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Reliability of 2D and 3D Pseudo-Continuous Arterial Spin Labeling Perfusion MRI in Elderly Populations – Comparison with 15O-water PET

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Abstract

Purpose—To investigate the reliability and accuracy of two pseudo-continuous arterial spin labeling (pCASL) sequences, using 2D gradient-echo echo planar imaging (EPI) and 3D gradient and spin echo (GRASE) as the readout respectively.

Materials and Methods—Each sequence was performed twice four weeks apart on 6 normal control subjects, 6 elderly subjects with mild cognitive impairment (MCI), and one participant with Alzheimer's disease (AD). Eight of these subjects also underwent H₂¹⁵O positron emission tomography (PET) scans on the same day or proximal to their second MRI scan. The longitudinal repeatability of EPI and GRASE pCASL were evaluated with the intra-class correlation coefficient (ICC) and within-subject coefficient of variation (wsCV).

Results—The ICCs of global perfusion measurements were 0.697 and 0.413 for GRASE and EPI based pCASL respectively. GRASE pCASL also demonstrated a higher longitudinal repeatability for regional perfusion measurements across 24 regions-of-interests (ICC=0.707, wsCV=10.9%) compared to EPI pCASL (ICC=0.362, wsCV=15.3%). When compared to PET, EPI pCASL showed a higher degree of spatial correlation with PET than GRASE pCASL, although the difference was not statistically significant.

Conclusion—3D GRASE pCASL offers better repeatability than 2D EPI pCASL, thereby may provide a reliable imaging marker for the evaluation of disease progression and treatment effects in MCI and early AD subjects.

Keywords

cerebral blood flow (CBF); perfusion; arterial spin labeling (ASL); echo planner imaging (EPI); gradient and spin echo (GRASE); Alzheimer's disease (AD); magnetic resonance imaging (MRI); positron emission tomography (PET)

INTRODUCTION

Alzheimer's disease (AD) affects more than 35 million people worldwide, 5.5 million in the United States, and causes tremendous social economical burden. The focus of treatment

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development for AD is to halt or change the disease process before neurons are irreversibly damaged. Evaluation of these potential treatments will benefit from brain imaging techniques that can identify patients at the earliest stages of the disease and can objectively measure disease progression. Amyloid deposition, detectable by PET, is one of the earliest pathological events in AD, but studies have shown that the level of deposition does not correlate well with cognitive decline^{1,2}. Brain atrophy detected using structural MRI represents relatively late changes in the AD process³. Functional and metabolic imaging markers such as cerebral blood flow (CBF) and cerebral metabolic rate of glucose (CMR_{glc}) show progressive changes during the conversion from mild cognitive impairment (MCI) to AD^{3,4}. Reduced CBF and glucose metabolism have been detected in AD, and to a lesser extent in MCI subjects, using existing nuclear medicine imaging techniques that rely on radioactive tracers.

Arterial spin labeling (ASL) perfusion MRI is an appealing approach for measuring perfusion in dementia by utilizing magnetically labeled arterial blood water as an endogenous tracer. ASL doesn't involve radiation or contrast agents, allows easy registration with structural MRI, and provides absolute CBF that has been shown to be reproducible across time scales from minutes, hours to days^{5,6}. To date, several groups have applied ASL to study AD and MCI. Characteristic patterns of cerebral hypoperfusion in temporoparietal association cortices, posterior cingulate cortex (PCC) and frontal cortex were detected using ASL in AD patients, and to a lesser extent, in MCI populations⁷⁻¹⁰ (see review⁴ for details). Interestingly, hyperperfusion in basal ganglia, amygdala and hippocampus have been reported in MCI and mild AD subjects, after effects of brain atrophy on CBF were adjusted^{9,11}. Based on these pilot studies, ASL is beginning to be accepted by the AD community as a promising imaging tool for monitoring disease progression in MCI and AD.

The reliability of ASL perfusion measurement has been assessed by several studies in typically young, healthy adult populations^{6,12,13,14}. To date, besides a small study conducted in 6 elderly subjects¹⁵, few studies have systematically and rigorously addressed the longitudinal repeatability and accuracy of ASL in elderly populations at risk for or diagnosed with dementia. Elderly populations may pose unique challenges for ASL since the signal to noise ratio (SNR) is likely reduced with potential vascular changes compared to younger populations. The primary purpose of the present study was therefore to establish the test-retest repeatability of pseudo-continuous ASL (pCASL) using repeated MRI scans approximately 4 weeks apart in a cohort of MCI, AD subjects and age matched controls. In addition, the accuracy of pCASL perfusion MRI was assessed by comparison with the gold standard of CBF measurement using 15O-water positron emission tomography (PET) which was conducted on the same day or proximal to the second MRI scan.

A recent trend in ASL development is the use of fast 3D sequences such as GRASE and SPIRAL, often in conjunction with background suppression, to improve the SNR and reliability of ASL perfusion measurements^{16,17}. In the present study, both 2D gradient-echo EPI based pCASL and 3D GRASE pCASL with background suppression (BS) were performed for comparison. We hypothesized that 3D GRASE pCASL will show improved test-retest reproducibility compared to 2D EPI based pCASL.

MATERIALS AND METHODS

Participants

A total of 14 participants were recruited and clinically assessed. All subjects provided written informed consent, which were approved by the Institutional Review Board and the Medical Radiation Safety Committee of the University. Thirteen participants completed 2 repeated MRI scans and were included in the analysis. They included 6 normal controls

(NC, 5 male), 6 MCI (3 male), and one AD subject (male). Subjects were all over 55 years of age with a mean age of 68 (SD = 5.85). All participants were sufficiently fluent in English and in good general health. The Mini Mental State Exam (MMSE) and the Clinical Dementia Rating Sum of Boxes (CDR-SOB) were performed on each participant (see Table 1 for detailed demographic and behavioral testing scores). Study exclusion criteria included contraindications to MRI and PET, history of major head trauma, other concurrent neurologic or psychiatric illnesses and abnormal structural MRI. Excluded medications included short or long acting nitrates, and warfarin or other drugs that may affect CBF (such as caffeine within 3h and nicotine within 1h of the imaging exam).

Pseudo-Continuous Arterial Spin Labeling MRI

Each subject underwent 2 MRI scans approximately 4 weeks apart on a 3T Siemens TIM Trio scanner, using body coil as the transmitter and 12-ch head coil as the receiver. Each MRI included a 3D MPRAGE sequence for T1 weighted structural MRI with the following specifications: 192 slices at 1mm slice thickness, voxel size: 1.0x1.0x1.0mm³, FOV=256mm, flip angle=9°, TR=1900ms, TE=3.25ms, rate-2 GRAPPA for a total scan time of 4 minutes 30 seconds. Two pCASL sequences were performed: 1) 2D EPI pCASL with the following parameters: FOV=220mm, matrix=64x64, TR/TE=4000/11ms, rate-2 GRAPPA, 24 5mm slices with a 1mm gap in the transverse orientation acquired from inferior to superior direction (35ms per slice), post-labeling delay (PLD)=1500ms, 40 pairs of label and control acquisitions with a total scan time of 5min 20sec; 2) 3D GRASE pCASL with the following parameters: FOV=220mm, matrix=64x64, TR/TE=4000/22ms, rate-2 GRAPPA in phase, 4/8 partial k-space in slice direction, 26 5mm slices with 7% oversampling rate, PLD=1500ms during which 2 nonselective inversion pulses were applied for BS, 30 pairs of label and control acquisitions with a total scan time of 4min. Although the acquisition was shorter for GRASE than EPI, the SNR of GRASE images was 40% higher than that of EPI. A M₀ image was acquired with a TR of 5s and without labeling pulses for 3D GRASE pCASL. For 2D EPI pCASL, the control image was used as M₀ since no background suppression was applied. In both sequences, an RF pulse train of 1500ms duration was applied 9cm beneath the center of the acquired slices, with a mean gradient of 0.6mT/m, and a maximum gradient of 6mT/m^{16,18}.

CBF Calculations

ASL images were corrected for motion, pairwise subtracted between label and control images followed by averaging to generate the mean difference image (ΔM). Quantitative CBF (f) maps were calculated based on the following equation¹⁸

$$f = \frac{\lambda \Delta M R_{1a}}{2 \alpha M_0 [\exp(-w R_{1a}) - \exp(-(\tau + w) R_{1a})]} \quad [1]$$

where R_{1a} (0.61sec⁻¹) is the longitudinal relaxation rate of blood, M_0 is the equilibrium magnetization of brain tissue, α (=0.85 for EPI, 0.77 to account for loss of efficiency by BS for GRASE) is the tagging efficiency¹⁹, τ (=1.5sec) is the duration of the labeling pulse, w (=1.5sec) is the post-labeling delay time (slice acquisition time was adjusted for 2D EPI) and λ (=0.9g/ml) is blood/tissue water partition coefficient. Equation [1] assumes that the labeled blood spins remain primarily in the vasculature rather than exchanging completely with tissue water, which is justified in elderly subjects in whom arterial transit times are likely prolonged²⁰.

Each ASL MRI scan was co-registered (using EPI and GRASE images respectively) to the T1 weighted structural MRI, and normalized to the Montreal Neurological Institute template

(MNI) with Statistical Parametric Mapping (SPM8) Software (www.fil.ion.ucl.ac.uk/spm8) using the non-linear normalization function with preserving concentration option. All images were smoothed with a 4 mm full width half maximum Gaussian kernel filter after normalization.

PET

Eight subjects also participated in one PET scan using the whole body ECAT EXACT HR+ Siemens PET Scanner. Subjects were given a physical exam by a physician to determine if the participant was healthy for the scan. If determined eligible (blood pressure below 140/90mmHg and good physical and mental health), subjects underwent H₂¹⁵O PET scan the same day or shortly after their second MRI scan. Six subjects received a PET scan the same day as their last MRI, and 2 subjects were scanned within two weeks after their second MRI (3 and 13 days later). During both MRI and PET scans, subjects were instructed to rest quietly with eyes closed.

For H₂¹⁵O PET, 10–15mCi of ¹⁵O-water was injected as a rapid bolus (<5 sec). A series of dynamic frames were acquired for a total of 2min following injection, and 3–4 injections were performed in each subject with a 10min break between each. Sixty-three slices in the axial plane were obtained with a resolution of 1.8mm × 1.8mm × 2.4mm (matrix=128 × 128). PET data were reconstructed using filtered back projection with corrections for attenuation and scatter. No arterial sampling was performed and relative CBF (rCBF) images were generated by averaging the dynamic frames in each scan with correction of tracer decay. A mean rCBF map was then calculated by averaging the 3–4 injections. Mean rCBF maps were normalized to the MNI space using the PET template provided by SPM8 and smoothed with a 4 mm FWHM Gaussian kernel. In each subject, PET rCBF maps were scaled so that the global mean CBF was 50ml/100g/min to adjust the variations in tracer dosage across subjects.

Statistical Analysis

For each subject, normalized structural MRI were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid compartments using SPM8. The GM and WM segmentations were combined to form a brain tissue mask. Mean ASL and PET CBF values were extracted from GM, WM and whole brain masks, as well as from 90 regions of interest (ROIs) defined by the Automated Anatomical Labeling (AAL) template ²¹.

The test-retest reliability of pCASL scans were evaluated with the classic intraclass correlation coefficient (ICC) and within-subject Coefficient of Variation (wsCV) using the SPSS software package (Chicago, IL). Separate comparisons were performed to evaluate test-retest reliability for GM, WM and whole brain (WB) CBF in all subjects between time-point 1 (Scan 1) and time-point 2 (Scan 2). Bland-Altman plots were generated to display the spread of data and to evaluate the measurement agreement between Scan 1 and 2 for whole brain, GM and WM mean CBF respectively. ICC and wsCV were also calculated for mean CBF values in 90 ROIs of the AAL template. Special attention was paid to 24 specific ROIs that have previously been reported to be implicated in MCI and AD ⁴. These regions included bilateral posterior cingulate, hippocampus, superior and inferior parietal, precuneus, parahippocampal, amygdala, superior temporal gyrus, fusiform gyrus, lingual gyrus, supramarginal and angular gyrus. ICC and wsCV values of GRASE and EPI pCASL were compared using the Wilcoxon signed-rank test across the 24 ROIs. Within-subject ANOVA was used to compare mean CBF values acquired using GRASE and EPI pCASL in GM, WM and WB respectively. Further, accuracy was determined by comparing MRI CBF measurements with PET CBF measurements across the 90 ROIs of the AAL template as well as across all brain pixels in each subject, using Pearson correlation coefficients.

Based on the mean variability of CBF measurements (wsCV) across 24 ROIs, power calculations were performed to determine the number of subjects (N) required to detect a given effect size for GRASE and EPI pCASL respectively¹⁴. The *sampsi* function with the *ancova* method provided by the STATA 10.0 software (College Station, TX, USA) was used for the calculation, assuming a conservative correlation coefficient of 0.25 to 0.5 between repeated measurements.

RESULTS

Subjects

Table 1 lists the demographic and clinical information of the 13 participants with their MMSE and CDR SOB scores. When split into clinical and nonclinical groups, participants did not differ in age ($p=0.334$), MMSE ($p=0.275$) or CDR SOB scores ($p=0.178$), based on Wilcoxon rank-sum test.

Qualitative comparison of CBF maps

Eight participants underwent pCASL EPI and pCASL GRASE MRI scans as well as H₂¹⁵O PET scans. The mean normalized CBF maps of the 8 participants for each technique are illustrated in Figure 1. Qualitatively, CBF maps obtained by the 3 techniques are comparable and show good contrast between GM and WM. Nevertheless, the GRASE CBF map has lower CBF values than those of EPI which is elaborated below.

Test-retest Repeatability

Thirteen participants underwent repeated MRI scans. PCASL EPI and pCASL GRASE showed moderate (ICC = 0.4–0.6) to good (ICC = 0.6–0.8) levels of test-retest reproducibility between repeated MRIs acquired 4 weeks apart. As summarized in Table 2, pCASL GRASE produced higher ICC values compared to pCASL EPI in GM, WM and whole brain. The wsCV values were also reduced in GRASE pCASL than EPI pCASL especially for WM CBF measurements. The above observation is further illustrated in Figure 2 of the Bland-Altman plots. The differences between 2 repeated scans were generally distributed within $\pm(10-15)$ ml/100g/min (or $\pm 2SD$) in GRASE pCASL, while they were distributed within approximately ± 20 ml/100g/min in EPI pCASL across GM, WM and whole brain. However, GRASE pCASL CBF measurement demonstrated a small negative bias (<5 ml/100g/min, n.s.) between the 2 repeated scans.

A similar pattern emerged when examining the reliability of CBF measurements across the 24 ROIs relevant to the progression of AD (see Table 3). The mean ICC across the 24 representative ROIs was 0.707 and 0.362, and the mean wsCV 10.9 and 15.3% for GRASE and EPI based pCASL, respectively. The Wilcoxon signed-rank test indicated significantly higher ICC ($p<0.001$) and reduced wsCV ($p<0.001$) using GRASE compared to EPI pCASL.

Quantitative CBF measurements

The mean CBF values measured by EPI and GRASE pCASL in GM, WM and whole brain are displayed in Figure 3. Consistent with Fig. 1, the mean CBF values were reduced in GM ($F(1,11)=55.4$, $p<.001$) and whole brain ($F(1,11)=16.9$, $p<.001$) in GRASE pCASL compared to EPI pCASL, based on within-subject ANOVA. In contrast, WM CBF was significantly greater in GRASE pCASL compared to EPI pCASL ($F(1,11)=28.1$, $p<.001$).

Comparison between ASL and PET

The accuracy of pCASL CBF measurements was determined by correlating the second pCASL CBF (Scan 2) and PET rCBF measurements across 90 ROIs of the AAL template as well as across all brain pixels in each subject. Representative ASL CBF and PET rCBF images from a 65-year-old subject (Female, MCI) are shown in Figure 4. GRASE pCASL maps show higher SNR while EPI pCASL maps show higher contrast between GM and WM. Statistically significant associations between pCASL CBF and PET rCBF were found for both GRASE and EPI sequences in ROI and pixel-wise correlations. When comparing mean CBF values across 90 AAL ROIs, pCASL EPI showed higher correlations with PET rCBF compared to pCASL GRASE (pCASL EPI: $r = .51$, $SD = .11$, $p < .001$; pCASL GRASE $r = .40$, $SD = .13$, $p < .001$). Figure 5 displays the correlation coefficients across the 8 participants. However, such difference between correlation coefficients of EPI and GRASE CBF was not statistically significant using the Wilcoxon signed-rank test ($p = 0.09$). Similarly, correlation analyses across brain pixels revealed significant associations between EPI and GRASE pCASL vs. PET rCBF (pCASL EPI $r = .53$, $SD = .06$, $p < .001$, PET and pCASL GRASE $r = .51$, $SD = .08$, $p < .001$, see Figure 5b). Again there was no significant difference between GRASE and EPI based pCASL scans ($p = 0.40$).

Sample Size Estimation

Figure 6 shows estimated sample size for a within-subject design including one baseline and one follow-up measurement based on the mean wsCV of 10.9 and 15.3% for GRASE and EPI pCASL respectively. For an expected CBF change of 15%, the sample size is around 10 and 20 for GRASE and EPI pCASL respectively with an assumed correlation coefficient of 0.25–0.5 between repeated measures ($\alpha = 0.05$ two-sided and power = 90%).

DISCUSSION

In the present study, we systematically evaluated the longitudinal reliability of 2 pCASL sequences with 2D EPI and 3D GRASE readout respectively in a cohort of 13 elderly subjects at risk for or diagnosed with AD. The results showed that 3D GRASE pCASL had a higher test-retest repeatability compared to 2D EPI pCASL, as manifested by greater ICC and lower wsCV values using GRASE pCASL for both global and regional perfusion measurements. The interval of approximate 4 weeks between repeated MRI scans represents a “real-world” situation for testing imaging markers in MCI and AD. The observed higher test-retest repeatability using 3D GRASE pCASL compared to 2D EPI pCASL may be attributed to the higher SNR of 3D acquisitions, reduced temporal fluctuations using background suppression, and reduced T1 relaxation of the label due to the single-shot excitation of 3D GRASE¹⁴. In addition, susceptibility effects in orbitofrontal and inferior temporal cortex are reduced using 3D GRASE compared to 2D EPI²². Based on our data, pCASL with 3D BS GRASE readout should be the method of choice for longitudinal imaging studies to follow disease progression and treatment effects in MCI and mild AD.

One shortcoming of 3D GRASE, however, is the spatial blurring due to modulations of k-space signals by the T2 relaxation curve, especially along the z-direction. It has been reported that the readout duration of 3D acquisitions should be less than πT_2 to ensure that blurring is less than the voxel size²³. With a T2 of ~100ms for GM and a T2 of ~80ms for WM at 3T, the readout durations for GM and WM should be less than 314 and 251ms, respectively, to minimize blurring effect. In the present experiment, we employed 14 spin echoes along the z-direction (4/8 partial k-space) resulting in an echo train length of 350ms. A small amount of spatial blurring is expected in 3D GRASE pCASL perfusion images. The calculated mean CBF values were significantly lower in GM and higher in WM using GRASE pCASL compared to EPI pCASL, suggesting partial volume effects between grey

and white matter using 3D GRASE. Segmented or multi-slab 3D acquisition is an effective approach to minimize spatial blurring, however at the cost of prolonged scan time. In addition, potential head motion between segmented acquisitions in uncooperative subjects poses a risk for scanning demented or stroke patients²⁴. An alternative solution to spatial blurring involves the catalyzation of a pseudo-steady state using variable flip angles (VFA) during the echo train to preserve the point-spread function of 3D GRASE²⁵. Both segmented 3D GRASE with improved motion resistance and VFA approaches are actively being pursued in our laboratory.

The use of BS in 3D GRASE pCASL caused approximately 10% reduction in the labeling efficiency, given that the efficiency of each of the 2 nonselective inversion pulses was 95%. Using the calibrated labeling efficiency of 0.77, the absolute CBF values of whole brain match closely between GRASE (45.2 ± 8.99 ml/100g/min) and EPI pCASL (47.8 ± 9.20 ml/100g/min). This result is consistent with previous studies on the efficiency of BS¹⁹, and supports that BS can be reliably applied for quantitative perfusion imaging using pCASL.

Various imaging modalities have been used to study AD. Morphometric, perfusion, metabolic, and more recently, functional connectivity and amyloid imaging data have furthered our understanding of the disease development and progression. In the clinical setting, structural MRI, FDG-PET and SPECT perfusion imaging have been routinely used to help with diagnosis. Compared to amyloid PET imaging, which measures amyloid plaques, one of the earliest pathological changes in AD, and structural MRI, which visualizes atrophy, a relatively late change in AD, the value of ASL perfusion MRI lies in that perfusion closely correlates with disease progression from MCI to AD, and therefore may serve as an imaging marker for therapeutic efficacy in clinical trials. For such purposes, quantitative MRI methods have unique advantages over FDG-PET which is not suitable for frequent scanning given required exposure to radioactivity. Establishing the longitudinal reliability and accuracy of these MRI methods is key to realize these advantages. The high longitudinal reliability of 3D GRASE pCASL demonstrated in the present study supports its use as a reliable measure of perfusion in MCI and AD patients.

There are several limitations of this study. First, the sample size is relatively small and may not represent an optimal sample of the MCI and AD population. Regression analysis of perfusion with behavioral assessments or clinical diagnosis was not feasible given that there was only one AD subject. Secondly, arterial sampling was not performed during the PET scan and therefore only relative CBF was obtained in the current 15O-water PET experiment. This is the reason that we chose to compare the spatial pattern of ASL CBF and PET rCBF maps using correlation analyses in individual subjects. Finally, the test-retest variability of pCASL was higher than those of automatic segmentation of structural MRI ($\sim 4.3\%$)²⁶ and amyloid PET ($\leq 10\%$)^{27, 28}. Compared to ASL repeatability studies performed on young healthy adults one week apart¹⁴ and on 6 elderly subjects during the same scanning session¹⁵ (ICC range 0.8–0.95), the ICC values of the present study were lower (range 0.4–0.8). This may be attributed to the challenges of ASL imaging in elderly populations (e.g., reduced CBF and prolonged arterial transit time) as well as the longer interval (~ 4 weeks) between repeated scans in the present study. Nevertheless, our sample size estimation indicated that approximately 10 subjects are needed for detecting a 15% CBF change with 90% power using 3D GRASE pCASL.

In conclusion, pCASL perfusion MRI with 3D BS GRASE readout is a promising imaging tool for the evaluation of MCI and AD. Further technical developments are needed for minimizing spatial blurring in 3D acquisitions.

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Figure 1. Average CBF maps of the 8 subjects participating in both PET and MRI experiments: a) PET, b) pCASL GRASE and c) pCASL EPI. PET rCBF maps were scaled to a global mean CBF value of 50ml/100g/min.

Figure 2. Bland-Altman plots of repeated CBF measurements using EPI pCASL (a, c, e) and GRASE pCASL (b, d, f) in whole brain (WB)(a, b), grey matter (GM)(c, d) and white matter (WM) (e, f) respectively.

Figure 3. Mean CBF values in GM, WM and WB acquired using EPI and GRASE based pCASL at two time points respectively, error bars indicate standard error.

Figure 4. Representative CBF maps of a 65 year old participant (female, MCI) acquired using different techniques: a) PET; b) pCASL GRASE and c) pCASL EPI. PET rCBF maps were scaled to a global mean CBF value of 50ml/100g/min.

Figure 5.

Pearson's correlation coefficients between EPI and GRASE pCASL vs. PET rCBF across 90 ROIs of the AAL template (a), as well as across all brain pixels (b) in the 8 subjects participating in both PET and MRI experiments.

Figure 6. Sample size for a within-subject design including one baseline and one follow-up measurement for GRASE and EPI pCASL respectively, with an assumed correlation coefficient of 0.25–0.5 between repeated measures ($\alpha=0.05$ two-sided and power=90%).

Table 1

Demographic and behavioral evaluation information of participants

	Gender	Age	Diagnosis	MMSE	CDR-SOB
MRI N=13	M=9, F=4	Avg=68, SD=5.85 Range=57-78	NC=6	NC=28	NC=.083
			MCI=6	MCI=28	MCI=.75
			AD=1	AD=20	AD=8.5
PET N=8	M=4, F=4	Avg=67, SD=6.51 Range=57-78	NC=3	NC=28	NC=.167
			MCI=4	MCI=27	MCI=.75
			AD=1	AD=20	AD=8.5

Table 2

Test-retest results of mean CBF (ml/100g/min) in grey matter, white matter and whole brain using 2D EPI and 3D GRASE based pCASL

	EPI				GRASE			
	CBF Scan 1	CBF Scan 2	ICC	CV	CBF Scan 1	CBF Scan 2	ICC	CV
Grey Matter	54.33 ± 10.84	54.72 ± 8.99	0.404	0.102	48.02 ± 10.37	52.33 ± 9.95	0.718	0.099
White Matter	25.75 ± 7.85	25.16 ± 10.50	0.424	0.256	31.56 ± 7.90	33.55 ± 7.30	0.623	0.117
Whole Brain	47.58 ± 9.96	48.01 ± 8.45	0.413	0.106	43.29 ± 9.55	47.20 ± 8.43	0.697	0.103

Table 3

Test-retest results of EPI and GRASE pCASL across 24 representative ROIs

	EPI CBF (mL/100 g/min)			GRASE CBF (mL/100 g/min)		
	Scan 1 Mean	Scan 2 Mean	ICC	Scan 1 Mean	Scan 2 Mean	ICC
Cingulum_Post_L	60.78	61.21	0.386	53.86	58.62	0.533
Cingulum_Post_R	46.90	49.68	-0.010	47.55	50.35	0.440
Hippocampus_L	47.13	49.65	0.306	38.81	42.98	0.784
Hippocampus_R	47.08	46.98	0.365	40.30	44.24	0.698
ParaHippocampal_L	39.85	40.91	0.380	37.06	40.83	0.745
ParaHippocampal_R	41.90	44.30	0.323	39.90	43.42	0.773
Amygdala_L	42.71	47.55	0.090	40.43	44.21	0.771
Amygdala_R	42.38	39.08	0.219	40.28	43.08	0.647
Fusiform_L	47.89	47.19	0.304	37.52	41.90	0.785
Fusiform_R	42.12	44.34	0.340	37.74	41.22	0.639
Parietal_Sup_L	46.13	48.40	0.534	37.52	40.50	0.749
Parietal_Sup_R	40.76	40.05	0.307	36.54	39.60	0.721
Parietal_Inf_L	55.55	59.02	0.616	49.28	53.11	0.756
Parietal_Inf_R	53.81	55.08	0.377	46.70	52.98	0.755
SupraMarginal_L	57.99	61.66	0.460	54.59	59.56	0.673
SupraMarginal_R	50.69	50.68	0.109	49.87	55.11	0.813
Angular_L	57.92	61.03	0.439	54.26	58.96	0.751
Angular_R	54.63	56.44	0.458	48.78	53.70	0.804
Precuneus_L	52.68	54.47	0.437	45.21	49.52	0.612
Precuneus_R	51.25	52.85	0.338	45.03	48.36	0.516
Temporal_Sup_L	59.35	58.44	0.431	52.11	57.35	0.721
Temporal_Sup_R	49.35	47.46	0.389	48.18	52.79	0.875
Lingual_L	55.21	53.12	0.429	44.11	47.49	0.644
Lingual_R	53.06	52.56	0.649	41.46	45.23	0.771
Average ± SD	49.88 ± 6.31	50.92 ± 6.68	0.362 ± 0.151	44.46 ± 5.96	48.55 ± 6.53	0.707 ± 0.103
			0.153 ± 0.034			0.109 ± 0.017