Reliability and reproducibility of perfusion MRI in elderly control subjects

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Introduction: Arterial spin labeling (ASL) is a non-invasive magnetic resonance imaging (MRI) technique capable of measuring cerebral blood flow (CBF) non-invasively in vivo (1). A reliable method for performing ASL would be important clinically for diagnosing and evaluating a range of pathologic disorders. Specifically, knowledge of reliability and reproducibility of ASL measurements as a function of time in healthy volunteers would be critical for comparison with longitudinal studies on patients with slowly developing pathologies such as Alzheimer's disease. Recently, such reproducibility studies were reported from several groups using different ASL schemes (2,3). In this study, we used the transfer insensitive labeling technique (TILT) pulsed ASL approach (4), which is independent of magnetization transfer effects and arterial label contamination to the perfusion measurement. The reliability and reproducibility of CBF quantification were evaluated in healthy elderly subjects over one year.

Materials and Methods: ***Subjects*:** The Institutional Review Board approved this study, and all subjects provided written informed consent before participating. 12 elderly healthy subjects (75±5 years) were scanned four times during one year with an interval of 3 months. ***Imaging*** was performed on a Philips 3.0T Achieva MR scanner (Philips Medical Systems, Best, The Netherlands), using standard body coil transmission and SENSE head coil reception. For CBF measurement, TILT images were acquired using a gradient echo single-shot EPI and TR/TE=2000/12ms, and TI of 1600ms was chosen to minimize contamination from labeled spins in blood, as previously described in Donahue et al. (5). Geometric parameters: FOV=240mm, matrix 80x80, slice thickness/gap=3mm/1mm, SENSE-factor=2. Nine slices were acquired. Each perfusion measurement consisted of 150 dynamics (75 control and 75 label images) with a scan time of approximately 5 minutes. Co-planar inversion recovery (IR) images were obtained to assist in coregistering the ASL data and for gray matter segmentation. For IR, a gradient echo EPI sequence was used with TR/TI/TE=3000/888.7/26ms. The geometry of IR was the same as for TILT except for the number of slices (22 slices for IR). Sagittal MPRAGE and double echo TSE anatomical images were also acquired. MPRAGE: TR/TE=6.8/3.1ms, flip angle =8, FOV=256mm, matrix 256x256, slice thickness=1.2mm. TSE: TR=3000ms, TE_1/TE_2=8/100ms, FOV=240mm, matrix 256x256, slice thickness=3mm. ***Data processing*:** TILT images were aligned using standard 3-D rigid body motion correction tool (FSL/FLIRT). After co-registration, the label images were subtracted from the control images to produce a CBF-weighted map. To transform the CBF-weighted data of each subject into the standard brain template produced by the Montréal Neurological Institute (MNI), a stepwise registration algorithm was used as illustrated in Fig 1. ASL to IR registration was performed using 6 degree of freedom (DOF) rigid body transformation. For both IR to TSE and TSE to MPRAGE registrations were accomplished using 7 DOF global transformation, and MPRAGE to MNI template registration used 12 DOF affine parametric transformations. Each step generated transformation matrix using FSL/FLIRT algorithm and all matrices were concatenated. The final concatenated matrix was used to transform the CBF map into MNI space. CBF was quantified in bilateral middle frontal gyrus (MFG). ***Statistics*:** The statistics was computed as described in Jahng et al. (6). The reliability was computed as an intraclass correlation coefficient (ICC), following the concept of Shrout and Fleiss (7), according to the equation: $ICC = n(\sigma_n^2 - \sigma_\varepsilon^2)/\sigma_{tot}^2$, where $\sigma_{tot}^2 = n(\sigma_n^2 - \sigma_\varepsilon^2) + k(\sigma_k^2 - \sigma_\varepsilon^2) + nk\sigma_\varepsilon^2$. σ_n^2 is the variance between subjects, σ_k^2 is the variance due to tests in each subjects, and n and k are numbers of subjects and tests, respectively. The reproducibility, expressed as within-subject variation coefficient (WSC), was computed according to the equation $WSC = k(\sigma_k^2 - \sigma_\varepsilon^2)/\sigma_{tot}^2$, and the coefficient of random noise was computed according to the equation $Noise = nk\sigma_\varepsilon^2/\sigma_{tot}^2$. As an alternative to the WSC, a coefficient of variation (CV) that equals to standard deviation/mean was also computed to estimate the reproducibility in perfusion images.

Fig 1: workflow of image coregistration.

Results and Discussion: The mean CBF value of MFG in control subject was 47.40±10.86 ml/100g/min which is consistent with the results reported from positron emission tomography (PET) gray matter CBF values (8). The reliability, reproducibility and the random noise of the mean CBF values are summarized in Tables 1 and 2. The data of 9 subjects from the first two scans were processed by 2 separate raters using the same post-processing method. Table 1 shows high reliability (ICCs > 0.96) and reproducibility (WSCs < 0.01) between the raters, indicating that the post-processing methods were effective and reliable. Table 2 shows the reliability and the reproducibility among four scans over a one year period. The reliability (ICC) decreased to 0.59~0.68 and the reproducibility (WSC) increased to approximately 0.08 and the random noise increased to greater than 0.24. Noise values were higher than WSCs overall, indicating that at a given ICC, noise is the greater contributor to fluctuations in perfusion signal rather than WSC. This indicates that the primary factor limiting reliability of CBF measurements with our ASL imaging and data processing is poor signal-to-noise ratio (SNR). Improving the SNR of ASL imaging at 3T, such as by acquiring more dynamics or by shortening TE with multi-shot readouts, can definitely increase the reliability. Nevertheless, our results underline the usefulness of ASL-TILT for longitudinal studies. It suggests this technique has potential for the study of monitoring disease progression of degenerative diseases such as Alzheimer's disease.

Table 1. The reliability, reproducibility between 2 raters in control subjects (9 subjects).

	left MFG	right MFG
ICC	0.9817	0.9630
WSC	0.0006	-0.0026
Noise	0.0177	0.0396
CV(%)	2.65	3.85

Table 2. The reliability, reproducibility between 4 scans over 1 yr in 12 control subjects

	left MFG	right MFG	Gray Matter
ICC	0.6829	0.5903	0.6799
WSC	0.0169	0.0499	0.0785
Noise	0.3000	0.3596	0.2415
CV(%)	12.20	13.70	13.90

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