The Effects of Dobutamine-induced Blood Pressure Changes on BOLD fMRI Signals in the Human Brain

H. Liu[1], C. Rainey[2], K. K. Lauer[3], L. Piacentine[2], A. Bloom[4], R. Risinger[2], E. Stein[5], S-J. Li[6]

[1]Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States, [2]Psychiatry, Medical College of Wisconsin, Milwaukee, WI, United States, [3]Anethesiology, Medical College of Wisconsin, Milwaukee, WI, United States, [4]Pharmacology, Medical College of Wisconsin, Milwaukee, WI, United States, [5]Neuroimaging Research Branch, Intramural Research Program, National Institute on Drug Abuse, Baltimore, MD, United States, [6]Biophysics, Medical College of Wisconsin, Milwaukee, Wi, United States

Introduction: Recent studies have applied fMRI methodologies to localize acute pharmacological effects and detect changes in regional brain activity induced by drugs (1, 2). There is, however, a concern whether the fMRI method used to map cognitive function can be simply and directly extended to neuro-pharmacological studies. For example, it is not clear how peripheral cardiovascular changes induced by drug administration could affect BOLD contrast in the brain. It is conceivable that the changes in blood pressure (BP) could cause global cerebral blood flow changes and therefore confound the detection of drug-induced neural activations. In the present study, we employed dobutamine, as a beta-adrenergic agonist, to increase BP and to determine the effect of the increased BP on the BOLD signal change in the absence of drug-induced CNS activity.

Materials and Methods: Seven (7) right-handed cocaine users (2 female and 5 male, age 37.8±6.5 years) were recruited into this study. The Institutional Review Board approved this study and a signed consent form was obtained from each subject before experiments were conducted. One iv line and one arterial line were placed in the subject's arm for drug delivery and for direct BP monitoring, respectively. Drug tolerance procedures were first performed outside of the MRI for safety. **fMRI Experiments:** Two consecutive fMRI sessions were conducted with a 30~60 minute rest interval between sessions on a GE Signa 1.5T scanner. The first session contained two 25 min scans. Infusion of saline (scan 1) and dobutamine (scan 2) were started at 5 min into the respective scans. The saline infusion was fixed at a rate of 0.7 ml/second with a total amount of 10 ml. Because of the variations in individual blood pressure responses to the drug, the rate of dobutamine infusion varied from 7~10 mg/kg/min during the 7~8 min infusion period. In the second session, a 30 min scan was performed (scan 3) and dobutamine was infused twice. The first infusion of dobutamine was started at 5 min into the scan and lasted for 3 min. The second infusion was started at 17 min into the scan and lasted for 3 min. The infusion rate of dobutamine in scan 3 was the same as in scan 2. Two sets of SPGR images were acquired prior to scan 1 and scan 3, respectively. During scans 1, 2 and 3, subjects were prompted to evaluate their feelings of "liking drug", "high", "queasy", "light headed" and "racing" in a random order once every minute. Whole-brain 2D axial images were collected using a hybrid pulse sequence: the top half of the brain was acquired with an EPI sequence and the inferior part of brain was acquired with an EPI pulse sequence with *z*-shimmed background gradient compensation to overcome the susceptibility artifacts at the inferior brain regions. A total of seventeen 5mm slices were acquired with FOV of 24cm, matrix size of 128 × 128, TE of 30 ms, 125 kHz bandwidth, and an equivalent TR of 6 seconds. **Data Analysis:** **A**nalyses of **F**unctional **N**euro**I**mages (AFNI) software was employed. The rejection threshold for rigid body motion was set at displacement of 2.5 mm and rotation of 2.5° as estimated by the AFNI *3dvolreg* program. To assess whether BP change induces BOLD signal in the human brain, two methods were employed: 1) a cross-correlation method to calculate the cross-correlation coefficient (cc) between the fMRI time course and the systolic blood pressure (SBP) profile (the diastolic blood pressure was not affected by dobutamine infusion); 2) and a nonlinear regression method with a differential exponential model (3) to calculate the percent change of area under the fitted curve (AUC%). The cc map and AUC% map were then converted to standard Talairach coordinates with thresholds of cc and F-statistic values corresponding to a Bonferroni corrected *p* value of 0.05. Analyses across individual subjects were performed to obtain group maps by using t-test of cc and AUC% of dobutamine infusion vs. null hypothesis and saline control, respectively. A clustering method was then applied with the minimum activation volume of 350 μl to achieve a corrected *p* of 0.05.

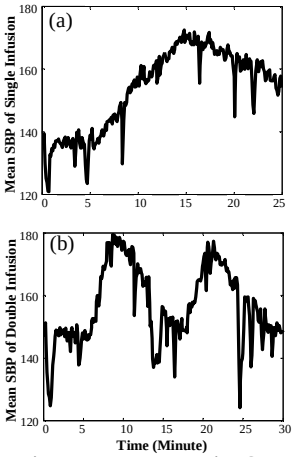

Figure 1. Mean Invasive SBP of Scan 2 and 3

Results and Discussions: As shown in Fig. 1a**,** the averaged SBP was elevated to about 130% of its baseline value in about 5 min by dobutamine infusion, sustained for 2~3 min and gradually dropped back to baseline after the infusion was stopped. Figure 1b showed the SBP changes in the double-infusion paradigm. Both Figs. 1a and 1b demonstrated the effectiveness of dobutamine to induce acute BP changes. As shown in Fig. 2, no global BOLD signal activation was seen due to the BP changes. However, the significant AUC% change occurred in the anterior cingulated region (BA 32) as shown in Fig. 2a, and positive correlations between BP changes and BOLD signal were found in the same region as shown in Fig. 2b. Figure 2c illustrates that there were no correlations between BP changes and BOLD signal changes when the double-infusion paradigm was employed. The presence of correlations between BP changes and BOLD signal changes in Figs. 2a and 2b could be related to an induced conditioned response, as the dobutamine BP increases were similar to cocaine-induced elevation of blood pressure and heart rate previously experienced by these cocaine users. These activations in Figs. 2a and 2b disappeared in the double-infusion paradigm as shown in Fig. 2c. This may be due to the habituation of such a conditional stimulus. We conclude that infusion of dobutamine significantly increased BP, but the increased BP did not induce a global change in BOLD signal, likely, in part, a consequence of cerebral autoregulation.

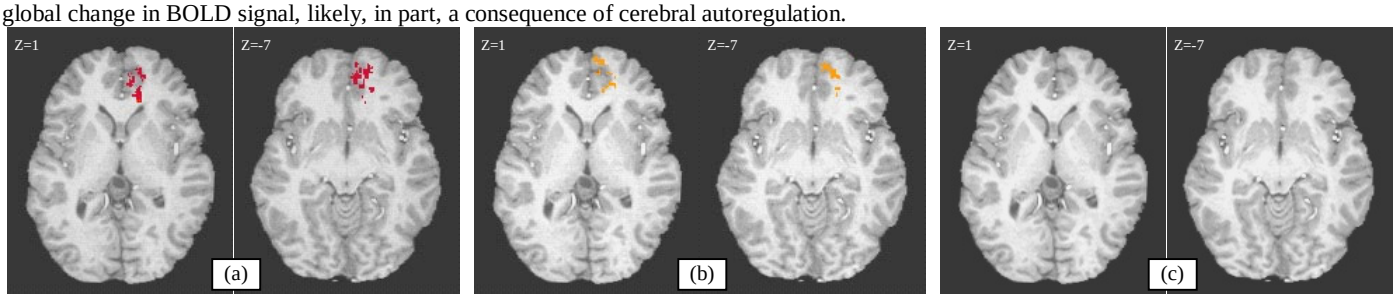

Figure 2. (a) AUC% map (dobutamine vs. saline df=12), (b) CC map (single dobutamine infusion df=6), (c) CC map (double dobutamine infusion df=5).

References: **1**. Stein et al., Am J Psychiatry, 155:1009-15. **2**. Breiter et al., Neuron, 19:591-611. **3**. Bloom et al., Human Brain Mapping 8:235–244.

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