The influence of voxel-wise rCBF covariates in pharmacological BOLD-fMRI studies

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Introduction

Blood Oxygen Level Dependent (BOLD) contrast has established utility in examining the modulation of cognitive networks by psychoactive compounds. In addition to neuronal effects of compounds, direct vascular effects can increase inter-subject response variability and may even confound interpretation of drug-related BOLD signal changes. Methods such as hyper-capnic or breath-hold challenges (1,2) have been proposed as 'physiological modulators' of the BOLD signal (3). However, it has also been demonstrated that the BOLD signal shows a strong dependence on resting state Cerebral Blood Flow (rCBF, (4)). Therefore, we propose an innovative approach in which voxel-wise rCBF values are employed as an 'image covariate' to reduce type-1 and type-2 errors in conventional statistical models used for the analysis of group differences in BOLD studies. We demonstrate the methodology in healthy volunteers after methylphenidate or placebo administration while executing a motor inhibition task.

Methods

16 healthy males performed a modified 'stop-signal' task (5) during BOLD scanning, 1.5h after oral administration of methylphenidate (40mg) or placebo, within a double-blind, crossover design. The task included 'continue' trials matched perceptually and in frequency to 'stop' trials but not requiring stopping. Performance was tracked, such that, on average, 50% of 'stop' trials failed. Activation related to these trials is discussed here. Images were acquired on a 3T GE Signa HDX scanner. rCBF maps were acquired in both placebo and methylphenidate sessions using pseudo-continuous ASL with a single-shot, 3D spiral FSE readout (6). BOLD fMRI data pre-processing (movement correction, normalisation and smoothing) and subject-level inference analysis were conducted using SPM-5. rCBF maps were also normalised and smoothed in SPM-5. Second-level analysis of the local differences in BOLD activation between methylphenidate and placebo conditions were computed using a paired t-test (FLAMEO, FSL 4.1.4, Oxford, UK). Analyses were performed with and without the addition of voxelwise rCBF image covariates. Resulting Z-statistic images were thresholded using a corrected cluster-significance threshold of $p<0.05$ according to Gaussian random field theory (Worsley, 1992).

Results

Administration of methylphenidate causes significant, almost ubiquitous reduction in rCBF (Fig. 1, p-voxel < 0.01, p-cluster < 0.05). Normalised maps of statistically significant differences in activation on error trials, after drug compared to placebo (p-voxel < 0.001, p-cluster < 0.05) are shown in Fig. 2 with and without inclusion of rCBF maps acquired for each subject at each session. Addition of the voxel-wise covariates leads to both increases and decreases in the extent of the significant activation differences. Areas in red correspond to the analysis without rCBF covariates. Areas in green show enhancement of activation after inclusion of voxel rCBF covariates. Areas in yellow remain unchanged.

Discussion

Prior to inclusion of rCBF covariates, methylphenidate increased activation in a network of areas during errors. In view of the decrease in rCBF caused by the drug and the inverse relationship between resting state CBF and the BOLD signal, we anticipated that inclusion of individual rCBF maps would lead to a decrease in the extent of activation differences between the two treatments, thus questioning their involvement in error-related modulation by methylphenidate. Areas showing this pattern included the posterior parietal and cingulate cortices (red). Areas of enhanced differences with rCBF covariate included left inferior frontal gyrus and the putamen (green), both positioned to allow modulation by methylphenidate based on receptor distributions. Importantly, many regions (yellow) were present in both maps, suggesting that drug-related vascular changes were not sufficient to explain BOLD signal changes. Our data demonstrate the importance of the inclusion of physiological modulators in BOLD-based pharmacological MRI studies and the value of a relatively simple inclusion of a voxel-wise CBF covariate, readily obtained with modern scanners.

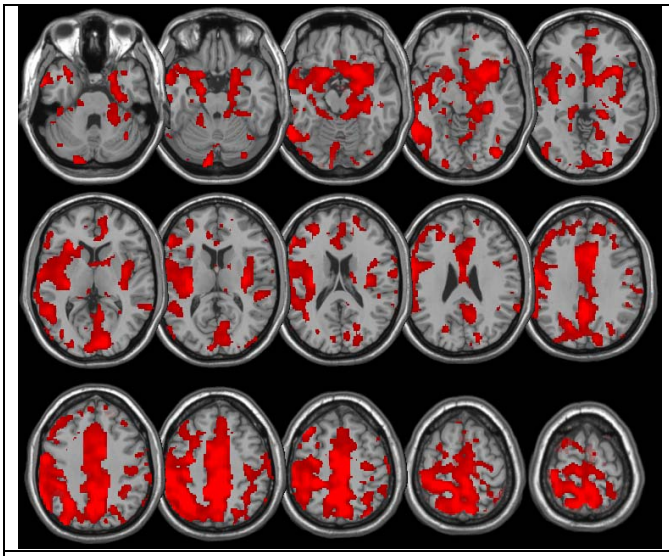

Figure 1: Drug induced **decreases in** rCBF

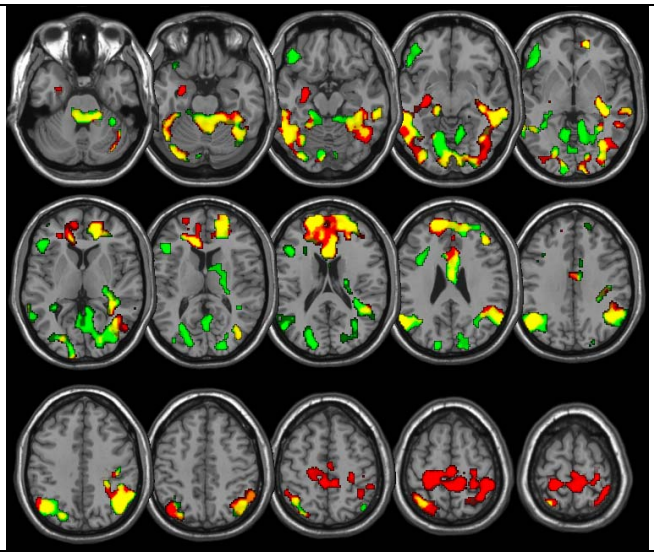

Fig. 2: Activation differences with **and without** voxel rCBF covariates

References

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