Baseline cerebral venous oxygenation determines response amplitude to functional activation

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INTRODUCTION: FMRI has been widely used to study brain functions, with the assumption that the fMRI signal is an indirect measure of the underlying neuronal activities. However, large variability in fMRI signals is often observed even with a homogeneous subject group using identical stimuli (1). The reasons for these observations are not well understood because of the complexity of the BOLD signal mechanism as well as insufficient understanding of neurovascular coupling. Therefore, it is not clear whether the fMRI signal variability (inter-subject and intra-subject) is simply due to random noise or has certain physiologic basis. In this study, we tested the hypothesis that the fMRI signal amplitude for an individual is modulated by his baseline blood-oxygenation-level. We used a newly developed method, T2-Relaxation-Uner-Spin-Tagging (TRUST) MRI (2), to estimate baseline venous oxygenation ($Y_{v,baseline}$) non-invasively and compared the results with the signal amplitude using different fMRI techniques, including BOLD, ASL and VASO fMRI.

METHODS: MR experiments (3T Tim Trio, Siemens) were performed on a total of 11 healthy subjects with informed consent. The TRUST MRI sequence is detailed in another abstract (2). Briefly, it uses the spin labeling principle to separate out the pure (venous) blood signal in the sagittal sinus and then uses T2-preparation pulses to modulate the signal with different T2-weighting. The measured venous blood T2 can be converted to Y_v with a well-known relationship between blood oxygenation and blood T2 (3). The $Y_{v,baseline}$ is only measured in the sagittal sinus, but it is well established that the oxygen extraction fraction (OEF, i.e. 1-Y_v) is homogeneous within the brain at resting state (4). Therefore, $Y_{v,baseline}$ is applicable to other brain regions. Flashing checkerboard visual stimulation was used for fMRI experiments. Each fMRI experiment consisted of 3 blocks of 30s ON and 54s OFF periods plus an OFF period at the beginning, resulting in a duration of 5'6". The order of the scans was: (first TRUST MRI), (BOLD, ASL and VASO fMRI in pseudo-randomized order across subjects), (second TRUST MRI). The TRUST MRI scan was performed twice because we wanted to evaluate whether there is any difference in baseline venous oxygenation before and after the fMRI experiments (fatigue or stress effects due to being inside the magnet and/or doing fMRI experiments). The imaging parameters were: for TRUST MRI, FOV=230mm, matrix=64x64, single-shot EPI, slice thickness=5mm, TR=8000ms, TE=19ms, TI=1200ms, repetition=4, scan duration 4'16"; for BOLD fMRI, TE=30ms, TR=3s, 32 slices; for ASL MRI, TR/TE/TI=3000/13/1500ms, 1 slice; for VASO fMRI, TR/TE/TI=3000/13/889ms, 1 slice.

Data were processed using in-house MATLAB scripts. Venous blood T2 was obtained from TRUST MRI (2) and the value was converted to Y_v using an *in vitro* calibration curve (3). ASL signals were converted to CBF values using a perfusion model (5). FMRI activation detection was based on cross-correlation with a box-car function (threshold cc>0.2, cluster size 3). For each fMRI experiment, activated voxels were detected and the signals were spatially averaged to give the signal amplitude for each subject.

RESULTS and DISCUSSION: Fig. 1 shows the activation maps for BOLD, ASL and VASO fMRI and their respective time-courses. The number of activated voxels were 534±237 (mean±SD, n=11), 73±30, 48±30 for BOLD (multi-slice), ASL (single-slice) and VASO (single-slice), respectively. Fig. 2a shows a significant correlation (p=0.026) between $Y_{v,baseline}$ and BOLD signal amplitude for all subjects, suggesting that individuals with higher baseline venous oxygenation tend to have smaller BOLD percentage signal changes. Since the fMRI task is a simple visual task and the activated voxels are all from early visual areas, it is reasonable to assume that the underlying neuronal activities are similar for all subjects. The correlation is therefore likely due to vascular differences. If this source of variation is accounted for by measuring the baseline Yv and use it as a linear regressor, one can considerably reduce the standard deviation within the group and thereby improve the statistical power in group analysis. In our data, the inter-subject BOLD variation decreased by 25.2% (from 0.41 to 0.31) after the regressor correction. The correlation between $Y_{v,baseline}$ and CBF percentage change (Fig. 2b) is even more significant (p<0.0001), and the regressor correction using $Y_{v,baseline}$ reduced the variation by 63% (from 23.4 to 8.6). Interestingly, there is also a significant (p=0.003) correlation between baseline Y_v and baseline CBF (Fig. 2c) among subjects. This relationship perhaps should not be surprising considering that the oxygen metabolism, CMRO2, is proportional to CBF x (1-Y_v), and higher blood flow means smaller fraction of oxygen needs to be extracted per unit volume of blood. There was no significant relationship between $Y_{v,baseline}$ and VASO signal changes, probably because the VASO signal reflects ΔCBV rather than ΔCBV/CBV (6). Comparing the beginning and the end of the MRI session (Fig. 2d), the global venous oxygenation did not change significantly (Two-tail paired t test, p=0.32). Based on our data, we speculate the following hypothesis: Different individuals have different baseline blood flow accompanied by different baseline venous oxygenation (the causality of these two remains to be determined). Upon activation, the absolute CBF increase (in ml/100g/min) for the subjects are similar (data not shown, also see (7)), which results in a lower percentage CBF change for the subjects with high baseline CBF. This lower ΔCBF/CBF results in lower ΔOEF/OEF, assuming ΔCMRO2/CMRO2 is similar across subjects. Since $\Delta Y_v = \Delta OEF = OEF_{baseline}$ x (ΔOEF/OEF), therefore for subjects with high baseline CBF (i.e. high $Y_{v,baseline}$), ΔY_v is smaller due to the double jeopardy of smaller $OEF_{baseline}$ and smaller ΔOEF/OEF. ΔY_v is of course expected to be the main contrast determining the BOLD signal.

REFERENCES: 1) Aguirre et al. NeuroImage 8: 360 (1998); 2) Lu ISMRM Abstract, submitted (2007); 3) Silvennoinen et al. MRM 49: 47 (2003); 4) Fox et al. PNAS 83: 1140 (1986); 5) Buxton et al. MRM 40:383 (1998); 6) Lu et al. MRM 50: 263. (2003); 7) Kastrup et al. NeuroReport 10: 1751 (1999).

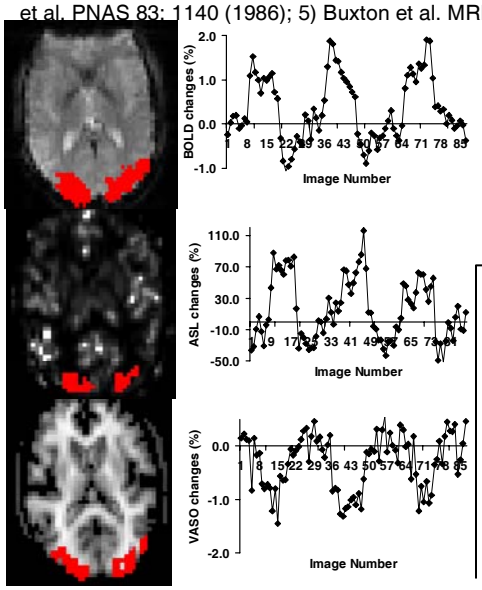

Fig. 1: FMRI activation maps and their corresponding time-courses for BOLD (top), ASL (middle) and VASO (bottom) techniques. TR=3s, Three visual stimulation blocks (30s) for each experiment.

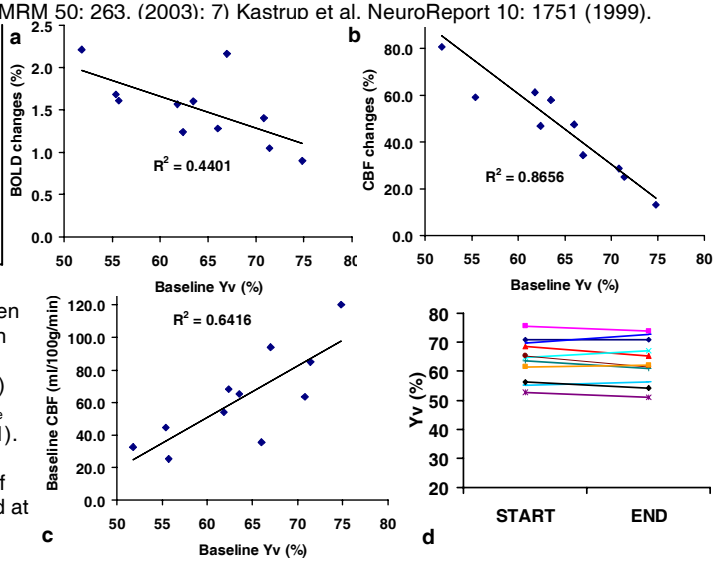

Fig. 2: (a) Correlation between baseline venous oxygenation and BOLD changes across subjects (n=11, p=0.026). (b) Correlation between $Y_{v,baseline}$ and CBF changes (p<0.0001). (c) $Y_{v,baseline}$ vs. $CBF_{baseline}$ (p=0.003). (d) Comparison of $Y_{v,baseline}$ at the beginning and at the end of the experiment session (p=0.32).