Characterisation of sensori-motor CBF and BOLD functional responses during early development with dual-echo pCASL and fMRI

Thomas Alderliesten[1,2], Esben Thade Petersen[3], Manon JNL Benders[1,2], Petra MA Lemmers[2], Alessandro Allievi[4], Julia Wurie[1], Serena J Counsell[1], Etienne Burdet[4], A. David Edwards[1,4], Jo V Hajnal[1,5], and Tomoki Arichi[1,4]

[1]Centre for the Developing Brain, King's College London, London, London, United Kingdom, [2]Department of Neonatology, University Medical Center Utrecht, Utrecht, Utrecht, Netherlands, [3]Department of Radiology, University Medical Center Utrecht, Utrecht, Utrecht, Netherlands, [4]Department of Bioengineering, Imperial College London, London, United Kingdom, [5]Division of Imaging Sciences and Biomedical Engineering, King's College London, London, United Kingdom

Target audience: Researchers and clinicians studying: early brain development, fMRI in infancy, biophysics of fMRI responses.

Background: Functional MRI (fMRI) is being increasingly used to study the development of functional brain activity and connectivity in infancy. These studies have demonstrated that even in preterm infants, the brain has an emerging but clearly defined functional neuroanatomy, with localized responses readily seen in many of the regions which equate to those identified in adult subjects [1]. However, the underlying biophysical origins of the measured blood oxygen level dependent (BOLD) contrast responses in this population are poorly understood. This is of particular importance as there are dramatic maturational changes in both the neural structure and vascular architecture of the brain during early life, which are likely to significantly alter the key neurovascular coupling relationship between neural activity and cerebral blood flow (CBF). Arterial Spin Labelling (ASL) can identify and quantify localized changes in CBF with greater spatial specificity than BOLD fMRI [2]. We therefore aimed to simultaneously measure functional ASL and BOLD responses following somatosensory stimulation in infants during their first year.

Methods: A total of 8 infants were studied; 3 during the preterm period (34+0, 34+4, and 34+4 weeks Post-menstrual age (PMA)); 3 at term equivalent age (38+2, 40+1, and 43+4 weeks PMA); and 2 infants at 6 months corrected age. Written parental consent was obtained for all subjects. Data was acquired with a 3-Tesla Philips MRI system (Best, NL) at St Thomas' Hospital London, with a custom 32-channel head coil (RAPID Biomedical GmbH, Rimpar, DE) for neonatal subjects or a standard 32-channel head coil for 6 month old infants. Functional stimulation (passive wrist extension and flexion) was performed using a custom-made and fully automated fMRI-compatible robotic interface, which has previously been shown to be capable of inducing robust functional responses in the primary somatosensory cortices of infants [3]. The robotic device was fitted to the right wrist of each subject prior to image acquisition, and a simple block paradigm was used consisting of 29 seconds of stimulation (frequency 0.5 Hz) alternating with 29 seconds of rest. Images were acquired using a dual echo pseudo continuous ASL (pCASL) sequence: TE1/TE2 9.2/45ms, TR 3636ms, FOV 144mm, x*y*z resolution 3*3*5mm, 6 slices, 0mm gap, SENSE factor 2.5, FA 90°, label duration 1650 ms, post-label delay 1550ms, 80 dynamics (tag+control), total scan time 10 minutes 2 seconds.

Data was analysed using FMRIB's software library (FSL: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) [4]. Standard pre-processing steps included motion correction, non-brain tissue removal using BET, spatial smoothing (FWHM 3mm); and high-pass temporal filtering (cut-off 50sec). Time-series analysis was then performed using general linear modelling (GLM) as implemented in FEAT (v6.0). Data from the first echo was used to analyse perfusion data after surround subtraction of the tag and control conditions. The data was explained by a convolution of the stimulation paradigm with a set of basis functions optimized for fMRI studies of infants [5]. A similar approach was used for modelling the BOLD signal present in data obtained from the second echo. Non-subtracted data was used with the control-tag condition of ASL modelled in as an additional explanatory variable. This was done to prevent ASL contamination still present at a TE of 45ms from identifying significant BOLD activation. Parameter estimates were converted to a z-statistic with a threshold of 2.3 and a corrected cluster significance level of $p<0.05$.

Results: Data of one preterm infant was discarded because of excessive motion. Passive motor stimulation resulted in well localized and positive amplitude BOLD functional responses in the contralateral (left) primary somatosensory cortex of 5 infants (2 preterm, 2 term, and one 6 month old). Good quality perfusion maps were obtained in 6 of the infants. A functional localized increase in CBF could be identified in only 4 subjects (1 preterm, 2 term, 1 6 month old). Although the identified CBF responses largely overlaid the BOLD responses, they were less diffuse and appeared more localized to the cortex. In a representative preterm (34+4 w) infant in whom BOLD and ASL activation could be identified (figure 1), the BOLD signal change was 1.4% and the change in ASL signal as seen on the subtracted perfusion images was approximately 30%.

Discussion and Conclusions: We describe the preliminary results of a simultaneous pCASL and BOLD fMRI experiment, which demonstrate the feasibility of the technique for shedding new light on the biophysical mechanisms underlying functional responses in infants. Although the CBF responses were seen to be similarly located as the identified BOLD responses, they were more spatially specific and located predominately in the cortex. The inherently low SNR of ASL and motion most likely prohibited identification of a functional CBF response in all infants. ASL adds a quantitative dimension to fMRI studies, which is relevant as CBF is known to modulate the BOLD response. Moreover, the magnitude of the CBF change may provide useful clinical information regarding auto-regulatory capability in preterm or otherwise compromised infants. Finally, simultaneous BOLD/ASL opens the door to estimating (relative) oxygen metabolism and neurovascular coupling, which might be associated with neurodevelopmental outcome later in childhood [6,7].

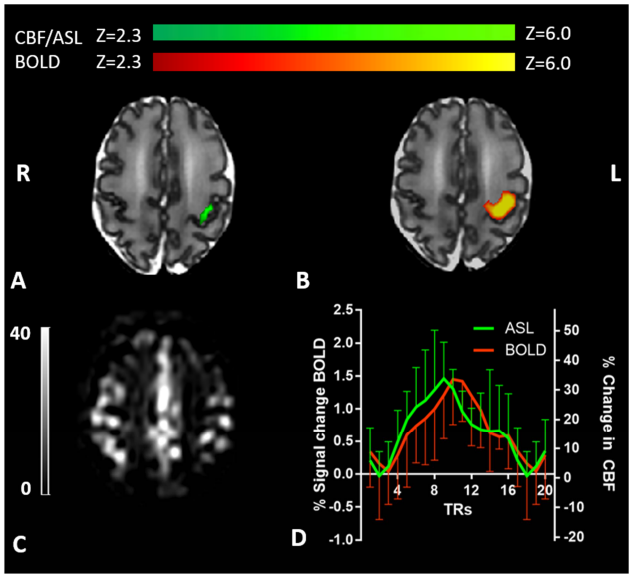

Figure 1: Results of a dual-echo pCASL and BOLD experiment in an infant at 34+4 weeks PMA, following passive motor stimulation of the right wrist. Shown are ***A***) the localized CBF response as identified at the first echo, **B**) the BOLD response identified with the second echo, **C**) the ASL perfusion map, and **D**) the mean peristimulus time-series for BOLD and ASL, scaled to overlay based on the max. signal change.

References: [1]. Seghier et al. Semin Perinatol 2010; 34(1):79-86; [2]. Pimentel et al. Hum Brain Mapp 2013; 34(1): 96-108; [3]. Allievi et al. Ann Biomed Eng 2013; 41(6): 1181-92; [4]. Smith et al. Neuroimage 2004; 23(supp1): s208-19; [5]. Arichi et al. Neuroimage 2012; 63(2): 663-73. [6] Uludag et al. Neuroimage 2004. [7] Grant et al J Cereb Blood Flow Metab