Is quantitative fMRI really better than plain BOLD in predicting cognitive function?

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INTRODUCTION: Given the well-known notion that the BOLD signal is complex function of several physiologic parameters and that it is difficult to directly interpret the signal in terms of neural activity, there has been a great deal of efforts in the past few years developing more quantitative fMRI methods, such as CBF-based fMRI (1), CBV-based fMRI (2), calibrated-fMRI (3), and fMRI normalization using cerebrovascular reactivity (4). While these newer approaches are in principle advantageous, the neuroscience and clinical community has been reluctant in adopting these innovations as the technical community has yet to show that these advanced markers can indeed provide a more accurate prediction of neural activity and cognitive function. The present study sought to provide, to our best knowledge, the first evidence in this regard. We compared between two markers, the plain BOLD signal and the BOLD signal after normalization with cerebrovascular reactivity (CVR), and exploited the natural variations in working memory (WM) performance across healthy individuals. We hypothesized that an individual's WM performance can be predicted (correlated) by his fMRI signal and that the normalized BOLD is a better predictor compared to plain BOLD.

METHODS: *FMRI task:* Fourteen young healthy subjects (8 males, age 27.4±2.9 y, range 24-34 y) were studied on a 3T (Philips). Each subject performed 4 runs of a classic WM task called N-back (5), while BOLD fMRI data were collected. Each N-back run (duration 6.5 min) consisted of 6 task blocks interleaved with 6 fixation blocks, with the duration of each block being 30 sec. During the task block, 20 numeric symbols (each for 1.5 sec) were displayed consecutively and the subjects were instructed to determine if the current number is the same as the 4th number (i.e., 4-back) displayed previously and to press buttons on their two hands accordingly. Additionally, four training runs were used before the actual scanning to help the subject get used to the task and for the performance to reach a steady state. The final WM score of each subject was quantified as the mean accuracy of the four runs during fMRI recording. *Imaging:* BOLD fMRI used: TR/TE=1500/30ms, voxel size 3.4x3.4x5mm^3, duration 6.5 min per run. In addition to the fMRI scans, we performed a CVR scan to measure the vasodilatory capacity of each individual, which is an important physiologic modulator of BOLD and has been proposed to be used to normalize BOLD fMRI signal (4). CVR was measured with a CO2-inhalation procedure that has been extensively tested (6-7). The imaging parameters used for CVR scan was the same as that for the fMRI scans, thus the CVR and fMRI data can be compared on a region-by-region basis. A T1-MPRAGE image was also acquired for each subject. *Analysis:* BOLD fMRI data were processed using standard GLM model and activation maps for task vs. fixation were obtained. CVR data were processed with previously described procedures to obtain CVR maps in % signal change/mmHg end-tidal CO2 change (6). ROIs were defined for two task-related brain networks: the visual-attention network (including left and right ventral visual areas, left and right middle frontal gyrus (MFG), and left and right inferior parietal gyrus (IPL)) (8-9), and the default mode network (including superior/medial frontal gyrus (SFG), posterior cingulated gyrus (PCC), left and right angular gyrus (AG), and left and right middle temporal gyrus (MTG)) (9). For each ROI, the averaged BOLD fMRI signal and the averaged CVR were obtained. Because of a linear relationship between fMRI signal and CVR (4,10), the normalized fMRI signal was calculated by $S_{fMRI,\ norm} = S_{fMRI}/CVR$. Mixed effect model was used to test the correlation between fMRI signal and WM accuracy. To limit the number of comparisons conducted, we only focused on the predictive value of activation in a network, instead of each individual region.

RESULTS and DISCUSSION: Fig. 1a showed that after training, the performance became relatively consistent during the fMRI scans. The WM accuracy across all subjects was 88.8-99.5% (mean±SD, 94.7±3.2%), providing reasonable range for correlation with fMRI signal. The group-level fMRI maps demonstrated task-induced activations (Fig. 1b) in the visual-attention network and deactivations (Fig. 1c) in the default mode network. ROI analysis revealed that, in task-activated regions, BOLD fMRI signal was positively correlated with CVR across individuals (p=0.0014, Mixed Effect Model using all ROIs within the visual-attention network, Fig. 2a), while in task-deactivated regions BOLD fMRI signal was negatively correlated with CVR (p=0.0007, Mixed Effect Model using all ROIs within the default mode network, Fig 2d). That is, an individual who has large vasodilatory capacity tends to have both greater activations and greater (in magnitude) deactivations. However, these vascular-related variations do not reflect neural function, thus the removal of these effect is the goal of the normalization.

There were no correlation between WM accuracy and the BOLD fMRI before normalization, for either activation signal in visual-attention network (Fig. 2b) or deactivation signal in default-mode network (Fig. 2e). Following normalization with CVR, however, the fMRI signal showed a significant correlation with WM accuracy. Interestingly, the relationship is most pronounced for deactivation signal (p=0.0026, Fig. 2f), although a weaker relationship was also observed for the activation signal (p=0.035, Fig. 2c). Specifically, an individual who has better WM performance tends to have both a lower activation and a lower (in magnitude) deactivation signal. This finding is consistent with the neural efficiency hypothesis in the cognitive neuroscience field (11).

In summary, this work presents the first direct evidence that quantitative measure of brain activation after accounting for vascular factors can provide a more accurate predictor of cognitive function. While previous studies (e.g. calibrated fMRI literature) have assumed or argued that this should be the case, the present study validated these assumptions. Our results showed that individuals with higher WM performance actually revealed less brain activation, a finding similar to those reported in the context of cognitive aging. Finally, our data showed a paradoxical finding that brain deactivation signal is more predictive of cognitive function compared to activation signal.

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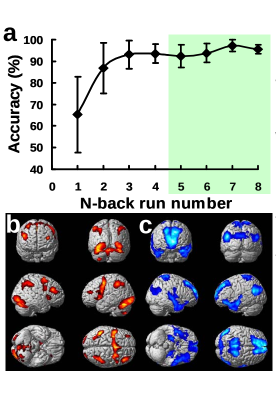

Fig. 1: Behavioral and imaging results of the N-back task. (a) Averaged WM accuracy across individuals. Eight runs were performed. The green box indicates the period of fMRI scans. (b) Activation map from group level one-sample t test. (c) Deactivation map from group level one-sample t test. P<0.001, cluster size> 200. N=14.

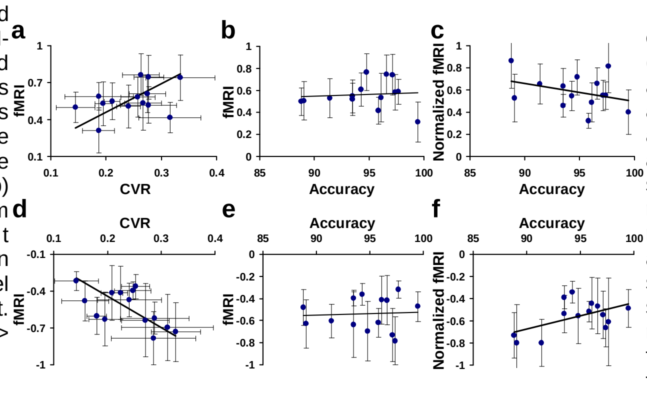

Fig. 2: Relationship among experimental measures. (a)-(c) Scatter plots between CVR and fMRI signal, between WM accuracy and fMRI signal, and between WM accuracy and CVR-normalized fMRI signal across subjects, respectively. Each dot represents the mean value of all six activated ROIs in one subject. Error bars are standard deviation across regions. N=14. (d)-(f) depict the same comparisons in the task-deactivated regions.