Simultaneous functional and quantitative ASL: an optimal tool for imaging ongoing pain states

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Introduction: Chronic pain is a significant medical health problem and causes a large financial burden in the developed world. Understanding how pain is perceived by the human brain holds promise in developing better treatments. Functional magnetic resonance imaging (fMRI) is a powerful tool for non-invasive mapping of neuronal activity in the living brain. Investigations of pain states have, until recently, relied on blood oxygenation level-dependent (BOLD) fMRI. However, the slow 'drifts' in BOLD signal make it ill-suited to image the neuronal correlates of chronic pain; since activity is usually ongoing and spontaneous. Conversely, the technique of arterial spin labelling (ASL) perfusion contrast offers good low-frequency noise properties [1, 2], making the technique a promising experimental utility for pain research. In this study we implemented a novel whole brain ASL method that is capable of detecting functional neuronal activity whilst simultaneously obtaining absolute quantification of key physiological parameters such as cerebral blood flow (CBF) and arterial arrival time (Δt). This is the first demonstration of such an ASL approach within a pain imaging context.

Methods: **ASL:** A pseudo-continuous ASL sequence [3] using gradient-echo EPI readout (TR=3.75s, TE=13ms, 6/8 k-space) was used. Twenty-six axial slices in ascending order (4×4×5.5mm voxels, 0.5mm inter-slice gap) were prescribed for each subject, providing whole brain coverage. The labelling plane was chosen optimally based on a time-of-flight scan of the neck, located ~8-10cm inferior to the centre of the 26 slices. A 90^{o} pre-saturation pulse was applied before the labelling pulses. The labelling duration was 1.4s and five different post labelling delay (PLD) times were adopted. The PLD values were generated according to Optimal Sampling Schedule theory [4], with their order pseudo-randomised. Ten healthy volunteers (2 female, 8 male, age 20-38) were scanned using a Siemens 3T Verio system fitted with a 32-channel head coil. **Stimulation:** For each subject, stimulation consisted of 8 blocks of independent 2-minute epochs (allowing 16 tag/control pairs), alternating between resting and activation states. During resting blocks, subjects were asked to lie still with their eyes closed. During activation blocks, a constant 512mN pin-prick pain stimulation was applied to the subjects' right hand to elicit a moderate pain experience (with an average numerical rating of 4.5/10). ASL data acquisition started 30 seconds after pin-prick stimulation had been applied. **Data Processing:** Data were concatenated offline and analysed using the FMRIB Software Library (FSL) [5]. Data were motion corrected followed by spatial smoothing (FWHM 8mm). The general linear model was adopted for modelling CBF and any contaminating BOLD effects. A separate regressor was introduced to take into account the signal differences induced by different PLD values. The multi-PLD schedule used in the pCASL acquisition allowed absolute quantification of CBF and arterial arrival time (Δt). Data during resting and pain states were fitted to the standard ASL kinetic model [6] separately on a voxel-by-voxel basis, using a Bayesian inference framework [7].

Results and Discussion: Fig. 1 shows the group Z-maps (n=10) for the perfusion activation, using a cluster forming threshold of 2.0, superimposed on the MNI152 standard brain template images. Significant bilateral CBF changes were found in the following regions: parietal operculum (z_{max}=3.85, left), posterior insular (z_{max}=3.51, left), anterior insular (z_{max}=3.32, left), mid insular (z_{max}=3.26, left), superior frontal gyrus (z_{max}=2.73, right), paracingulate gyrus (z_{max}=2.71, right); Significant unilateral CBF changes were found in left central operculum (z_{max}=3.48). Localised perfusion activations on the left sensory cortex and perfusion de-activations on the occipital lobe were also seen sub-threshold.

Table 1 shows the calculated mean CBF values across all 10 subjects for different regions of interest. Quantification results show that within the left and right insular, there is a respective 8.5% and 5.7% increase in CBF values during pain sessions compared to those during resting sessions, averaged across all subjects. This numbers may suffer from partial volume effects, and will benefit from better grey/white matter segmentation.

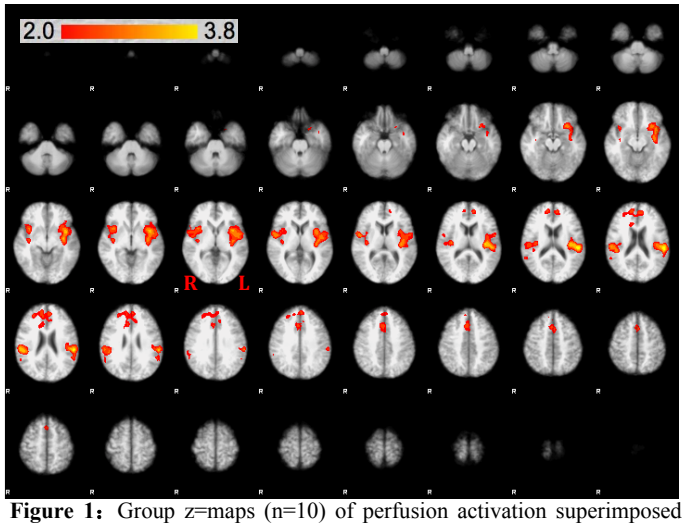

Figure 1: Group z=maps (n=10) of perfusion activation superimposed on the MNI152 standard template brain. Cluster forming threshold 2.0.

Conclusion: We have implemented a pCASL-EPI technique to study ongoing pain states. Using a model pain stimulation paradigm we have shown this technique to be robust in detecting functionally relevant and anatomically localized brain activities associated with ongoing pain stimuli. We are confident that the quantitative nature of this technique, along with its whole brain coverage, support the use of this optimised technique for future ASL investigations of chronic pain.

Acknowledgements: The authors wish to thank Dr Daniel Bulte, Dr Michael Chappell, and Mr Thomas Okell for insightful discussions.

	Whole Brain	Left Insular at Rest	Left Insular during Pain	Right Insular at Rest	Right Insular during Pain
CBF (ml/min/100ml)	73.8±17.4	94.4±23.4	102.4±26.4	104.6±27.6	110.6±30.0

Table 1: Quantification results of CBF and arterial arrival time values across 10 subjects.

Reference: [1] Detre et al, MRM 1992;23:37; [2] Wang et al, MRM 2003;49:796; [3] Dai et al, MRM 2008; 60:1488-1497; [4] Xie et al, MRM 2008; 59:826-834; [5] Smith et al, NeuroImage 2004;23(S1): 208; [6] Buxton et al, MRM 1998;40:383-396; [7] Chappell et al, IEEE TSP 2009; 57:223-236.