COMPARISON OF PHYSIOLOGIC MODULATORS IN EVENT-RELATED FMRI

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INTRODUCTION: Since normal variations in fMRI responses are considerable across subjects, it is critical to understand and account for these inter-subject variations, in order for fMRI to be possibly used as a personalized diagnostic tool for brain diseases. Previous studies have reported a few physiologic modulators that could explain the inter-subject variations and may potentially be used for fMRI normalization, including baseline venous oxygenation (1), cerebrovascular reactivity (2,3), resting state BOLD signal fluctuation (4) and baseline cerebral blood flow (5). However, most of these modulation effects were demonstrated only in primary sensory and motor cortices using a block design fMRI. It is not clear whether these modulators could be useful in event-related fMRI using a more cognitively relevant task, which has smaller but more realistic signal amplitude compared to simple visual or motor tasks. Furthermore, it is not clear that, when a task activates multiple brain regions, whether a global measure of physiologic parameter is sufficient for use in all regions. In this work we conducted an event-related, episodic memory fMRI in a group of young, healthy subjects, and investigated the dependence of fMRI signal on each of the aforementioned physiologic modulators. The presence/absence of modulation effect was studied in two focal brain regions activated by this task. Potential relationship among the four modulators was also investigated.

METHODS: Twenty five young healthy subjects (11 males, age 27.0±5.5 y, range 20-35 y) were studied on a Philips 3T MRI scanner. Each subject received 3 fMRI runs with 32 pictures in each run. Each picture appeared for 3s followed by a fixation period of 4-17s (randomized). The subjects were instructed to determine if there is water in the picture and to press buttons accordingly. Tasks of similar type are widely used in cognitive neuroscience and clinical fMRI studies. Standard BOLD fMRI imaging parameters were used: TR/TE=2000/25ms, voxel size 3.4x3.4x3.5mm^3, duration 5.75 min per run. In addition, four physiologic parameters previously reported to have a modulatory effect on fMRI signal were measured. *Global baseline venous oxygenation (Yv)* was determined in the sagittal sinus using a TRUST MRI technique (6) with the following parameters: voxel size 3.44x3.44x5mm^3, TR=8000ms, TI=1200ms, four TEs: 0ms, 40ms, 80ms and 160ms. *Cerebrovascular reactivity (CVR)* was measured with CO2 induced hypercapnia (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 BOLD EPI images were acquired continuously. *Resting state BOLD fluctuation* was quantified by acquiring BOLD EPI images while the subject fixated on a white cross sign on the dark screen. *Baseline cerebral blood flow (CBF)* was determined by a phase-contrast MRI method with the imaging slice positioned at the level of brain's feeding arteries (internal carotid/vertebral arteries) to obtain the total blood flow to the brain (8). Then the per-brain-volume CBF was calculated as whole-brain CBF/intracranial volume determined from a T1w anatomic image. For data processing, the EPI images were realigned and transformed into the MNI space, and the activation t score map was obtained for each subject. The fMRI modulation effects were assessed in two focal ROIs, occipital lobe and medial temporal lobe (MTL), using anatomic masks provided by the AAL software (9). To concentrate our analysis on activated voxels, only the top 5000 and 1000 activated voxels within the occipital lobe and MTL, respectively, were included in the signal averaging. The fMRI signal amplitude was determined from the peak signals in the estimated HRF. The physiologic modulators were quantified using their respective data (6,7,4,8). We note that baseline Yv and CBF were whole brain values, while CVR and resting state fluctuation were region-specific values (i.e. separate sets of values for occipital lobe and MTL). For statistical analysis, mixed effect model was used to test the correlation between fMRI signal and physiologic modulators using data from all three fMRI runs.

RESULTS and DISCUSSION: Fig. 1 shows group-level activation maps demonstrating activations in the occipital lobe and MTL. The averaged fMRI signal in the occipital lobe and MTL ROIs were 0.95±0.28% (n=25, mean±SD) and 0.49±0.15%, respectively, showing an amplitude much lower than the previous block design results (1,3). The values of the four physiologic modulators were: Yv 63.9±6.9%, CBF 59.6±7.4ml/100g/min, CVR 0.23±0.04%/mmHg CO2 for occipital lobe and 0.20±0.05%/mmHg CO2 for MTL, Resting state fluctuation 0.0045±0.0011 (fraction, unitless) for occipital lobe and 0.0039±0.0011 for MTL. In the occipital lobe, we found a significant correlation between Yv and fMRI signals (multiple-comparison-corrected P=0.006) (blue symbols in Fig. 2a) and between CVR and fMRI signals (P<0.001) (Fig. 2b). The signs of the correlations were in agreement with previous studies using block paradigms (1-3), i.e., an individual with lower baseline Yv and higher CVR tends to have a greater BOLD fMRI signal. The fMRI signals in the MTL were generally lower in amplitude, but showed similar correlations, i.e. negative correlation between Yv and fMRI signals (P=0.037) (pink symbols in Fig. 2a) and positive correlation between CVR and fMRI signals (P<0.001) (Fig. 2b). Note that our measure of Yv is a global one and not region-specific, thus the observation of a correlation with both occipital and MTL ROIs strongly suggest that global measures of baseline venous oxygenation is sufficient for the purpose of fMRI normalization. This notion is also supported by the observation that the fMRI signal amplitude in occipital lobe and MTL is correlated across subjects (P<0.001) (Fig. 1c)

We did not observe a significant correlation comparing fMRI signal to baseline CBF or resting state fluctuation in either brain regions, although the sign of the relationship agreed with previous reports (4,5). The lack of correlation may be due to the smaller signal changes in the event-related design.

Across different physiologic modulators, a significant correlation was found between the global baseline Yv and CBF (P=0.003) (Fig. 3a), as well as between regional CVR and resting state fluctuation (P=0.015 and P=0.044 for occipital and MTL ROIs, respectively) (Fig. 3b).

In summary, this work extends previous findings in block-design to the more widely used event-related design, and showed the modulation effect of physiologic parameters on fMRI signals. Furthermore, it was found that global measures of modulators may be sufficient for the purpose of normalizing fMRI signals in multiple brain regions. Finally, some of the fMRI modulators may be of similar physiologic origin, thus need not be acquired redundantly.

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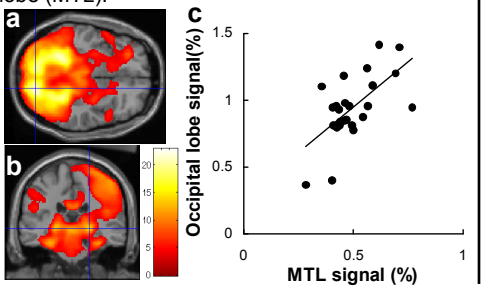
Fig. 1: (a-b) Activation map from group level one-sample t test. (c) Scatter plot between fMRI signals in the occipital lobe and medial temporal lobe (MTL).



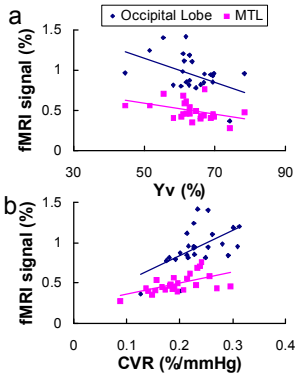


Fig. 2: Scatter plots comparing fMRI signal to (a) Yv and (b) CVR across subjects (n=25). The fMRI signal plotted was the average of three fMRI runs.

Fig. 3: Scatter plots (a) between baseline Yv and CBF, and (b) between CVR and resting state fluctuation across all subjects (n=25).