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On the sensitivity of ASL MRI in detecting regional differences in cerebral blood flow☆

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Abstract

Arterial-spin-labeling (ASL) magnetic resonance imaging (MRI) provides a noninvasive tool to measure cerebral blood flow (CBF) and is increasingly used as a surrogate for baseline neural activity. However, the power of ASL MRI in detecting CBF differences between patient and control subjects is hampered by inter-subject variations in global CBF, which are associated with non-neural factors and may contribute to the noise in the across-group comparison. Here, we investigated the sensitivity of this technique and proposed a normalization strategy to better detect such a difference. A "model" situation was employed in which two visual stimuli (i.e. cross fixation and flashing checkerboard) were presented to two groups of subjects to mimic "control" and "patient" groups (N=7 for each group), respectively. It was found that absolute CBF (aCBF) in the occipital lobe in the checkerboard group was 26.0% greater compared to the fixation group, but the level of significance was modest (P=.03). In contrast, when normalizing the CBF with whole-brain CBF or CBF in a reference region [termed relative CBF (rCBF)], the statistical significance was improved considerably (P<.003). For voxel-based analysis, the rCBF indices correctly detected CBF differences in the occipital lobe in the across-group comparison, while aCBF failed to detect any significant cluster using the same statistical threshold. We also performed Monte Carlo simulation to confirm the experimental findings and found that the power improvement was most pronounced when signal-to-noise-ratio is moderate and the underlying CBF difference was small. The simulation also showed that, with the proposed normalization, a detection power of 80% can be achieved using a sample size of about 20. In summary, rCBF is a more sensitive index to detect small differences in CBF, rather than the much-sought-after aCBF, since it reduces data noise caused by inter-subject variations in global CBF.

Keywords: ASL MRI; Cerebral blood flow; pCASL; Sensitivity; Perfusion; Group analysis

1. Introduction

Cerebral blood flow (CBF) is a physiological parameter reflecting blood supply to the brain and is typically written in units of ml blood per 100 g tissue per min. It has been shown to be a sensitive marker for cerebrovascular diseases such as stroke, arterial stenosis and vascular dementia [1–3]. Moreover, CBF measurement has played a major role in non-invasive assessment of neural activity since it can be associated with neural activity via neurovascular coupling [4,5]. This relationship has led to the development and wide application of human brain mapping techniques using positron emission tomography (PET) or functional magnetic resonance imaging (MRI) [6–8]. More recently, much attention was received to assess baseline neural activity between patient and control subject groups, by comparing the resting CBF values [9–12]. Such applications may have great potentials in understanding disease mechanism in neurological and psychiatric disorders.

Traditionally, CBF measurement is conducted by injecting radioactively labeled tracers followed by imaging the signals using single photon emission computed tomography (SPECT) or PET [13,14]. However, the applications of these techniques in brain disorders are limited by the need of exogenous agent as well as the use of radioactive materials. Arterial spin labeling (ASL) MRI is a noninvasive technique that has the potential to provide a quantitative assessment of CBF within 5-10 minutes [15–22]. There have been

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increasing numbers of studies that use ASL MRI in comparing resting CBF between patients and controls, under the assumption that CBF is a surrogate of local neural activity. However, such efforts have encountered a few difficulties, mainly because of large inter-subject variations in CBF. These variations are due to nonneural factors such as breathing pattern, physiologic state and even consumption of caffeine [23–25], which modulate CBF in a global fashion and contribute to the sources of noise in group comparison. Therefore, it is not yet clear how sensitive ASL MRI is in detecting regional neural activity differences between patients and controls and which is the best strategy to detect such differences.

In this work, we conducted experimental measurements and numerical simulation to show that raw CBF values should be normalized against CBF of the whole-brain or a reference region before conducting regional comparison. Normalization is useful for factoring out global modulation effects, thereby increasing the sensitivity of ASL MRI in detecting regional CBF differences between two subject groups. We used a model condition in which we simulated a "patient" group by having the subjects view a flashing checkerboard and compared their CBF to that of a "control" group of subjects viewing a fixation. Group comparison was conducted on the raw CBF values (denoted as absolute CBF, aCBF) and on the CBF values normalized against whole-brain values [(denoted as relative CBF_{WB} ($rCBF_{WB}$)] or a central brain region [denoted as relative CBF_{CR}, ($rCBF_{CR}$)]. In addition, numerical simulation was conducted to confirm the experimental findings and assess the ASL detection power under typical signal-to-noise-ratio (SNR).

2. Materials and methods

2.1. Experiment

Experiments were performed on a 3T MR system (Philips Medical Systems, Best, the Netherlands) using body coil transmission and head coil reception. The protocol was approved by the Institutional Review Board. A total of 14 healthy subjects (10 males, four females; 21–54 years of age) participated in the study after informed written consent was obtained. The subjects were divided into two groups, one group (n=7, age 28.9±12.3, five males, two females) was shown a white cross and the other group (n=7, age 29.3±7.6, five males, two females) was shown a flashing checkerboard at 4 Hz, to mimic the "control" and "patient" groups, respectively. In addition, the "patient" group was also shown a white cross to serve as an intragroup control.

A balanced pseudo-continuous ASL (pCASL) sequence was used to measure CBF following previous studies by Wu et al. and Wong [26,27]. Imaging parameters for pCASL experiments were: single-shot gradient-echo Echo Planar Imaging (EPI), field of view (FOV)=240×240, matrix=80×80, voxel size=3×3 mm^2, 27 slices acquired in ascending order, slice thickness=5 mm, no gap between slices, labeling duration=1650 ms, post labeling delay=1525 ms, TR=4020 ms, TE=14 ms, SENSE factor 2.5, time interval between consecutive slice acquisitions=35.5 ms, number of controls/labels=30 pairs, RF duration=0.5 ms, pause between RF pulses=0.5 ms, labeling pulse flip angle=18°, bandwidth=2.7 kHz, echo train length=35, and scan duration 4.5 min. In addition to the pCASL scan, a time-of-flight (TOF) angiogram and a phase-contrast (PC) velocity MRI were performed to obtain aCBF values following procedures established previously [28]. The TOF angiogram was performed to visualize the internal carotid arteries (ICA) and vertebral arteries (VA) and to correctly position the PC velocity MRI slice. The imaging parameters were: TR/TE/flip angle=23 ms/3.45 ms/18°, FOV=160×160×70 mm^3, voxel size 1.0×1.0×1.5 mm^3, number of slices=47, one saturation slab of 60 mm positioned above the imaging slab to suppress the venous vessels, duration 1 min 26 s. The slice of the PC velocity MRI was oriented perpendicular to the ICA and VA and the parameters were: single slice, voxel size=0.45×0.45 mm^2, FOV=230×230 mm^2, TR/TE=20/7 ms, flip angle=15°, slice thickness=5 mm, maximum velocity encoding=80 cm/s, and scan duration=30 s.

A high-resolution T1-weighted image was also acquired with the following parameters: Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence, TR/TE=8.3 ms/3.8 ms, flip angle=12°, 160 sagittal slices, voxel size=1×1×1 mm^3, FOV=256×256×160 mm^3 and duration 4 min.

2.2. Data analysis

The pCASL control and label images were realigned using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK) and the aCBF maps were calculated based on a procedure described previously [28]. Briefly, a difference image was calculated for each pair of the control and label images. The 30 difference images were then averaged. Slice timing correction was conducted to account for different post-labeling delay times for different brain slices. From the PC velocity MRI, the total flux in the four feeding arteries (left/right internal carotid arteries, left/right vertebral arteries) was calculated, and this is the blood flow to the entire brain. The volume of the entire brain was estimated from the MPRAGE data, from which the average blood flow per unit brain mass was calculated in units of ml/100 g per minute. Next, the MPRAGE brain mask was applied to the pCASL difference images and the whole-brain averaged pCASL signal (in units of MR signal) was calculated. Comparing these two averaged values, the conversion constant between pCASL MR signal and the physiologic unit was obtained and was used to calibrate the pCASL signal for individual voxels, yielding aCBF maps. The aCBF maps were spatially normalized to the brain template of Montreal Neurological Institute (MNI). Calculation of rCBF maps was based on two different normalization methods. In the first method, aCBF of each