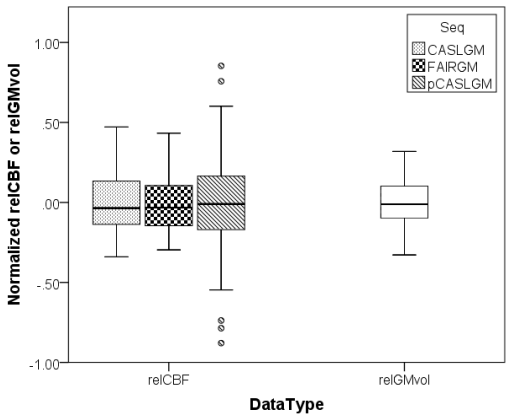
Intersubject variability in cerebral blood flow is great than structural variability

Y. Chen[1], H. Rao[1], and J. A. Detre[1]
[1]Center for Functional Neuroimaging, University of Pennsylvania, Philadelphia, PA, United States

Introduction Resting brain metabolism represents roughly 20% of total body metabolism despite accounting for only 2% of the total body mass[1]. Arterial spin labeling (ASL) uses endogenous blood water as a nominally diffusible tracer to non-invasively quantify cerebral blood flow (CBF), which is tightly coupled to regional brain metabolism. While CBF is known to be modulated by age and gender[2], little is know about intersubject variability in CBF, which may be reflective of individual phenotypic differences. To assess the extent individual variability in CBF, we retrospectively analyzed de-identified ASL data from a large number of subjects, and compared the between-subject variance in gray matter CBF to the variance in gray matter volume (GMvol) to test the hypothesis that metabolic variance exceeds structural variance.

Methods ASL and high-resolution anatomical data from healthy subjects recruited for other projects were pooled and analyzed for the current study. All scans were performed on a 3.0T whole-body scanner (Siemens TIM Trio, Erlangen, Germany) equipped with either an eight-channel receive-only head coil or circularly polarized transmit/receive head coil (Bruker, Germany). A total of 136 subjects (72 male, 32 ± 17 years old) were included in the data analysis. The ASL data were a combination of three ASL sequences: pseudo-continuous ASL[3] (pCASL, n=103), continuous ASL[4] (CASL, n=38) and FAIR[5] (n=20) with commonly used parameters for healthy subjects. Some subjects were scanned with all three sequences. Quantitative CBF maps were calculated using pre-published models[6] and co-registered to the anatomical images using SPM5. Individual gray matter (GM) masks were generated by segmenting each subject's anatomical, thresholded at 0.75 and applied to the CBF maps for extraction of mean GM CBF. Mean GMvol was calculated as product of total GM probability and voxel volume. To facilitate comparison between volume and CBF, which have very different scales, relative CBF (relCBF) and GM volume (relGMvol) defined as (x-mean(x))/mean(x), where mean(x) refers to the average over the entire cohort, were used for variance comparison statistical tests.

Results Bar and whisker plot of the relCBF values for all three sequences are shown with relGMvol. Outliers are shown as circles outside the T-bars. As is evident from the plot, relGMvol has smaller variance than the relCBF values of the three sequences. Pairwise F-test results of variance comparison between relCBF and relGMvol, as well as the respective standard deviations (SD) are shown in the table below. For all three sequences, the one tailed p-values were smaller than 0.05, indicating SD of relCBF was significantly higher than that of relGMvol. Levene's test statistics showed that the SDs of relCBF between the three sequences were not significantly different (p=0.10). The bottom table shows the results of linear regression on the pCASL CBF and GMvol data, with age and gender as independent variables. As expected, both age and gender account for significant amount of variability in both CBF (age nearly significant) and GMvol. However, the lower R^2 for the CBF data suggest there are additional sources of variability in CBF as compared to GMvol.



Sequence	SD of relCBF	SD of relGMvol	F-Test
pCASL	0.29	0.13	F(105,135)=5.32, p<0.00001
FAIR	0.21		F(20,135)=2.84, p=0.0002
CASL	0.18		F(38,135)=2.13, p=0.0009
Levene's Test	W=2.30, p=0.10		

Discussion The SD of CBF is significantly greater than that of GMvol. In a subset of 12 subjects, repeated measures of pCASL yielded a within-subject coefficient of variation (CV) of 8.5% for scans separated by 1 week[7]. Intersubject variability was much larger; 14% in that subset and 17% in this larger cohort, suggesting that the greater intersubject variance reflects biological variability rather than measurement error. The reduced R^2 fit for the age and gender linear model to the CBF data as compared to the GMvol data also suggest that there are additional sources of variability associated with CBF. While intersubject variability could be at least partially attributable to uncontrolled differences in physiological factors such as caffeine intake and alertness in these data, or technical factors such as labeling efficiency, it is likely that at least some of the variability reflects true phenotypic differences in CBF. For example, a recent study demonstrated that resting frontal CBF before sleep deprivation strongly correlates with performance after sleep deprivation[8]. Combined with our results, this suggests resting CBF can be a potential marker for phenotypic differences among individuals. The ability to non-invasively quantify CBF with ASL MRI in large numbers of subjects will allow the concept to be further explored and validated.

References

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	pCASL CBF			GM volume		
	Coefficient	t	p-value	Coefficient	t	p-value
Age	-0.2	-1.86	0.07	-2.6	-7.12	<0.001
Gender	15.8	4.31	<0.001	-42.3	-3.46	0.001
Intercept	52.3	8.42	<0.001	831.2	39.84	<0.001
Model Fit	F(2,103)=9.93, p=0.0001, R^2=0.14			F(2,133)=35.58, p<0.0001, R^2=0.34		