HETEROGENEITY AND REPRODUCIBILITY OF CEREBRAL PERFUSION AND CAPILLARY VOLUME FRACTION MEASUREMENTS, DERIVED FROM COMBINED ARTERIAL SPIN LABELLING AND INTRAVOXEL INCOHERENT MOTION IMAGING OF THE HEALTHY ADULT BRAIN

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Introduction Arterial spin labeling (ASL) is a non-invasive technique which can be used to measure cerebral blood flow (CBF) by magnetically labeling water molecules in the arterial blood supply. The presence of a blood-brain barrier in the brain means labeled water molecules cannot be described as a freely diffusible tracer, hence a number of two-compartment models have been developed which separate the ASL signal arising from the intra- and extra-vascular space [1], [2]. These require ASL data to be collected over a range of inflow times (TI), and produce estimates of CBF, bolus arrival time (BAT) and PS/v_{bw} (ratio of capillary permeability-surface product, PS, to the capillary volume fraction, v_{bw}). Both PS and v_{bw} have the potential to provide clinically useful information, however, using ASL data alone, only the PS/ v_{bw} ratio can be calculated. Values of v_{bw} can be derived independently by acquiring diffusion weighted imaging (DWI) data over a range of *b*-values, and fitting the data to the intravoxel incoherent motion (IVIM) model [3]. We have previously shown that realistic values of PS can be calculated in the human brain by incorporating local v_{bw} measurements into a two-compartment ASL model [4]. However, as the IVIM model is rarely applied to DWI data acquired in the brain, due to relatively small cerebral capillary volume fractions (~5%), we aimed to investigate the regional variability and reproducibility of v_{bw} estimates acquired in healthy adult subjects, and the subsequent heterogeneity and reproducibility in two compartment ASL models which incorporate these data.

Methods All experiments were performed using a Siemens 1.5 T Avanto MR system. Ten healthy subjects (22-32 years, mean 27 years) were imaged using a diffusion weighted single shot EPI sequence, with diffusion gradients applied in three perpendicular directions, and the following imaging parameters: TR=3.2 s, TE=120 ms, 3.6x3.6x5.0 mm resolution, 20 slices, NEX=4, b-value = 0,20,40,80,120,160,200,300,500,1000 mm^2/s, scan time=6.4 min. This was followed by a FAIR pulsed-ASL sequence, with 3D single shot GRASE data acquisition (details in [5]), with the following imaging parameters: TR=3.0 s, TE=31.6 ms, NEX=8. The FOV and resolution were identical to the diffusion weighted scan, and measurements were made at 12 inflow times (TI), ranging from 0.2 to 2.4 s in 0.2 s intervals, with total scan time=9.6 minutes and background suppression. Imaging was repeated (without repositioning) in 5 of the subjects after 20 min, to test reproducibility. Intra-subject registration was performed for all repeat scans, and data were spatially smoothed using a 6mm FWHM Gaussian kernel to reduce artefacts due to imperfect registration. DWI data were fit to the IVIM model [3] to determine the volume fraction of the diffusion signal linked to blood-water in the capillary network (v_{bw}), which appears as a fast 'pseudo-diffusion' component at low b-values (b<~200 s/mm^2). Local v_{bw} data were then combined with the multi-TI ASL data, and values of CBF, BAT and PS were estimated using the two compartment model described in [2]. Analysis was carried out using raw data from five regions of interest (ROIs), each of 64.8mm^3 volume (4 voxels), at identical positions in the temporal (#2), occipital (#3), frontal (#4) and parietal (#5) lobes within each subject. ROIs 2-5 were remote from large arteries (identified as bright foci in ASL data acquired at short TI). A further ROI (#1) was placed close to ROI #2, but overlapping a large artery.

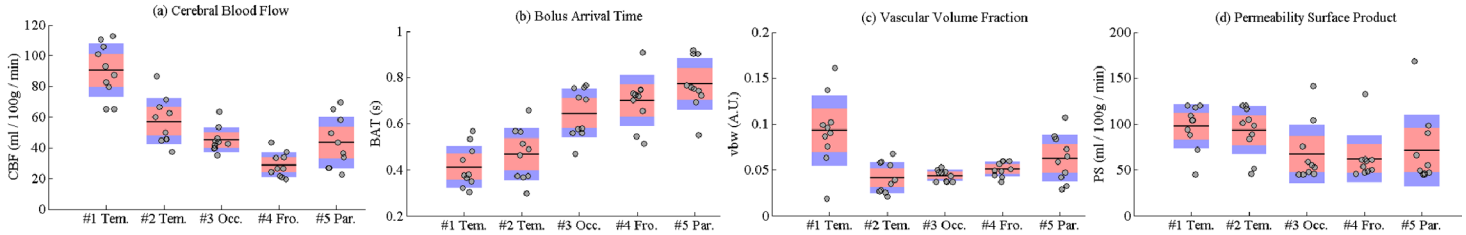

***Figure 1**. Regional values of (a) CBF, (b) BAT, (c) v_{bw} and (d) PS in all ten subjects. Boxes show 95% CI in red and SD in blue. Solid black line=mean.*

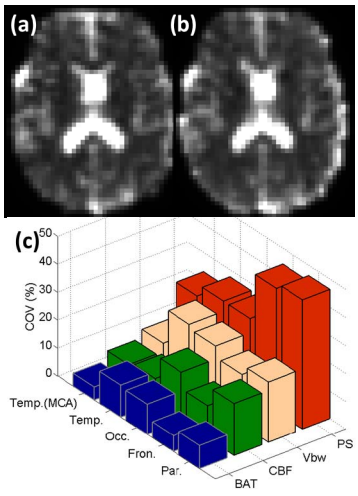

***Figure 2**. Maps of v_{bw} in one subject, for initial (a) and repeat (b) scan. (c) COV in the fitted parameters from the test, re-test scans on five subjects.*

Results ***(1) Regional Variation***. Mean values of CBF, BAT, v_{bw} and PS over all ROIs were 52.9±13.1 ml/100g, 0.60±0.11 s, 0.058±0.019, and 78.1±29.4 ml/100g/min respectively (mean±SD). ROI #1, which overlapped an artery, produced the highest values of CBF and shortest values of BAT (90.5±15 ml/100g/min and 0.41±0.09 s respectively). ROI #4 (frontal) produced the lowest and most uniform values of CBF (28.7±8.0 ml/100g/min). v_{bw} values showed the greatest heterogeneity in ROI #1 (temporal+artery, 0.093±0.039) and were lowest and most uniform in ROI #3 (occipital, v_{bw} =0.044±0.006). Mean PS was lowest in ROI #4 (frontal, PS=61.9±25.5 ml/100g/min), and greatest and most uniform in ROI #1 (temporal+artery, PS=97.4±23.4 ml/100g/min). ***(2) Reproducibility***. Intra-subject repeatability [6], averaged for all ROIs (with coefficient of variance (COV) shown in brackets), in CBF, BAT, v_{bw}, and PS was 16 ml/100g/min (13%), 0.10 s (8%), 0.02 (19%) and 57 ml/100g/min (34%) respectively. ROI #1 (temporal+artery) showed the best repeatability in all four fitted parameters, with COV of 4.7, 7.9, 10.8 and 22.9 % in BAT, CBF, v_{bw}, and PS respectively. Repeatability was poorest for CBF and PS in ROI #5 (parietal, COV=19%, 46% respectively), and BAT and v_{bw} in ROI #2 (temporal, COV=11%, 24% respectively).

Discussion We have used smaller ROIs compared to the majority of ASL reproducibility studies, however, the repeatability of BAT and CBF values show good agreement with previous publications[7], [8]. Using IVIM, physiologically sensible values of v_{bw} were obtained in the temporal, occipital and frontal lobes (with particularly low heterogeneity in the occipital lobe), but values are overestimated and heterogeneous in the parietal lobe, or when an ROI overlaps a large cerebral artery. The moderate reproducibility of v_{bw} (19%) may be influenced by functional dynamic changes brought about by neuronal activation, and is an area that warrants further research. The intra-subject COV of our PS values (34%) is 18% lower than [1], and our inter-subject COV in PS (38%) is 28% lower than [2], suggesting that, although our repeatability values of PS are high, significant improvements in reproducibility and heterogeneity between subjects can be realized when measured, rather than fixed, values of v_{bw} are used in a two-compartment ASL model.

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References [1]LM Parkes et al., *MRM* 48(1) 2002 pp. 27-41 [2] K Li et al. *MRM* 53(3) 2005 pp. 511-518 [3] D Le Bihan et al. *Radiology* 161(2) 1986, pp. 401 -407. [4]PW Hales et al. *Preceedings of the 19th Annual Meeting of the International Society for Magnetic Resonance in Medicine*, Montreal, Canada, 2011. [5] M Günther et al. *MRM* 54(2) 2005 pp. 491-498 [6] JM Bland et al. *BMJ* 313 (7059) 1996, p. 744 [7] PM Figueiredo et al. *J Magn Reson Imaging* 21(6) 2005, pp. 676-682 [8] ET Petersen et al. *NeuroImage* 49(1) 2010, pp. 104-113.