A COMPARISON OF PHYSIOLOGIC MODULATORS OF FMRI SIGNALS

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INTRODUCTION: A critical prerequisite for fMRI to be possibly used for personalized disease diagnosis is that we have to understand and account for differences in fMRI signals across healthy subjects, so-called "normal variations". Recently, much attention has been focused on the physiologic markers that can explain the inter-subject variations. Several potential modulators of fMRI signals have now emerged: baseline venous oxygenation by TRUST MRI (1), cerebrovascular reactivity by hypercapnia (2,3), resting state BOLD signal fluctuation (4) and baseline CBF (5). A remaining issue is then to assess whether these modulators are all equivalent or they provide complementary information thus can be combined to account for the maximum fraction of variability. Here we conducted visual-stimulation fMRI in a group of young, healthy controls and compared the above four modulators in explaining the variations in fMRI signals. The benefit of each parameter is assessed in the context of the acquisition time and conditions.

METHODS: Experiments were performed on nine healthy subjects (age 28±4 y, range 23-33, 3 M, 6 F) on a 3T scanner (Philips). The vision of the subjects was corrected using MR-compatible corrective lenses, whenever necessary. The fMRI experiment used visual stimulation (blue-yellow flashing checkerboard) via a back-projection system. The four potential modulatory parameters were acquired as follows. Global baseline venous oxygenation was determined in sagittal sinus using a recently developed TRUST MRI (6). TRUST sequence parameters: voxel size 3.44x3.44x5mm^3, TR=8000ms, TI=1200ms, four TEs: 0ms, 40ms, 80ms and 160ms. Previously cerebrovascular reactivity (CVR) measurement used breathholding task (2,3). Here we used CO2 breathing as it allows us to monitor/record the end-tidal CO2 level and to use it in the general linear model analysis (7). The subject breathed room-air and 5% CO2 (mixed with 21% O2 and 74% N2) in an interleaved fashion (switching every 1 min) while we continuously acquired BOLD EPI images. BOLD parameters: TR/TE=1500/30ms, voxel size 3.4x3.4x5mm^3. Resting state BOLD fluctuation was quantified by acquired BOLD EPI images while the subject fixated on a cross sign on the screen. A previous study used ASL MRI to obtain quantitative estimation of CBF (5). However, ASL quantification can be sensitive to transit time, trailing time and labeling efficiency. We have therefore used phase-contrast MRI to estimate whole-brain CBF in units of ml/min. The phase-contrast slice was positioned at the level of internal carotid/vertebral arteries based on a time-of-flight angiogram. A T1w image was also acquired to determine intracranial volume. The per-volume CBF is then given by whole-brain CBF/intracranial volume.

For clarity, we summarize the four parameters and their respective acquisition techniques in Table 1.

For data processing, the EPI images were transformed into the MNI space. An anatomic mask of occipital lobe (8) was applied and only the activated voxels within the mask are considered. For regression analysis between fMRI signals and the physiologic modulators, the baseline oxygenation and CBF used whole brain values since our measurements for them do not have spatial information. For the CVR and resting state fluctuation, the activated voxels used for fMRI signal averaging were used for their averaging.

RESULTS and DISCUSSION: Fig. 1 shows a representative dataset for the four physiologic measurements. The data quality in all four techniques was satisfactory, and the subjects did not experience any adverse effects from the CO2 breathing. For the visual fMRI scan, robust visual activation was observed in the visual cortex in all subjects. Over the entire group of subjects, the visual fMRI signal was 3.53±0.56% (n=9, mean±SD). The averaged values of the four physiologic modulators were: Baseline oxygenation 63.5±4.8%, Cerebrovascular reactivity 0.31±0.07%/mmHg CO2, Resting state fluctuation 0.0051±0.0022 (fraction, unitless), CBF 45.1±7.4ml/100g/min. Fig. 2 shows the correlation between the fMRI signal amplitude and each of the physiologic modulators across the subjects. Despite the relatively small sample size, a clear correlation ($p<0.1$) can be found in all four plots. The trends of the correlations are also in agreement with previous reports: fMRI signal is greater in subjects with lower baseline oxygenation (1), higher vascular reactivity (2,3), higher resting state fluctuation (4), and lower baseline CBF (5). A step-wise linear regression analysis revealed that the four parameters combined together can explain 69% of the inter-subject variations (i.e. R^2) observed in our data. However, the majority of this can be achieved by combining CVR with any one of the other three parameters (CVR+oxygenation 60%, CVR+resting state 66%, CVR+CBF 67%). That is, adding more than two (including CVR) parameters did not provide statistically significant improvement in reducing the variations. This is also confirmed by the finding that baseline oxygenation, resting state fluctuation, and baseline CBF are all inter-correlated (oxygenation vs resting state R=0.77, oxygenation vs CBF R=0.73, resting state vs CBF R=0.71).

In summary, inter-subject variations in fMRI signals can be explained by multiple physiologic parameters. Some of these modulators (baseline oxygenation, resting state signal fluctuation, baseline CBF) appear to be of similar origin, possibly all reflecting the basal state of the individual. Thus, the measurement of one parameter may be sufficient to account for that portion of the variability. Cerebrovascular reactivity, on the other hand, represents a separate source of variability and, ideally, should be accounted for on a subject-by-subject basis.

REFERENCES: 1) Lu et al. MRM, 60:364, 2008; 2) Thomason et al. HBM, 28:59, 2007; 3) Handwerker et al. HBM 28:846, 2007; 4) Kannurpatti and Biswal NeuroImage, 40:1657, 2008; 5) Liau et al. ISMRM, 854, 2008; 6) Lu and Ge, MRM, 60:357, 2008; 7) Yezhuvath et al. ISMRM, 2345, 2008; 8) Tzourio-Mazoyer et al. NeuroImage, 15:273, 2002.

Table 1: Summary of the fMRI signal modulators considered in this study.

	Technique	Scan duration	Task requirement	Caveat
Baseline oxygenation (%)	TRUST	4min 16sec	Rest	Special pulse sequence
Cerebrovascular reactivity (%BOLD/mmHg CO2)	BOLD EPI	7min	Breathing 5% CO2	Additional apparatus and setup time
Resting state fluctuation (SD/mean)	BOLD EPI	5min	Fixating on a cross	Assuming identical breathing fluctuation for all subjects
CBF (ml/100g/min)	Phase contrast	6min 30sec	Rest	Flow pulsation artifacts

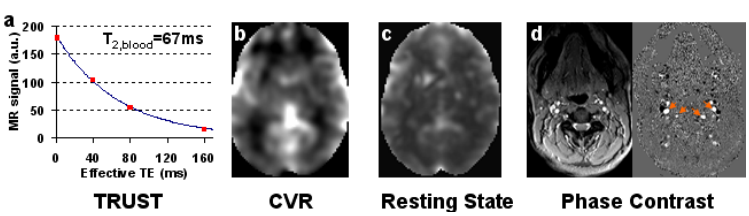

Fig. 1: Data from each of the physiologic measurement in one subject. (a) TRUST MR signal as a function of TE. Red symbols represent experimental data and the solid curve represents the fitted mono-exponential curve. The decay time constant is the blood T2. (b) CVR map from the hypercapnia experiment. (c) Map of std/mean from the time courses of the resting state BOLD data. (d) Anatomic image (left) and velocity map (right) from the phase contrast scan. Arrows indicate the internal carotid and vertebral arteries.

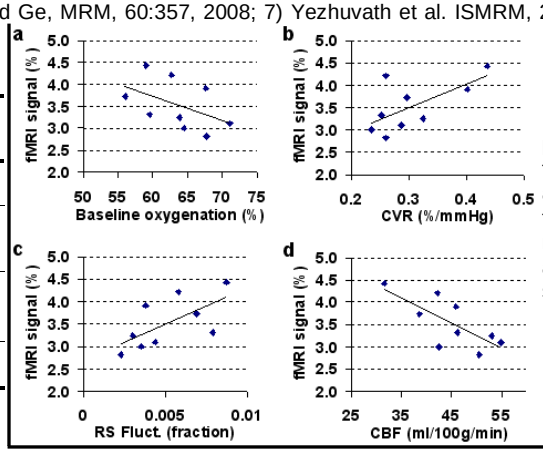

Fig. 2: Scatter plots between fMRI signal and each of the physiologic modulators across subjects (n=9).