Maximizing Statistical Power of ASL MRI in Detecting Regional CBF Differences

S. Aslan[1], and H. Lu[1]
[1]AIRC, UT Southwestern Medical Center, Dallas, TX, United States

INTRODUCTION: Cerebral blood flow (CBF) reflects how much blood passes through the capillary bed in the brain and is written in units of ml/100g/min. Although typically considered as a vascular parameter, CBF has played a major role in experimental investigation of neural activity in vivo, because CBF is coupled to neural activity under most circumstances. As a result, there is great interest in psychiatry and neurology community in using CBF to probe neural dysfunction in brain disorders (1), especially after recent technical advances in non-invasive mapping of CBF using the Arterial-Spin-Labeling (ASL) technique. The question is then how sensitive is ASL MRI in detecting regional activity difference between patients and controls and what is the best strategy to detect such a difference. In this work, we conducted numerical simulations and experimental measurements to answer these questions. For experiment, we used a model condition in which we simulated a "patient" group by having the subject view a flashing checkerboard and compared their CBF to that of a control group of subjects viewing a fixation. We propose that relative CBF is a more sensitive index to detect neural difference, rather than the much-sought-after absolute CBF, because it reduces the physiologic noise due to inter-subject variations in global CBF.

METHODS: *Experiment*: A total of 16 healthy controls (age 29±7 years) were studied on a 3T scanner (Philips). The subjects were divided into two groups, one group was shown a white cross and the other group was shown a flashing checkerboard at 4 Hz, to mimic the "control" and "patient" groups, respectively. For each subject, CBF was measured using a pseudo-continuous ASL (PCASL) technique. For quantification of absolute CBF, a phase-contrast MRI was also performed as described previously (2). In addition a high resolution T1 image was also acquired. Imaging parameters for pCASL scan were: voxel size=3x3mm, TR=4s, labeling duration/delay=1.6/1.5s, 30 pairs of controls/labels, RF interval 1ms, RF duration 0.5ms, flip angle 18º. In addition, the "patient" group also had a PCASL scan under fixation condition to serve as an intra-group control. The images were realigned and the absolute CBF (aCBF) maps were calculated using the method described previously (2). The relative CBF (rCBF) was obtained by dividing the aCBF value of each voxel by the whole brain aCBF of that subject. These images were spatially normalized to MNI template for statistical comparison. Voxel-based analysis used SPM's group comparison function to conduct t-test on each voxel in the brain. Region-of-interest (ROI) analysis was conducted by averaging the CBF values in a region (e.g. occipital lobe), which was then compared across the two subject groups. *Simulation* was conducted to confirm the experimental findings and to assess what is detection power under typical SNR of ASL and CBF difference. The aCBF of a brain region can be written as aCBF(S,r,d)=S*f(r,d)+n, where aCBF is subject specific (S) and region specific (r), and is also dependent on the physiologic state (d, diseased or healthy). S is the whole-brain CBF and is different from one person to another, but does not contain information about regional deficit. It contributes to the noise in group-level statistical comparison and is what we aim to remove by rCBF. f(r,d) is the disease effect and is what we want to detect. n is the random noise associated with MRI data. Simulation was conducted for aCBF and rCBF=aCBF/S, to assess which parameter can yield more powerful difference given the same raw data. The power was assessed by the probability of detecting a significant difference.

RESULTS and DISCUSSION: *Experiment*: Visual stimulation is expected to increase CBF in the occipital lobe. We therefore first compared the aCBF in the occipital lobe between the "control" and "patient" groups and found a 20.7% (n=8) increase, but the p-value was marginal (0.03). For the same data, if we were to calculate the rCBF (i.e. aCBF/whole brain CBF) then conduct the statistical comparison. The percentage change decreased to 15.9%, but interestingly the p value improved to 0.0004, a 75 fold change. Similar results were found in the voxel based analysis. With a threshold of p=0.001 and cluster size of 100 voxels, comparison on aCBF data yielded no significant voxels. On the other hand, comparison on rCBF correctly identified the visual cortex as having significant differences (Fig. 1a). For confirmation, Fig. 1b shows the results from the intra-subject comparison (comparing aCBF in the same subjects under fixation and flashing conditions, essentially a simple visual CBF-based fMRI), identifying the same regions with CBF changes. We have also tested to see if such an improvement in sensitivity is also applicable for intra-subject comparison. We have therefore conducted rCBF comparison between fixation and flashing conditions for the same group and the results are shown in Fig. 1c. No apparent improvement is observed. Therefore, the reason we see an improvement in the across-group comparison is because normalization of voxel aCBF with whole brain aCBF removed the global CBF variation across subjects, which is a significant source of noise if not accounted for. The experimental findings are consistent with the simulation results. Fig. 2 shows the detection power as a function of SNR and CBF differences. It can be seen that the rCBF plot (left) has a higher power compared to the aCBF plot (right). Such an improvement is particularly pronounced when the SNR is high and CBF difference is moderate. In essence, it states that, when the CBF difference is large and SNR is high, then the detection power is excellent for both aCBF and rCBF. Similarly, when the CBF difference is small and SNR is low, everything is buried in noise and no improvement can be made with normalization. Only in the intermediate situation, the rCBF shows a clear advantage. Interestingly, most of neuropsychiatric studies fall into this range (CBF difference between patient and control group is around 10-20% and the SNR of the data is about 5-10). In summary, our results suggest that, when it comes to detect regional CBF differences between two subject groups, rCBF is a more sensitive marker. Under typical SNR and neuropsychiatric CBF changes, ASL MRI is capable of detecting CBF deficit in patients.

REFERENCES: 1) Alsop DC. et al. Ann Neurol. 47:93 (2000). 2) Aslan S. et al. Magn Reson Med. *In Press*.

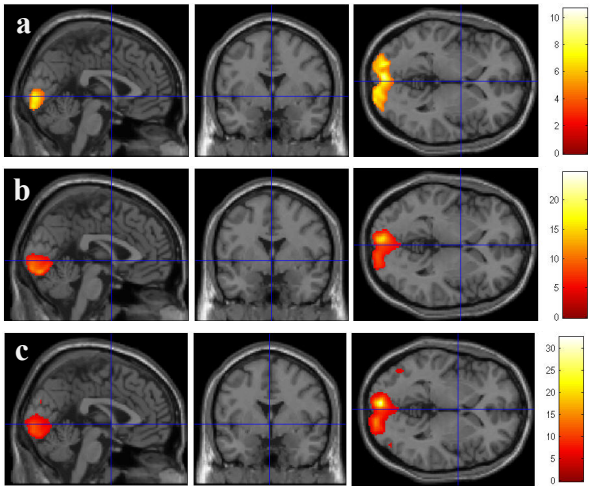

Figure 1. Voxel based analysis a) inter-group rCBF b) intra-group aCBF and c)intra-group rCBF are shown.

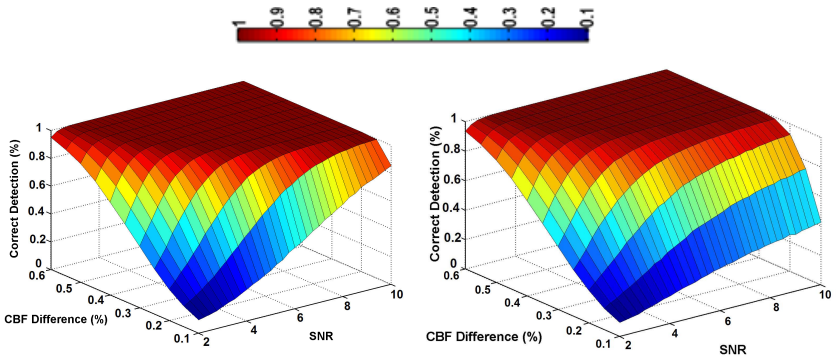

Figure 2. Simulation results for a) rCBF and b) aCBF of inter-group are shown.