A Novel BOLD fMRI Assay of Human Central Nervous System Dopamine Function: The Effects of D-Amphetamine on Photic Activation to Blue Light

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Introduction

The catecholamine neurotransmitter dopamine mediates a variety of neuronal functions and is implicated in the pathophysiology of Parkinson´s disease, attention deficit disorder, schizophrenia, and substance abuse. Pharmacologic MRI has been successful in demonstrating dopamine-specific receptor and functional changes in animal models, raising the exciting possiblity that such methods can be directly applied to the study of dopamine in humans (3, 9). Such work in humans is complicated by the limitations on manipulation of neurotransmitter function and the complexity induced by direct dopaminergic innervation of cerebral microvasculature (7). Evidence from a variety of studies suggests that the human visual system might serve as a paradigmatic system for developing a human assay of dopamine function. A variety of visual systems dysfunctions are present in schizophrenia, including altered blood oxygen level dependent (BOLD) functional MRI (10) and altered EEG during photic driving (6). In Parkinson´s disease, blue color vision and blue-cone electroretinogram are impaired (2, 5). Similarly, in cocaine-withdrawn individuals, blue-cone electroretinogram is reduced, and correlates with degree of drug craving (4, 11, 12). Based on these observations, we designed a study to test the effects of the dopamine releasing drug d-amphetamine on the BOLD (8) response to red and blue light in humans.

Methods

Fifteen volunteers were recruited for 22 functional MRI scans. MR scans were performed on a 1.5 Tesla (T) Signa Echo-Speed (General Electric) whole body magnetic resonance scanner (level 5.8). Anatomical localizing images were obtained prior to functional imaging. For BOLD imaging gradient echo EPI axial images collected in an oblique plane parallel to the calcarine fissure were used to assess photic stimulation-induced BOLD signal changes. Three locations of 5 mm thickness with 0 mm skip were obtained to include the calcarine cortex and adjacent regions. Acquisition parameters were TR = 2 S, flip angle = 90 degrees, matrix = 64 x 64 pixels FOV = 20 x 20 cm, 3x3 mm in-plane resolution. 256 images were obtained at each location using a 5 inch receive-only surface coil. Color photic stimulation was delivered via a custom-designed set of stimulus goggles having three sets of light emitting diodes (LEDs) that emit light at 470 nm (blue), 570 nm (green), and 660 nm (red). Subjects received oral placebo or 2.5 mg d-amphetamine and then underwent 5 trials of photic stimulation with alternating iso-intense red and blue light at a flash frequency of 8 Hz. Pixel activation was determined using cross-correlation (1). Mean pixel activation in a 1x4 ROI from right and left primary visual cortex was analyzed for all subjects for each color. Cross correlational time series analyses were used to analyze the effects of drug versus placebo condition on activation across the 5 trials (approximately 10 minutes/trial). Wald Chi^2 analysis was used to compare the mean BOLD signal change across all trials for different conditions.

Results

There were no effects of age or sex on BOLD response. Mean signal change measures to assess the effect of drug versus placebo revealed significant effects for blue light, with the mean BOLD signal change being 28% higher in the drug (2.04%) condition than in the placebo (1.60%) condition. For blue light under the drug condition, there was a significant effect of time following drug administration on BOLD signal change (Z=-2.471, P=0.013) with decreasing BOLD signal over time. For blue light in the placebo condition, there was no significant effect of time on BOLD signal change (Z=-0.355, P=0.722). Figure 1 displays plot of blue light response across all trials. Solid squares represent drug, open diamonds represent placebo. Similarly to blue light, for red light, the overall mean was also significantly different in the Wald Chi^2 analysis, with the mean BOLD signal change being 30% higher in the drug (1.24%) condition than in the placebo (0.95%) condition. However, there was no significant effect of drug over time for red light (Z=-0.470, P=0.638). Similarly, there was no effect of time on BOLD signal response following placebo administration (Z=-0.880, P=0.379) for red light. Figure 2 displays plot of red light response across all trials.

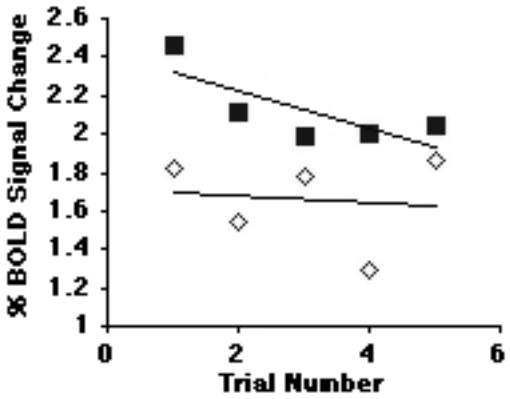

Figure 1 - Activation vs. trial number for blue light stimulus.

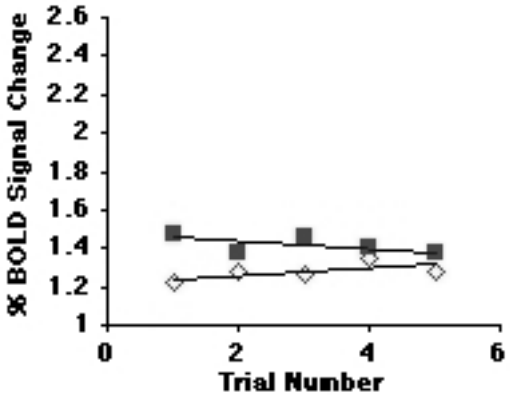

Figure 2 - Activation vs. trial number for red light stimulus.

Discussion

While the BOLD signal change to red and blue photic stimulation in V1 increased following d-amphetamine, blue-light induced BOLD signal change showed a time-dependent sensitivity to the drug. We propose that these responses are mediated by complex hemodynamic and neuronal influences of dopamine acting at a variety of sites, and suggest that blue light is differentially affected by d-amphetamine induced dopamine release.

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