Pulsed arterial spin labelling perfusion imaging at 3T: estimating the number of subjects required in common designs of clinical trials

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Introduction The coupling between neural activity and cerebral perfusion is the basis of most applications of non-invasive functional magnetic resonance imaging (FMRI), commonly exploited as blood oxygenation level dependent (BOLD) fMRI. Recent advances in MRI hardware and software have made it increasingly viable to non-invasively measure cerebral perfusion or cerebral blood flow (CBF) itself, a physiological parameter that can be expressed in physical units (typically ml /100g brain tissue / min). Pulsed arterial spin labelling (PASL) is an increasingly common and repeatable technique [1]. It is likely to find a place in clinical trials and in particular the investigation of pharmaceutical agents active in the central nervous system. ASL CBF measures have been applied in pre-clinical pharmacological studies [2] and have recently been utilised in human pharmacological investigations into caffeine [3], sevoflurane [4] and remifentanil [5]. For pharmacological ASL to be viable as a tool in basic neuroscience research, clinical research and drug development, it needs to be repeatable enough and sensitive enough to detect perfusion changes in small cohorts. In this study, we aimed to determine the sample sizes necessary to detect regional changes in CBF in common types of clinical trial design.

Methods Two groups (N_A = 15 and N_B = 14) underwent ASL imaging at 3T (GE HDx). Group A attended a single session whereas Group B attended two sessions on separate days. Whole brain CBF maps were acquired using a pulsed ASL PICORE QUIPSSII sequence with GE-EPI readout (TR=2.2s, TE=19.8ms, matrix=64x64, FOV/slice=240/7mm, flip=80º, 16 slices, TI1=700ms, TI2=1350ms, reps=160 giving 80 tag-control pairs). A single shot EPI (M_0) scan was acquired (TR=∞) along with a T1-weighted whole-brain structural scan (1x1x1mm voxels). *Pre-processing:* motion correction; tag/ control time series were interpolated to the TR, subtracted and averaged to give CBF maps; M_0 of blood was estimated using the average white matter M_0 derived from the calibration scan; CBF maps were quantified using standard QUIPSSII CBF model [6] and transformed into MNI space. *ROIs:* Regions often implicated in pain processing [7] were chosen as ROI examples along with grey matter (GM) and visual cortex: the ACC and PCC, the precuneous, insula and somatosensory (SI+SII) cortices and the thalamus. Mean CBF values were calculated on a subject-by-subject basis in each ROI for each of the scans. Repeatability between sessions for Group B was computed for each ROI using intra-class correlation coefficients (ICC) [1]. The stability of the CBF measures was determined by calculating quantified CBF values for increasing lengths of the Group A data (i.e. 4, 6, 8 … tag/control pairs). Power calculations were performed to determine the number of subjects (*N*) required to detect a given effect size using the equation: $N = 2\,\sigma^2 (Z_{1-\alpha/2} + Z_{1-\beta})^2 / (effect\ \ size)^2$. A significance level of 0.05 (one-sided) and a detection power of 80% were assumed. Three types of comparisons were investigated: between groups, a two period cross-over (i.e. within subjects between sessions) and a within-subject within-session dosing. The variance, σ^2, for the each of the calculations was estimated with Group A vs. Group B1 data, Group B1 vs. Group B2 data and Group A first half vs. Group A second half data respectively. For each ROI, curves were calculated that compared the percentage flow change ranging from 1% to 50% to the number of subjects required to detect the effect.

Results Variability in mean CBF values across the ROIs exists in each of the sessions suggesting between-region differences in perfusion (e.g. from 36.1±6.1 (SI+SII) to 68.5±15.9 (insula)). However, the relative differences between ROIs are consistent across sessions with repeatability between Group B sessions demonstrated by large (>0.81) ICC values in all ROIs. It was found that after approximately 40 tag/control pairs, the mean CBF values across the subjects are within 5% of their final (80 tag/control pairs) value for all ROIs. Variance across subjects also reached stability after 40 tag/control pairs suggesting that repeatable CBF measures could have been obtained in Group A in half the time. This allows within-session variance to be calculated by splitting the data in two. Required sample sizes for the 3 types of study designs were estimated which vary substantially (Figure 1). To detect a 15% increase (or decrease) in CBF between groups on a per-ROI basis, approximately 20-40 subjects are needed in each group. Only 5-10 subjects are required in total to detect a similar increase in a within-session design. In the case of a crossover design, there is large variability in the number of subjects required across the ROIs but, in general, less than 15 are needed to detect a 15% change. For comparison, if a 10% change was expected, at least 34 subjects are required for detection in all areas with a crossover design.

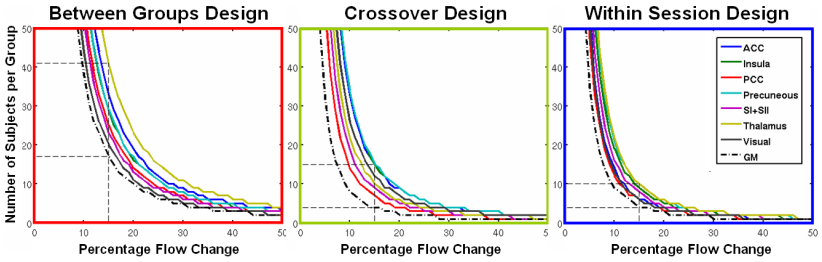

Figure 1: The group size required to detect a 15% change in CBF for each of the designs

Discussion Our implementation of a pulsed ASL technique appears to be sufficiently sensitive in small cohorts to detect regional differences in CBF such as may be expected in studies of pharmacological intervention. Stability and reproducibility of the measures in line with previous studies has been demonstrated [1]. For efficient clinical trial design, data must be collected within the minimum time possible. It has been shown that CBF measures in this study could have been collected in half the time (3 minutes) with little impact on sensitivity. Previous studies of CBF response to pharmacological interventions such as caffeine [3], sevoflurane [4] and opiods [5] have been primarily within session designs, thus have not suffered problems of insufficient sample size. Fewer pharmacological studies have been conducted as between-session or crossover designs. The study has demonstrated the feasibility of using these more standard clinical trial designs for investigating CBF changes due to pharmaceutical interventions.

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