58 Aanerud J, Borghammer P, Chakravarty MM, Vang K, Rodell AB, Jónsdottir KY, et al. Brain energy metabolism and blood flow differences in healthy aging. J Cereb Blood Flow Metab. 2012 Jul;32(7):1177–87.
59 Zimmerman B, Sutton BP, Low KA, Fletcher MA, Tan CH, Schneider-Garces N, et al. Cardiorespiratory fitness mediates the effects of aging on cerebral blood flow. Front Aging Neurosci. 2014 Apr 7;6:59.
60 de Vis JB, Hendrikse J, Bhogal A, Adams A, Kappelle LJ, Petersen ET. Age-related changes in brain hemodynamics; a calibrated MRI study. Hum Brain Mapp. 2015 Oct;36(10): 3973–87.
61 Zhang N, Gordon ML, Ma Y, Chi B, Gomar JJ, Peng S, et al. The age-related perfusion pattern measured with arterial spin labeling MRI in healthy subjects. Front Aging Neurosci. 2018 Jul 17;10:214.
62 Beason-Held LL, Goh JO, An Y, Kraut MA, O'Brien RJ, Ferrucci L, et al. Changes in brain function occur years before the onset of cognitive impairment. J Neurosci. 2013 Nov 13; 33(46):18008–14.
63 Amano T, Meyer JS, Okabe T, Shaw T, Mortel KF. Stable xenon ct cerebral blood flow measurements computed by a single compartment double integration model in normal aging and dementia. J Comput Assist Tomogr. 1982 Oct;6(5):923–32.
64 Eberling JL, Jagust WJ, Reed BR, Baker MG. Reduced temporal lobe blood flow in Alzheimer's disease. Neurobiol Aging. 1992 Jul–Aug;13(4):483–91.
65 Ishii K, Sasaki M, Yamaji S, Sakamoto S, Kitagaki H, Mori E. Demonstration of decreased: posterior cingulate perfusion in mild Alzheimer's disease by means of H215O positron emission tomography. Eur J Nucl Med. 1997 Jun;24(6):670–3.
66 Ishii K, Sasaki M, Yamaji S, Sakamoto S, Kitagaki H, Mori E. Paradoxical hippocampus perfusion in mild-to-moderate Alzheimer's disease. J Nucl Med. 1998 Feb;39(2): 293–8.
67 Huang C, Eidelberg D, Habeck C, Moeller J, Svensson L, Tarabula T, et al. Imaging markers of mild cognitive impairment: multivariate analysis of CBF SPECT. Neurobiol Aging. 2007 Jul;28(7):1062–9.
68 Firbank MJ, He J, Blamire AM, Singh B, Danson P, Kalaria RN, et al. Cerebral blood flow by arterial spin labeling in poststroke dementia. Neurology. 2011 Apr 26;76(17):1478–84.
69 Mak HK, Chan Q, Zhang Z, Petersen ET, Qiu D, Zhang L, et al. Quantitative assessment of cerebral hemodynamic parameters by QUASAR arterial spin labeling in Alzheimer's disease and cognitively normal elderly adults at 3-Tesla. J Alzheimers Dis. 2012;31(1):33–44.
70 Alexopoulos P, Sorg C, Förschler A, Grimmer T, Skokou M, Wohlschläger 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 Feb;262(1):69–77.
71 Codispoti KET, Beason-Held LL, Kraut MA, O'Brien RJ, Rudow G, Pletnikova O, et al. Longitudinal brain activity changes in asymptomatic Alzheimer disease. Brain Behav. 2012 May;2(3):221–30.
72 Binnewijzend MAA, Benedictus MR, Kuijer JPA, van der Flier WM, Teunissen CE, Prins ND, et al. Cerebral perfusion in the predementia stages of Alzheimer's disease. Eur Radiol. 2016 Feb;26(2):506–14.
73 Lajoie I, Nugent S, Debacker C, Dyson K, Tancredi FB, Badhwar A, et al. Application of calibrated fMRI in Alzheimer's disease. Neuroimage Clin. 2017 May 16;15:348–358.