Normalization of fMRI signal with basal physiologic state improves sensitivity in differentiating subject groups

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INTRODUCTION: Recently, we have developed a T2-Relaxation-Under-Spin-Tagging (TRUST) technique to quantitatively estimate cerebral venous oxygenation (Y_v) in units of percentage (1), and have shown that stimulation-evoked fMRI signal is inversely correlated with $Y_{v,baseline}$ across subjects (2). Specifically, individuals with higher baseline oxygenation tend to have a smaller fMRI signal and vice versa, when using identical stimuli. This provides an opportunity to use TRUST MRI as a normalization factor to reduce inter-subject variations, and to improve sensitivity of fMRI in detecting group differences. This improvement will be beneficial for the study of psychiatric disorders and comparison of pre/post drug treatment, thereby substantially extending the potential clinical utility of fMRI. Here we aim to test the utility of TRUST MRI in distinguishing subject groups in a "model" situation. Checkerboards flashing at 8Hz and 4Hz are presented to two healthy control groups, respectively. Comparison between the groups with and without using TRUST MRI is conducted to assess whether or not TRUST MRI can improve the statistical significance of the results.

METHODS: MR experiments (3T Achieva, Philips) were performed on a total of 13 healthy subjects (7 for 8Hz and 6 for 4Hz, the groups were randomly assigned) with informed consent. It is well established that the BOLD fMRI signal is dependent on the flashing frequency, greatest when using an 8Hz stimulus and lower when using a higher or lower frequencies (3). The vision of the subjects was corrected using MR-compatible corrective lenses, whenever necessary. Vital physiologic signs, including blood pressure, heart rate, arterial oxygenation, and end-tidal CO2, were measured before they entered the magnet room. Stimulus paradigm included 10s flashing and 50s fixation and repeated 4 times. An extra 50s of fixation was used at the beginning of the experiment. Activation detection was based on cross-correlation with a standard BOLD response determined in one of our previous studies (4). The largest activation cluster was determined and this always corresponds to the occipital lobe regions (visually verified). To account for the effect of ROI size on the signal amplitude, only the 500 voxels that have the highest cross-correlation were included in signal average. TRUST MRI (~4 min) was also performed at resting condition to estimate $Y_{v,baseline}$ (1). The BOLD fMRI parameters were: TR=500ms, flip angle 37 degrees (to maximize CNR and to reduce inflow effect), TE=30ms, SENSE factor 2, matrix 64x64, voxel size 3.44x3.44x5 mm^3, 1mm gap.

RESULTS and DISCUSSION: Robust activations were detected in all subjects, including both the 8Hz and the 4Hz groups. An example of the voxels that were used for signal average is shown in Figs. 1a and b. Fig. 1c shows the averaged signal time-courses for both groups. The physiologic parameters, blood pressure, heart rate, arterial oxygenation, end-tidal CO2, and breathing rate, showed no significant differences between the groups. TRUST MRI yielded baseline venous oxygenation of 62.1±2.8% and 51.0±15.1% in the 8Hz group and 4Hz group, respectively. While not planned, the 4Hz group was found to have a wider spread of Y_v and a lower mean value, although the group values are not significantly different (p=0.082, Student t test). The BOLD signal amplitude before TRUST normalization was 2.71±0.20% and 2.44±0.32% for the 8Hz and 4Hz group, respectively. The Student t test yielded p=0.1007, not yet reaching statistical significance. The Y_v values from TRUST MRI were then used to normalize the BOLD signals by using a linear regression: $S=a_1*X_1+a_2*X_2+a_0$, where S is the BOLD signal amplitude, X_1 is the flashing frequency, X_2 is the baseline Y_v. The normalized BOLD signal is then calculated as $S_{norm}=S-a_2*X_2$. It was found that the results after normalization showed significant difference between the 8Hz and 4Hz groups (Fig. 2 middle) and the p value showed an ~100 fold reduction. In TRUST MRI, Y_v is estimated by comparing experimentally determined venous blood T2 to a calibration plot specifying the relationship between T2 and Y_v. We also tested to see whether blood T2 can be used as a normalization factor, thereby eliminating the need to assume/measure the calibration plot. Fig. 2 (right) plots the results, showing that venous blood T2 can yield similar normalization effect. One can also use previously established relationship between fMRI signal and Y_v to do normalization: i.e. Normalized Signal = Observed Signal + Y_v*0.0374, where 0.0374 is the slope obtained from our previous study (2). The results were similar to the direct regression (without using previous data) findings (p=0.0007) and the results were comparable between Y_v or blood T2 normalization. Note, however, that similar stimulus types and brain regions should be used when using slope determined in previous data or literature. Regression analysis was also performed using each of the physiologic parameters (i.e. blood pressure, heart rate, arterial oxygenation, end-tidal CO2, and breathing rate) as the regressor, and no significant difference between 8Hz and 4Hz was found using any of these parameters at a p value threshold of 0.05 (corrected for multiple comparisons). Another way to understand the data is to look at them in a scatter plot (Fig. 3). If we consider that the parameter-of-interest (in this case the stimulus frequency, but could also be patients vs. controls, or pre vs. post-drug treatment) is the only parameter affecting the fMRI signal amplitude, we are only looking at the data in one dimension (Fig. 3, left), which may show a considerable overlap. If we can identify a physiologic modulator affecting the fMRI signal and measure this modulator, we can then look at the data in two-dimensions (Fig. 3, right), in which the effect of parameter-of-interest is more obvious and detectable. In fact, in this example, the Y_v-normalized fMRI signals were completely separated (e.g. by using 2.533% as a threshold) between 8Hz and 4Hz, giving a 100% sensitivity and specificity.

In summary, TRUST MRI can provide a means to normalize fMRI signals across subjects and to improve the sensitivity of detecting fMRI signal differences between two groups of subjects. This may benefit fMRI studies of psychiatric and neurological disorders.

REFERENCES: 1) Lu ISMRM Abstract 256, (2007); 2) Lu et al. ISMRM Abstract 613, (2007); 3) Singh et al. MRM 49: 108 (2003); 4) Lu et al. MRM 56: 546 (2006).

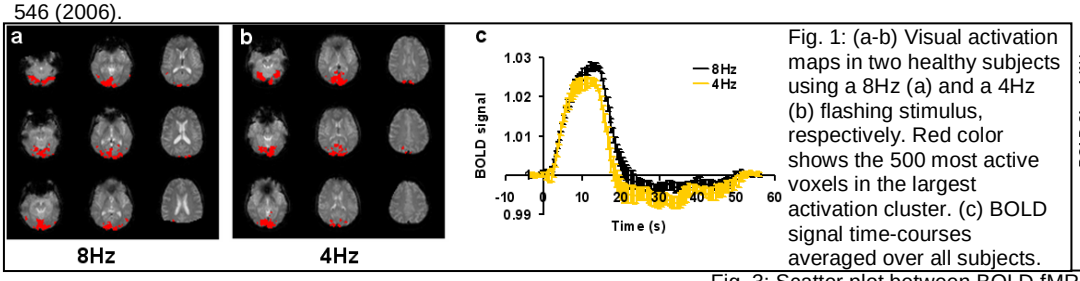

Fig. 1: (a-b) Visual activation maps in two healthy subjects using a 8Hz (a) and a 4Hz (b) flashing stimulus, respectively. Red color shows the 500 most active voxels in the largest activation cluster. (c) BOLD signal time-courses averaged over all subjects.

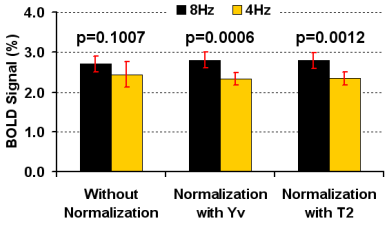

Fig. 2: Comparison of BOLD signal amplitudes between the 8Hz group and the 4Hz group. Error bars indicate the standard deviations. The TRUST MRI results (Y_v and T2 for middle and right plots, respectively) were used to normalize the BOLD signals across subjects, which yielded improved statistical significance.

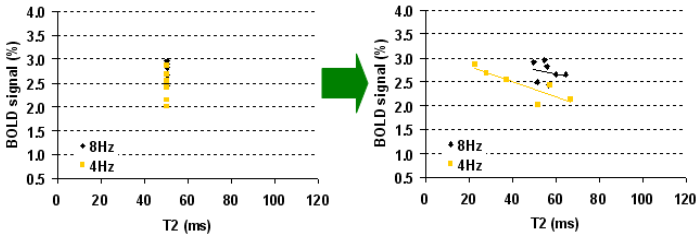

Fig. 3: Scatter plot between BOLD fMRI signals and baseline T2. If the baseline T2 is not measured (left), one has to assume it is the same for every subject and the data can only be investigated in one dimension, which shows a large overlap. When baseline T2 is measured individually using TRUST MRI (right), much of the inter-subject variation can be explained by the baseline T2 and the groups are better separated.