Sensitivity of CASL MRI to Quantitative Regional and Global Changes Associated with Pain

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Introduction. The imaging of cerebral activity associated with pain and painful states has important implications for the study of clinical pain syndromes, including the potential of providing objective biomarkers in a field complicated by the ambiguities of subjective report. Capturing data to elucidate mechanisms of pain processing, concurrent with subjective data, would not only strengthen credibility of proposed treatments, but also would provide a method with which to corroborate self-report. Much of current functional neuroimaging is dominated by BOLD based fMRI, but this method provides "activation data," i.e., changes between states, and not absolute activity levels. Arterial spin labeling methods, however, can measure rCBF quantitatively as well as show the pattern of cerebral activity associated with any state. This is of great value when there may be impairments in resting baseline and also for identifying important global changes, e.g., in mean cortical activity. Paradoxical reductions in global rCBF have been reported in certain pain conditions and remain controversial and unexplained. [1]. The ability to quantify rCBF changes could also offer new insights when attempting to assess the relative significance of an observed change in activation pattern.

Materials and Methods. Five healthy subjects at the University of Alabama at Birmingham Medical Center participated in this preliminary phase of evaluating several categories of painful stimulation using continuous arterial spin labeling (CASL) MRI. Informed consent was obtained from all subjects, including 22 healthy controls that were used to help define the normal baseline state. Subjects were scanned during the following conditions: resting baseline, heat pain involving repeated heat pulses delivered to the upper surface of the right hand via a contact thermode, cold pain using repeated immersions of the hand into ice water every 20 sec for 10 sec, and ischemic pain in response to exsanguination of the right arm for four minutes. Participants provided pain ratings using a 10-point scale, following each scan condition.

MR Sequences: All subjects were imaged on a 3T, Philips Achieva clinical scanner, using a transmit/receive head coil. Supra-tentorial slices extending from cerebellum to top of the cerebrum were acquired continuously in ascending order during resting baseline and each of the three pain states using single shot spin echo planar imaging; acquisition matrix 80x80, TR/TE: 5 sec/42 msec; acquired spatial resolution: 3.59 x 3.65 x 8 mm; interslice gap 1.5 mm; adiabatic-through-fast passage labeling pulse; labeling offset 80 mm; labeling delay 1400 msec; labeling duration 2400msec; 10 sec per dynamic; 30 dynamics). [2-5]

Data Analysis: CASL data was stored as raw echo amplitudes and transferred to a separate workstation for rCBF computations [1-4] using custom software written in MATLAB™. The 30 pairs of labeled and control images were first corrected for motion and then averaged to produce a single set of perfusion sensitive images. Changes in rCBF were analyzed using a local ROI method [2-3] and compared to the 22 controls with Statistical Parametric Mapping (SPM5) analysis.

Results: All pain conditions induced significant regional activations with some variation as to extent, magnitude and global cortical effects. *Figure 1*. CASL rCBF images (slice 7 of 13) in subject during rest (upper) and during cold presser pain of the right forearm (lower). *Figure 2*. ROI analysis example. Resting scan (upper) and scan during right hand cold presser pain inducement (lower) analyzed for changes in ROIs at slice 9 (of 13). The graph shows a boxplot analysis of rCBF mean (small circle), median, and the variance in each of 16 cortical sectors running in a circumferential manner from the left frontal lobe (region 1) to the posterior of the brain (regions 8,9) and then to the right frontal lobe (region 16). ROI number 4 and 5 in left hemisphere peri-rolandic region show maximum rCBF during pain scan. *Figure 3:* SPM analysis of each pain scan compared to 22 controls typically showed significant ($p < 0.01$) activation in thalamus, left somatosensory cortex and anterior cingulate. The figure is an example of a subject during a heat pain scan who reported high discomfort. Highly significant activation is seen in the anterior cingulate.

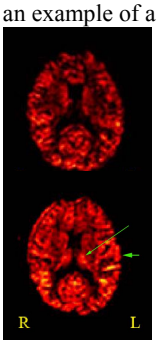

Fig 1

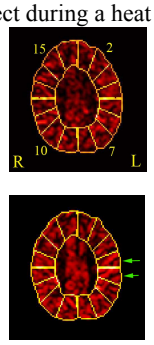

Figure 2a

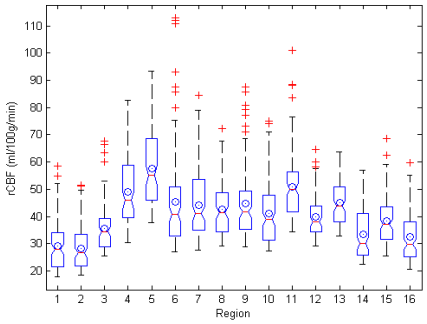

Figure 2b

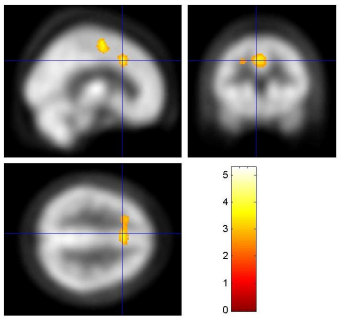

Figure 3

Tables 1 and 2 show mean rCBF values for the thalamus and for all cortical ROI (using the ROI system of figure 2)

Table 1. Thalamic rCBF (ml/100g/min)

	Rest	Cold**	Heat**	Ischemic**
Left	51.5±9.3	75.9±10.7*	55.7±7.0	60.4±6.7 *
Right	48.9±7.7	59.6±12.2*	46.1±5.9	47.3±8.5

Table 2. Mean cortical rCBF (ml/100g/min)

	Rest	Cold	Heat	Ischemic
Left	52.4±9.6	73.4±9.3*	58.1±3.1*	52.8±2.3
Right	55.0±7.4	71.2±9.6*	55.5±2.7	53.8±2.4

Mean of top 10% voxel values. *significant increase **significant asymmetry (P>.01)

Discussion:

Robust changes were recorded in thalamic, peri-rolandic and anterior cingulate regions in each pain condition, as well as in mean hemispheric cortical rCBF during cold and heat pain. The cold presser task induced significantly greater absolute increases in thalamic and mean cortical activity compared to the other pain conditions, suggesting it is a good choice when appropriate for pain research utilizing neuroimaging. There was no evidence of reduction in mean cortical rCBF during any of our pain conditions. The CASL technique itself appears to be a sensitive measure of pain related cerebral activity, offering absolute quantification of state dependent physiological change as well as any baseline impairments. It should thus be very suitable for the study of clinical pain syndromes.

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