*Clinical Research Report*

*Journal of* INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(9) 3788–3795

DOI: 10.1177/0300060518779716
journals.sagepub.com/home/imr
SAGE

# Test–retest reliability of perfusion of the precentral cortex and precentral subcortical white matter on three-dimensional pseudo-continuous arterial spin labeling

**Mengqi Liu[1,2], Zhiye Chen[1,2] and Lin Ma[1]**

**Abstract**

**Objective:** This study was performed to evaluate the test–retest reliability of perfusion of the cortex and subcortical white matter on three-dimensional spiral fast spin echo pseudo-continuous arterial spin labeling (3D-ASL).

**Methods:** Eight healthy subjects underwent 3D-ASL and structural imaging at the same time each day for 1 week. ASL data acquisition was performed in the resting state and right finger-tapping state. Cerebral blood flow (CBF) images were calculated, and the CBF values of the precentral cortex (PCC) and precentral subcortical white matter (PCSWM) were automatically extracted based on the structural images and CBF images.

**Results:** In the resting state, the intraclass correlation coefficient (ICC) of the bilateral PCC was 0.84 (left) and 0.81 (right) and that of the bilateral SCWM was 0.89 (left) and 0.85 (right). In the finger-tapping state, the ICC of the bilateral PCC was 0.91 (left) and 0.87 (right) and that of the bilateral PCSWM was 0.87 (left) and 0.92 (right). The CBF value of the left PCC and PCSWM was not significantly different between the resting state and finger-tapping state on two ASL scans.

**Conclusion:** 3D-ASL provides reliable CBF measurement in the cortex and subcortical white matter in the resting or controlled state.

[1]Department of Radiology, Chinese PLA General Hospital, Beijing, China
[2]Department of Radiology, Hainan Branch of Chinese PLA General Hospital, Sanya, China

**Corresponding author:**
Lin Ma, Department of Radiology, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China.
Email: cjr.malin@vip.163.com

**Keywords**
Arterial spin labeling, cortex, magnetic resonance imaging, reliability, subcortical white matter, cerebral blood flow

Date received: 18 February 2018; accepted: 8 May 2018

## Introduction

Conventional arterial spin labeling (ASL) is commonly used in clinical practice. ASL techniques include continuous ASL,[1] echo-planar imaging and signal targeting with alternating radio frequency (EPISTAR),[2] the flow-sensitive alternating inversion recovery (FAIR) sequence,[3,4] and quantitative imaging of perfusion using a single subtraction (QUIPSS).[5] These techniques can provide cerebral blood flow (CBF) information *in vivo* without the need for exogenous tracers.[1,6,7] However, limitations include low signal intensity, limited spatial coverage of the brain, and rapid T1 decay of the labeled spins.[8]

Three-dimensional (3D) spiral fast spin echo (FSE) pseudo-continuous ASL (3D-ASL) is a novel non-enhanced perfusion sequence on the MR750 3.0T magnetic resonance imaging (MRI) system (GE Healthcare, Milwaukee, WI, USA). Advantages of this technique include 3D acquisition, spiral k-space filling, and an FSE pulse sequence, all of which further expand the clinical application range of ASL. Therefore, assessment of the reliability of 3D spiral FSE ASL appears to be more important before its large-scale application.

In previous studies, continuous pulsed ASL and 3D pseudo-continuous ASL had good test–retest reliability for CBF on 1.5T scanners[9,10] and a 3.0T scanner.[11] A recent study showed that 3D pseudo-continuous ASL provided reliable whole-brain CBF measurement in young and elderly adults compared with [$^{15}$O] water positron emission tomography in patients with Alzheimer's disease on a 3.0T scanner.[12] However, these studies mainly focused on voxel-wise comparisons throughout the whole brain[12,13] and did not discuss the test–retest reliability in the cerebral cortex and subcortical white matter.

Vessels on the brain surface and cerebrospinal fluid in the sulcus may contaminate the CBF measurement of the adjacent cortex and subcortical white matter. Therefore, the reliability of CBF measurement in the cerebral cortex and subcortical white matter should be evaluated. In one study, the reproducibility of pseudo-continuous ASL was assessed at 1.5T and 3.0T.[14] The researchers suggested that the fluctuations in the perfusion signal seen over the longer term at both 1.5T and 3.0T were likely to reflect genuine fluctuations in resting-state perfusion and that the physiological contributions to the variability of the regional ASL perfusion signal should be further clarified.

We performed the present study to (1) investigate the reliability of 3D-ASL in the precentral cortex and precentral subcortical white matter in the resting state over a 1-week interval and (2) clarify the reliability of 3D-ASL in the precentral cortex and precentral subcortical white matter with respect to whether the technique is affected by physiological fluctuations.

## Methods

### *Subjects*

This study included healthy adults recruited from our medical school. All were

righted-handed and highly educated. The exclusion criteria were cranium trauma, inflammatory disease of the central nervous system, and use of psychoactive drugs or hormones. No subjects were permitted to perform heavy exercise or drink caffeinated beverages within 1 hour of the scanning session. Written informed consent was obtained from all subjects, and the study was approved by the ethics committee of the local institutional review board.

## MRI acquisition

All subjects were scanned twice at the same time each day for 1 week. MRI data were acquired on a DISCOVERY MR750 3.0T MRI system (GE Healthcare), and a conventional eight-channel phased-array head coil was used. First, conventional MRI data, including T2-weighted, T1-weighted, and diffusion-weighted imaging data, were obtained for general assessment. The structural image data were acquired by a high-resolution 3D T1-weighted fast spoiled gradient recalled echo (3D T1-FSPGR) sequence [repetition time/echo time (TR/TE) = 8.6/3.5 ms, flip angle = 12°, field of view (FOV) = 22 × 22 cm, matrix = 256 × 256, slice thickness = 1.2 mm, number of excitations = 1]. Volumetric perfusion imaging was performed using a pseudo-continuous ASL tagging scheme with a 3D interleaved spiral FSE readout with the following parameters: TR/TE = 5128/15.9 ms, flip angle = 111°, FOV = 20 × 20 cm, x,y matrix = 1024 × 8 (spiral acquisition), slice thickness = 3.0 mm, slice number = 50, number of averages = 3, and acquisition time = 3 min 22 s. The labeling duration was 1.5 s, and the post-labeling delay (PLD) was 1.5 s. The first ASL data acquisition was performed with a PLD of 1.5 s in the resting state, and the second ASL data acquisition was performed with a PLD of 1.5 s and continuous tapping of the right finger. All subjects underwent two MRI scans using identical scan protocols.

## CBF images calculation

All MRI structural and ASL data were processed using Statistical Parametric Mapping 8 (SPM8) running under MATLAB 7.6 (MathWorks, Natick, MA, USA), Advantage Windows workstation (FuncTool; General Electric, Milwaukee, WI, USA), and FreeSurfer (v5.0.0; http://www.freesurfer.net/).

ASL data (including perfusion-weighted images and proton density-weighted images) were processed, and 50 axial CBF images were acquired based on the following equation according to the reported literature:[15–20]

$$f = \frac{\lambda}{2\alpha T_{1b}\left(1 - e^{\frac{\tau}{T_{1b}}}\right)} \cdot \frac{(s_{con} - S_{lbe})\left(1 - e^{-\frac{t_{sat}}{T_{1b}}}\right)}{S_{ref}} \cdot e^{\frac{w}{T_{1b}}}$$

where $f$ is flow; $\lambda = 0.9$ (brain–blood partition coefficient); $\alpha = 0.85$ (labeling efficiency); $T_{1b} = 1.6$ s (T1 value of blood); $T_{1g} = 1.2$ s (T1 value of gray matter); $\tau = 1.5$ s (labeling duration); $S_{con}$, $S_{lbe}$, and $S_{ref}$ are the signals of the control, label, and reference images, respectively; $t_{sat} = 2$ s (saturation time for proton density images); and $w$ is the PLD.

## CBF quantitation of precentral region

Automatic CBF quantitation of the precentral cortex and precentral subcortical white matter were carried out as follows. (1) All T1-weighted images were checked visually for artifacts and then underwent volumetric processing using FreeSurfer software. A mask of each individual precentral cortex and precentral subcortical white matter was generated based on volumetric labeling according to the aparc.a2009s atlas,[21] and each segment was inspected

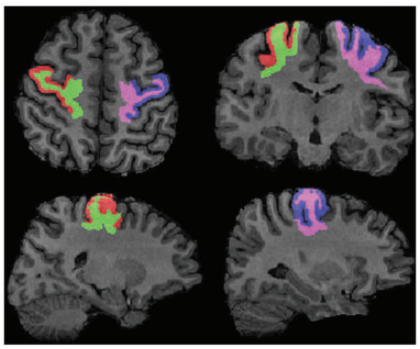

**Figure 1.** Masks of the bilateral precentral cortex and precentral subcortical white matter were obtained from volumetric labeling. Red, left precentral cortex; green, left precentral subcortical white matter; blue, right precentral cortex; pink, right precentral subcortical white matter.

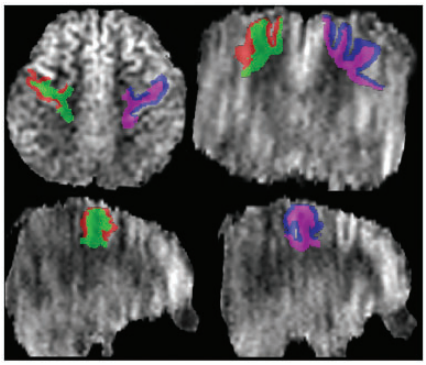

**Figure 2.** The cerebral blood flow values of the bilateral precentral cortex and precentral subcortical white matter were extracted. Red, left precentral cortex; green, left precentral subcortical white matter; blue, right precentral cortex; pink, right precentral subcortical white matter.

visually for the accurate segment and labeling (Figure 1). (2) CBF images were coregistered with 3D T1-FSPGR images, and the CBF values of the precentral cortex and precentral subcortical white matter were extracted based on the CBF images (Figure 2).

### *Statistical analysis*

The reliability was evaluated using the intraclass correlation coefficient (ICC) and Bland–Altman plot for the CBF variance of the precentral cortex and precentral subcortical white matter at the same PLD over a 1-week interval during the same session. The paired $t$ test was applied to compare the CBF values of the left precentral cortex and left precentral subcortical white matter during the same session. The statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

### *Subjects*

The subjects of this study were eight healthy adults (six men and two women) with an age ranging from 21 to 33 years (mean age, 23.8 years).

### *Reliability of CBF measurement of precentral cortex and precentral subcortical white matter*

Table 1 shows that good reliability of CBF measurement was obtained in the bilateral precentral cortex (ICC: left, 0.84; right, 0.81) and precentral subcortical white matter (ICC: left, 0.89; right, 0.85) in the resting state for the two measurements. In the finger-tapping state, good test–retest measurement reliability was also confirmed in the bilateral precentral cortex (ICC: left, 0.91; right, 0.80) and precentral subcortical white matter (ICC: left, 0.87; right, 0.92) (Figure 3).

### *Comparison of CBF value of left precentral cortex and precentral subcortical white matter in resting state and finger-tapping state*

Hyperperfusion of the left precentral gyrus was demonstrated in one subject in the

**Table 1.** Test–retest reliability of cerebral blood flow in precentral cortex and precentral subcortical white matter in resting state and finger-tapping state over a 1-week interval

| | Cerebral blood flow (mL/100 g/min) | | |
|---|---|---|---|
| | First measurement | Second measurement | ICC (95% CI) |
| Resting state | | | |
| PCC | | | |
| Left | 49.29 ± 9.13 | 54.58 ± 7.37 | 0.84 (0.22–0.97) |
| Right | 52.4 5 ±2.4 | 56.28 ± 6.12 | 0.81 (0.06–0.96) |
| PCSWM | | | |
| Left | 42.95 ± 7.28 | 48.13 ± 7.02 | 0.89 (0.43–0.98) |
| Right | 45.10 ± 5.08 | 46.95 ± 4.87 | 0.85 (0.27–0.97) |
| Finger tapping | | | |
| PCC | | | |
| Left | 47.83 ± 10.87 | 54.05 ± 15.99 | 0.91 (0.53–0.98) |
| Right | 55.58 ± 9.76 | 55.58 ± 13.20 | 0.87 (0.33–0.97) |
| PCSWM | | | |
| Left | 41.62 ± 8.17 | 47.22 ± 13.55 | 0.87 (0.34–0.97) |
| Right | 48.15 ± 7.91 | 47.48 ± 7.64 | 0.92 (0.61–0.99) |

PCC, precentral cortex; PCSWM, precentral subcortical white matter; ICC, intraclass correlation coefficient; CI, confidence interval.

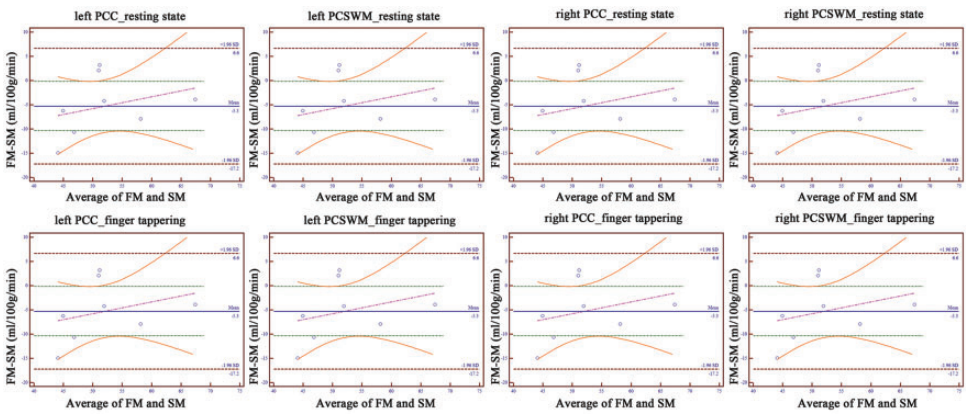


**Figure 3.** Bland–Altman plot of CBF difference in cerebral blood flow (CBF) of the left precentral cortex (PCC) and precentral subcortical white matter (PCSWM) for the normal subjects in the resting state and right finger-tapping state over a 1-week interval. FM, first measurement; SM, second measurement; X-axis, average of CBF value for FM and SM, respectively; Y-axis, the different CBF values for two measurements; circle, the subject; brownish-red dotted line, 1.96 standard deviation; purple dotted line, regression line of difference; light yellow dotted line, 95% confidence interval.

finger-tapping state on two 3D-ASL scans (Figure 4); the other subjects showed no significant hyperperfusion in the finger-tapping state. Table 2 shows that the CBF value of the left precentral cortex and precentral subcortical white matter was not significantly different between the resting state and finger-tapping state on two ASL scans.

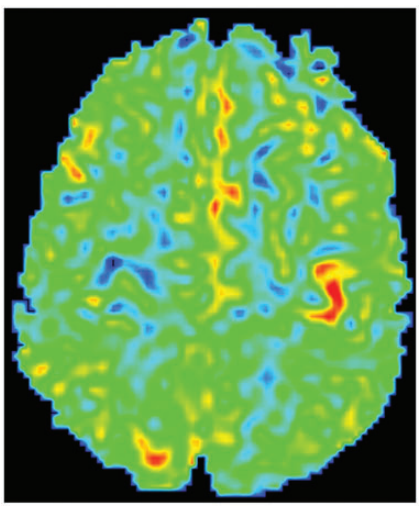

**Figure 4.** Hyperperfusion of the left precentral gyrus was demonstrated in a 23-year-old woman in the finger-tapping state on two three-dimensional spiral fast spin echo pseudo-continuous arterial spin labeling scans.

## Discussion

Good reliability of CBF measurement was observed in the bilateral precentral cortex and precentral subcortical white matter with an ICC of >0.8 in the resting state. This finding suggests that the CBF value was reliable for both the cortex and subcortical white matter. Although the cerebrospinal fluid and small vessels in the adjacent sulcus might affect the measurement of the CBF in the cerebral cortex and subcortical white matter, volumetric labeling prevents subjective measurement errors. Therefore, the measurement method used to obtain the CBF value might be an important factor for evaluation of test–retest reliability, especially for measurement of the CBF in the cerebral cortex, and is worth investigating in future. Our results also indicate that measurement of the CBF in the cortex and subcortical white matter would expand the clinical application range of 3D-ASL because of its high reliability.

Additionally, the right finger-tapping test demonstrated good test–retest reliability of CBF measurement in the precentral cortex and precentral subcortical white matter (ICC: 0.87–0.92). This finding indicates that physiological effects do not

**Table 2.** Comparison of cerebral blood flow in left precentral cortex and precentral subcortical white matter in resting state and finger-tapping state in the same session

| | Cerebral blood flow (mL/100 g/min) | | | |
|---|---|---|---|---|
| | Resting state | Finger tapping | *t* value | *P* value |
| First measurement | | | | |
| PCC | 49.29 ± 9.13 | 47.83 ± 10.87 | 1.21 | 0.27 |
| SCWM | 42.95 ± 7.28 | 41.62 ± 8.17 | 1.04 | 0.34 |
| Second measurement | | | | |
| PCC | 54.58 ± 7.37 | 54.05 ± 15.99 | 0.16 | 0.88 |
| SCWM | 48.13 ± 7.02 | 47.22 ± 13.55 | 0.33 | 0.75 |

PCC, precentral cortex; PCSWM, precentral subcortical white matter.

contribute to the CBF measurement variability and that the CBF values of the cortex and subcortical white matter were reliable.

Although hyperperfusion of the left precentral gyrus was observed in one subject, the CBF values showed no statistically significant difference between the resting state and finger-tapping state. A previous study[22] demonstrated that finger tapping could increase the blood oxygenation level-dependent (BOLD) signal, which might be associated with gradient echo planar imaging applied in functional MRI. The increased BOLD signal could be acquired at a high temporal resolution to adequately sample the BOLD response in functional MRI. In the current study, FSE was applied in 3D-ASL, which might not be sensitive to the T2* effect and had relative temporal resolution. This indicates that the BOLD effect is not a general manifestation in 3D-ASL.

High reliability of 3D-ASL in the cortex and subcortical white matter is important for the clinical application of this new sequence. However, this study included only healthy subjects. More reliability studies that include different factors, such as different controlled states, ages, disease entities, and scanning locations, should be performed.

In the present study, the volume-labeling method was used to generate masks of the bilateral precentral cortex and precentral subcortical white matter based on the individual structure images, and the CBF measurement was automatically obtained from the CBF images by the mask. This CBF measurement method could exactly match the target brain regions and acquired all CBF values of all voxels in the target brain regions, thus avoiding the subjective errors of the regions-of-interest method.

One limitation of this study is that the sample was relatively small. Another limitation is that the reliability of a more controlled state (cognitive state, visual stimulation, etc.) and different disease entities was not evaluated; this should be performed in future studies.

In conclusion, the current study demonstrated that 3D-ASL had good reliability of CBF measurement in the cortex and subcortical white matter in both the resting state and a controlled state, truly reflecting the perfusion state of the brain.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Hainan Provincial Natural Science Foundation of China (818MS153), the Special Financial Grant from the China Postdoctoral Science Foundation (2014T70960), and the Foundation for Medical and Health Sci & Tech innovation Project of Sanya (2016YW37).

## References

1. Detre JA, Leigh JS, Williams DS, et al. Perfusion imaging. *Magn Reson Med* 1992; 23: 37–45.
2. Edelman RR, Siewert B, Darby DG, et al. Qualitative mapping of cerebral blood flow and functional localization with echo-planar MR imaging and signal targeting with alternating radio frequency. *Radiology* 1994; 192: 513–520.
3. Kim SG. Quantification of relative cerebral blood flow change by flow-sensitive alternating inversion recovery (FAIR) technique: application to functional mapping. *Magn Reson Med* 1995; 34: 293–301.
4. Tsekos NV, Zhang F, Merkle H, et al. Quantitative measurements of cerebral blood flow in rats using the FAIR technique: correlation with previous iodoantipyrine autoradiographic studies. *Magn Reson Med* 1998; 39: 564–573.

5. Wong EC, Buxton RB and Frank LR. Quantitative imaging of perfusion using a single subtraction (QUIPSS). *Neuroimage* 1996; 3: 702–708.
6. Parkes LM, Rashid W, Chard DT, et al. Normal cerebral perfusion measurements using arterial spin labeling: reproducibility, stability, and age and gender effects. *Magn Reson Med* 2004; 51: 736–743.
7. Amann M, Achtnichts L, Hirsch JG, et al. 3D GRASE arterial spin labelling reveals an inverse correlation of cortical perfusion with the white matter lesion volume in MS. *Mult Scler* 2012; 18: 1570–1576.
8. Campbell AM and Beaulieu C. Comparison of multislice and single-slice acquisitions for pulsed arterial spin labeling measurements of cerebral perfusion. *Magn Reson Imaging* 2006; 24: 869–876.
9. Floyd TF, Ratcliffe SJ, Wang J, et al. Precision of the CASL-perfusion MRI technique for the measurement of cerebral blood flow in whole brain and vascular territories. *J Magn Reson Imaging* 2003; 18: 649–655.
10. Jahng GH, Song E, Zhu XP, et al. Human brain: reliability and reproducibility of pulsed arterial spin-labeling perfusion MR imaging. *Radiology* 2005; 234: 909–916.
11. Wu B, Lou X, Wu X, et al. Intra- and inter-scanner reliability and reproducibility of 3D whole-brain pseudo-continuous arterial spin-labeling MR perfusion at 3T. *J Magn Reson Imaging* 2014; 39: 402–409.
12. Xu G, Rowley HA, Wu G, et al. Reliability and precision of pseudo-continuous arterial spin labeling perfusion MRI on 3.0 T and comparison with 15O-water PET in elderly subjects at risk for Alzheimer's disease. *NMR Biomed* 2010; 23: 286–293.
13. Corouge I, Esquevin A, Lejeune F, et al. Arterial spin labeling at 3T in semantic dementia: perfusion abnormalities detection and comparison with FDG-PET. In: *MICCAI 2012 Workshop on Novel Biomarkers for Alzheimer's Disease and Related Disorders* 2012, pp.32–40.
14. O'Gorman RL, Coward HJ, Zelaya FO, et al. Reproducibility of pseudo-continuous ASL at 1.5T and 3T. *Proc Intl Soc Mag Reson Med* 2007; 15: 1419.
15. Jarnum H, Steffensen EG, Knutsson L, et al. Perfusion MRI of brain tumours: a comparative study of pseudo-continuous arterial spin labelling and dynamic susceptibility contrast imaging. *Neuroradiology* 2010; 52: 307–317.
16. Alsop DC and Detre JA. Reduced transit-time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow. *J Cereb Blood Flow Metab* 1996; 16: 1236–1249.
17. Wang J, Zhang Y, Wolf RL, et al. Amplitude-modulated continuous arterial spin-labeling 3.0-T perfusion MR imaging with a single coil: feasibility study. *Radiology* 2005; 235: 218–228.
18. Garcia DM, Duhamel G and Alsop DC. Efficiency of inversion pulses for background suppressed arterial spin labeling. *Magn Reson Med* 2005; 54: 366–372.
19. Dai W, Garcia D, de Bazelaire C, et al. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. *Magn Reson Med* 2008; 60: 1488–1497.
20. Herscovitch P and Raichle ME. What is the correct value for the brain–blood partition coefficient for water? *J Cereb Blood Flow Metab* 1985; 5: 65–69.
21. Destrieux C, Fischl B, Dale A, et al. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage* 2010; 53: 1–15.
22. Wang LL, Leach JL, Breneman JC, et al. Critical role of imaging in the neurosurgical and radiotherapeutic management of brain tumors. *Radiographics* 2014; 34: 702–721.