Cerebral Blood Flow Measurements in Elderly Using Arterial Spin Labeling at 3T

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Introduction

The world's population aged 60 years or over is predicted to grow by 56% from 901 million to 1.4 billion by the year 2030 [1]. It is well known that aging is associated with impaired cognitive performance and an increased risk for developing dementia. As a result, the social challenges and the burden for healthcare systems and on society directly related to increases in the aging population will become enormous. A healthy lifestyle – consisting of a healthy diet combined with increased physical activity levels – protects against cognitive impairment [2]. Underlying mechanisms still remain unclear, but it has been considered that improving brain

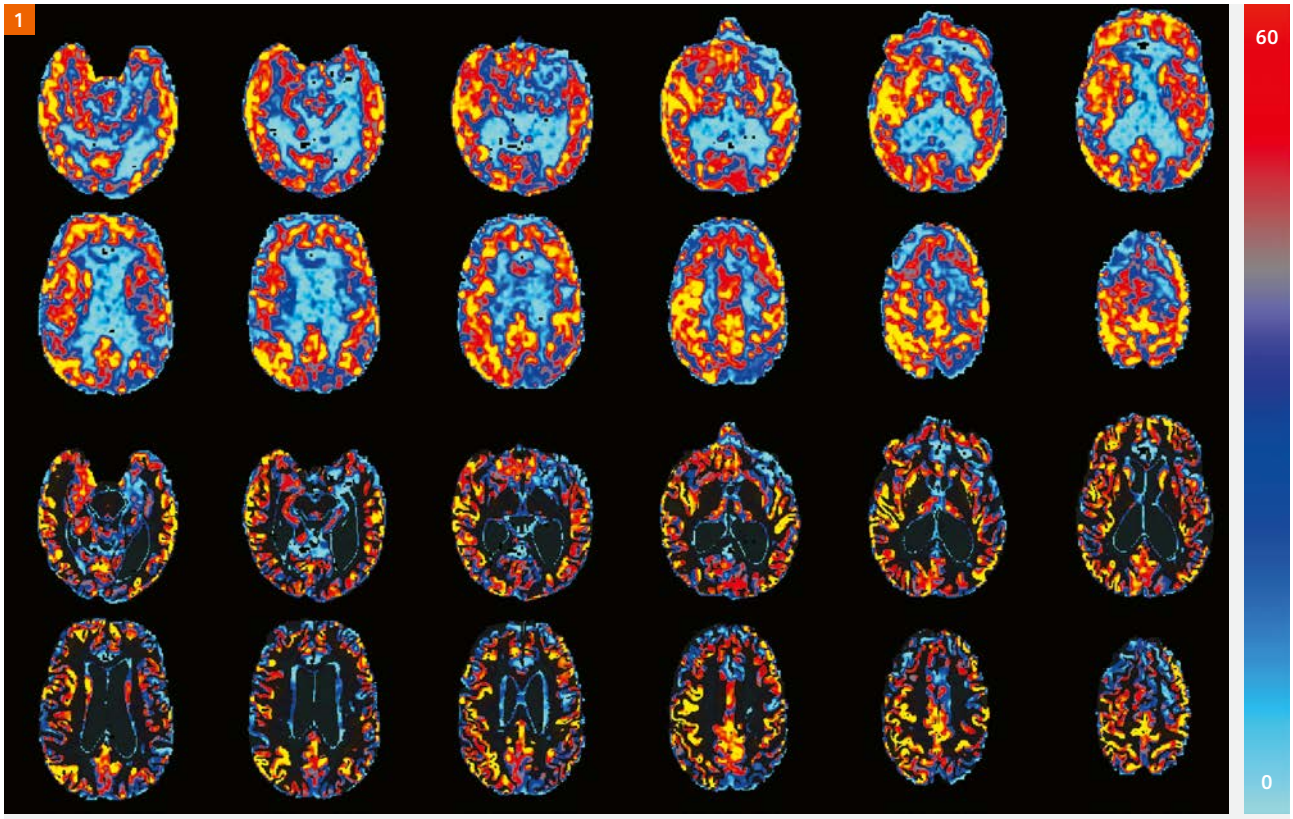

Figure 1:
Cerebral blood flow (CBF) maps showing the amount of blood flow in a particular region of the brain in mL/100 g tissue/min (scale shown by color bar). The lower two rows depict gray matter CBF, while other brain tissues are masked.

vascular health may be a key aspect [2–5]. In this respect, effects on cerebral blood flow (CBF), which is defined as a sensitive physiological marker of brain vascular health [6, 7], are of major interest because compromised vascular health in the human brain most likely precedes the development of an impaired cognitive performance [8–10]. Normal aging is associated with a progressive decline in global CBF by approximately 0.45% to 0.50% per year in middle-aged and elderly adults [3, 11, 12], and these perfusion changes are strongly associated with changes in cognitive performance and the risk to develop dementia [3, 10, 13]. Therefore, many trials have focused on middle-aged and elderly adults who are also at increased vascular risk, allowing for improvement through lifestyle-based intervention strategies. Furthermore, age-related changes in cognitive performance are mainly attributed to a decrease in gray matter CBF, which results in an suboptimal removal of metabolic waste products, and supply of oxygen and nutrients to the cerebral cortex [14]. In fact, the mean gray matter CBF was 15% lower in late middle-aged subjects suffering from metabolic syndrome compared to age-matched healthy controls, and was also associated with lower cognitive performance [15]. In addition, CBF in specific cognitive control brain regions, such as the fusiform gyrus (attention), hippocampus (memory) and prefrontal cortex (executive function), are also of major interest [16]. Furthermore, hypoperfusion in the posterior cingulate cortex and precuneus (combines attention with information from memory and perception), which are part of the default mode network that is also associated with cognitive control, has been consistently observed in subjects with decreased cognitive performance [17].

Methods for measuring CBF in humans include Positron Emission Tomography (PET) and MRI techniques, such as Dynamic Susceptibility Contrast (DSC), Dynamic Contrast Enhanced (DCE) and Arterial Spin Labeling (ASL) [3]. PET measures the amount of ^{15}O-labeled water radiotracer delivered to the brain tissue by blood flow and is considered the current gold standard approach to quantify CBF [18, 19]. However, the invasive nature, the requirement of an onsite cyclotron and large partial volume effects, which are caused by low spatial resolution, reduce the usefulness of this technique [19]. Also, DSC and DCE are invasive as they employ injections of gadolinium-based contrast agents. As a promising alternative approach, ASL enables the non-invasive assessment of CBF using magnetically-labeled water molecules in arterial blood as an endogenous tracer. The signal difference between label and control images (with and without prior labeling of the arterial blood water) can be scaled to yield highly repeatable quantitative measures of CBF [6]. In a recent systematic review, PET was compared with ASL to measure CBF. The work concluded that ASL is an appropriate alternative method for accurate and reproducible quantification of gray matter CBF [19].

In our recent review, we summarized the impact of specific dietary determinants and physical exercise on CBF, and examined the relation between these effects and potential changes in cognitive performance [3]. We concluded that these lifestyle factors may increase CBF, thereby improving cognitive performance. However, well-designed intervention studies investigating the potential of diet and exercise on CBF are still warranted. Especially, longitudinal studies involving middle-aged and elderly adults at increased vascular risk, who are also known to be at increased risk of cognitive impairment and dementia, would be of major interest [3]. Therefore, our current research at the Department of Nutrition and Movement Sciences at Maastricht University is focused on the long-term impact of specific dietary components and physical exercise on both CBF and cognitive performance. We primarily target overweight and slightly obese elderly while using ASL to quantify changes in (regional) CBF. For example, in one of our ongoing projects, we are conducting a tightly-controlled, progressive, intervention study investigating the specific effects of aerobic-based exercise training – three times a week at 70% maximal power for a total duration of eight weeks – on brain vascular health. Besides potential beneficial effects on CBF, a healthy lifestyle may also

- preserve the structural integrity of white matter,
- protect from iron accumulation and
- attenuate brain athrophy [20–23].

Therefore, fluid-attenuated inversion recovery (T2-FLAIR), R2* maps calculated from T2*-weighted gradient-echo (GRE), and T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) images are also obtained to assess structural status of the brain. These MRI-scans are used to visualize, for example, white matter signal abnormalities (T2-FLAIR), iron accumulation (R2*) and brain volume (MPRAGE). In fact, these brain changes are age-dependent, and are also associated with cognitive performance and the risk of developing dementia [24–29]. A detailed description of this trial has been provided on ClinicalTrials.gov (NCT03272061).

The purpose of this article is to demonstrate the utility of ASL for the non-invasive (region-specific) quantification of CBF in elderly, and to discuss the potential link between CBF and structural brain status (e.g. presence of white matter signal abnormalities, iron accumulation and brain athrophy).

Material and methods

Participant

During this ongoing study, multiple study participants will be scanned. Below, we present example data from one of them. The participant was a 67-year-old male with a body mass index (BMI) of 28.9 kg/m^2 without known medical complaints. He did not use medication prior to and during the study and was sedentary as assessed by the international physical activity questionnaire (IPAQ).

Data acquisition and sequence

Measurements were performed on a 3T MAGNETOM Prisma^{fit} MRI-system (Siemens Healthcare, Erlangen, Germany) using a 64-channel head-neck coil (Siemens Healthcare, Erlangen, Germany) at the Scannexus research facilities in Maastricht. The participant was placed head-first-supine in the scanner. The eye centers were taken as a reference for the magnet isocenter position, which was at the level of the pons to minimize B_0 offsets in the labeling region. Furthermore, the labeling plane was positioned perpendicular to the carotid and vertebral arteries.

Perfusion-weighted images were acquired using pseudo-continuous arterial spin labeling (PCASL)[1] with a background-suppressed 3D GRASE readout (TR 4000 ms, TE 13.6 ms, GRAPPA 2, labeling duration 1750 ms, post-labeling delay (PLD) 2000 ms and ten label-control repetitions, duration: 9 min). Nineteen slices with a voxel resolution of 3.0 mm isotropic were acquired. PCASL was used because it has a higher temporal signal-to-noise ratio (tSNR) as compared to pulsed ASL (PASL) and continuous ASL (CASL) [30]. In order to allow CBF quantification, an M_0 image without magnetization preparation and with a TR of 20 s was also acquired [31].

A prototype PCASL sequence1 from Siemens Healthcare was used which includes an optimized background suppression containing four inversion pulses, which results in a tissue signal suppression > 99% [32, 33]. This strong background suppression guarantees both a reduced influence of physiological noise and an increased CBF tSNR without compromising temporal resolution or efficiency. The latter is especially useful in frail elderly populations, who are prone to head motion.

One high-resolution anatomical MPRAGE scan was also performed (TR 2400 ms, TE 2.18 ms, TI 1040 ms, 1.0 mm isotropic resolution, 8° flip angle and 160 sagittal slices, duration 6 min). In addition, a T2-FLAIR image was acquired (TR 9000 ms, TE 89 ms, TI 2500 ms, voxel size 1.0 x 1.0 x 3.0 mm, 150° flip angle and 50 axial slices, duration 3 min). Furthermore, a GRE sequence with four echo times was obtained (TR 31 ms, TE1 2.73 ms, TE2, 7.65 ms, TE3 13.61 ms, TE4 21.86 ms, voxel size 0.9 x 0.9 x 1.0 mm, 12° flip angle and 144 axial slices, duration 5 min). The field-of-view across the various sequences was kept constant for accurate registration and anatomical localization.

Processing

A quantitative CBF map was estimated from the ASL-data using FSL software (http://fsl.fmrib.ox.ac.uk/fsl)[2]. Brain extraction, along with tissue segmentation was performed for the MPRAGE image using Volbrain [34]. First, all ASL images and the corresponding M_0 image were realigned separately employing rigid-body co-registration to the middle ASL run using the FLIRT routine to correct for motion. Next, the mean difference between label and control images was calculated. Analysis was performed following the recommendations of the ASL White Paper and using the Bayesian kinetic inference method [31, 35, 36], the BASIL tool was used and voxel-wise calibration was performed with the M_0 image. Each of the four background suppression pulse has an efficiency of 0.93, which results in a cumulative labeling efficiency of 0.64. Blood hemoglobin concentrations (ctHb) were also determined as the kinetic model inversion depends on the T1 of blood. The T1 of blood can be estimated based on the ctHb using the following equation: 1000/T1a (ms) = 0.016 x ctHb (g/dL) + 0.317 [37].
The used T1 of gray matter was 1330 ms, while for bolus arrival time 1300 ms was assumed. Spatially regularized partial volume correction was performed according to the paper of Zhao et al. [38]. As an alternative method, the CBF in each voxel could also be calculated for PCASL using the formula as proposed by Alsop et al. [31]:

$$CBF = \frac{6000 * \lambda * (SI_{control} - SI_{label}) * e^{\frac{PLD}{T1_{blood}}}}{2 * \alpha * T1_{blood} * SI_{PD} * (1 - e^{-\frac{\tau}{T1_{blood}}})} \quad \left(\frac{mL}{100\ g\ tissue/min}\right)$$

Where λ is the brain/blood partition coefficient in mL/g, $SI_{control}$ and SI_{label} are the time-averaged signal intensities in the control and label images respectively, $T1_{blood}$ is the longitudinal relaxation time of blood in seconds, α is the labeling efficiency, SI_{PD} is the signal intensity of a proton density weighted image, and τ is the label duration [31].

[1] *WIP, the product is currently under development and is not for sale in the US and in other countries. Its future availability cannot be ensured.*

[2] *The information shown herein refers to products of 3rd party manufacturers and thus are in their regulatory responsibility. Please contact the 3rd pary manufacturer for further information.*

The final ASL image containing CBF values in mL/100 g tissue/min was co-registered using affine transformation to the brain extracted MPRAGE image using the FLIRT routine. The mean gray matter CBF was calculated by taking the mean CBF over the gray matter mask (with a threshold of 0.6). The regional gray matter CBF was calculated using the Oxford-Harvard atlas, which was co-registered using the affine transformation matrix from the Montreal Neurological Institute (MNI) to MPRAGE image. T2* maps were obtained from the multi-echo GRE data using a mono-exponential fit ($f(TE) = S_0 e^{-TE/T2^*}$). In a subsequent step, all T2* values above 500 ms were set to 0 and the R2* map (= 1/T2*) was obtained. T2-FLAIR and R2* images were also co-registered to the MPRAGE image using Rigid Body Transformations (FLIRT routine).

Results and discussion

Figure 1 shows CBF maps representing the local brain perfusion, which has been quantified for each voxel in mL/100 g tissue/min. Since our main outcome is gray matter CBF, we masked the remaining brain tissues as illustrated in the lower two rows. Mean gray matter CBF has been reported to be significantly lower in apparently healthy elderly as compared to younger subjects ($n = 37$, mean age: 72.1 ± 8.7 years; 42.7 ± 8.8 mL/100 g/min vs. $n = 11$, mean age: 29.3 ± 5.3 years; 52.6 ± 9.3 mL/100 g/min) [39]. The case presented in this article had a mean gray matter CBF of 28.7 mL/100 g/min (see Figure 1), which may partly be explained by his high BMI (28.9 kg/m^2) that falls in the overweight range and by his sedentary behavior. Also, regional CBF in, for example, the precuneus that is strongly dependent on age [40] was found to be significantly lower in the elderly compared to the young population (43.3 ± 11.5 mL/100 g/min vs. 51.4 ± 8.7 mL/100 g/min) [39]. The presented case showed a CBF in the precuneus region of 24.4 mL/100 g/min. Interestingly, the T2-FLAIR showed the presence of white matter signal abnormalities (Fig. 2A) that can be classified as periventricular and deep white matter hyperintensities [41]. In addition, the high R2* showed iron accumulation in deep gray matter regions (Fig. 2B), while the MPRAGE image demonstrated ventricular enlargement and brain athrophy (Fig. 2C).

White matter signal abnormalities and iron accumulation in deep gray matter areas have been associated with aging, cognitive performance and dementia [26, 27]. Age-related patterns of brain atrophy have also been linked to cognitive performance and the risk of dementia [28]. Furthermore, ventricular enlargement has been suggested to be an age-dependent risk marker for cognitive decline [42]. A potential relationship between CBF and structural brain status has been suggested. Reduced gray matter CBF may be associated with subcortical brain athrophy in the presence of white matter signal abnormalities [43], and may also relate to iron accumulation [27]. In fact, gray matter CBF was associated with white matter signal abnormalities independent of age. However, the decline of CBF with advancing age may also possibly exacerbate deterioration of white matter integrity [44–46]. Additionally, iron accumulation may plausibly reflect reduced CBF [47], due to a reduced delivery of iron binding complexes to

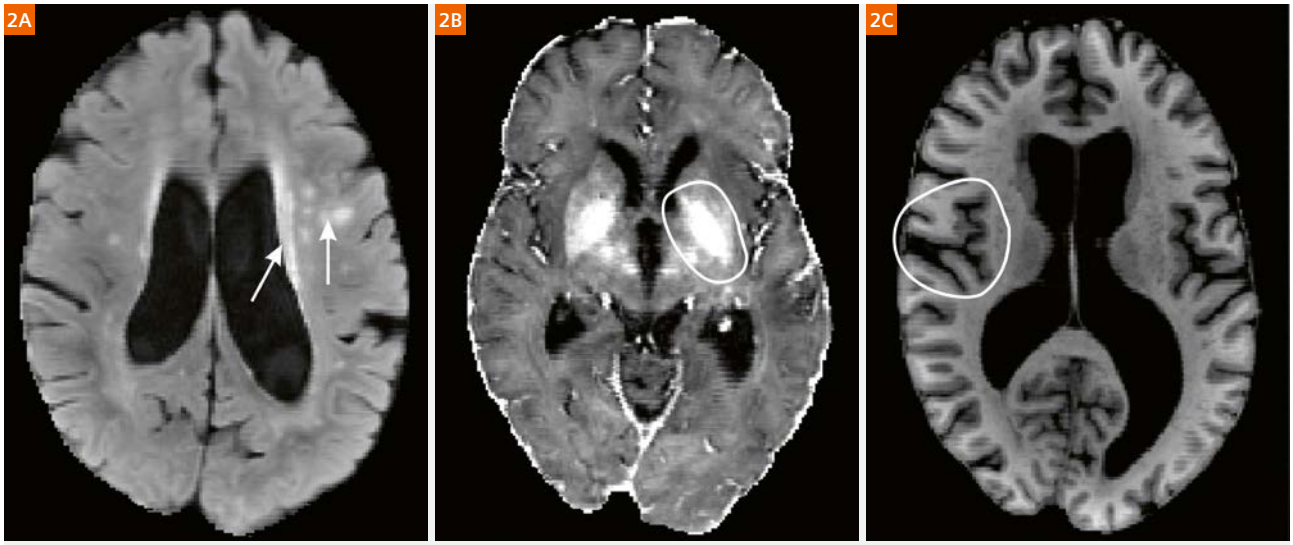

Figure 2:
(2A) T2-FLAIR, **(2B)** R2* maps calculated from T2*-weighted gradient-echo (GRE) and **(2C)** MPRAGE images showing structural brain status. White matter signal abnormalities and iron accumulation appear bright (i.e. hyperintense) on the T2-FLAIR image and the R2*-weighted gradient-echo image, respectively. The MPRAGE shows a decrease in brain volume and ventricular enlargement.

the brain [48]. In contrast, others have reported that age-associated reductions in regional CBF may be independent of concurrent age-dependent brain athrophy.

Therefore, CBF can remain unaltered in regions of brain atrophy [39]. These studies demonstrate a potential dissociation between brain atrophy and hypoperfusion specific to normal aging.

The development of the aforementioned structural brain changes is relatively slow and mostly without noticeable onset of symptoms linked to dementia. In fact, decreases in cognitive performance may be determined by the severity of these structural brain changes. Cognitive impairment may remain asymptomatic until structural brain changes have affected a significant proportion of the brain [29]. However, the causal relationship between CBF and structural brain changes still remains unclear. Therefore, innovative research investigating a potential causal relationship between lifestyle-induced structural brain changes and changes in CBF – using different MRI modalities – is urgently needed.

In conclusion, a healthy lifestyle may attenuate the age-related cognitive decline by improving CBF, which serves as a sensitive physiological marker of brain vascular health, maintaining sufficient CBF throughout the brain. Additionally, CBF can be quantified using ASL – an accurate and reproducible non-invasive MRI method – and may be associated with structural brain status assessed by T2-FLAIR, R2* maps and MPRAGE images.

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