ASL phMRI After a Single Dose of Oral Citalopram

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Introduction

Pharmacological MRI (phMRI), the combination of pharmacological challenge and imaging, is a novel and noninvasive method for assessing drug effects on brain function. To date, most phMRI has been based on blood-oxygenation-level-dependent (BOLD) contrast acquired during intravenous drug administration. Because BOLD provides nonquantitative measure that is dependent on both physiological and biophysical factors, it is poorly suited to studies over hours or days required to study orally administered drugs. An alternative to BOLD is arterial spin labeling (ASL), which provides an easily interpreted, quantitative physiological parameter—cerebral blood flow (CBF). While the earliest ASL phMRI studies focused on vasoactive drugs such as acetazolamide[1], CBF can also be used as a biomarker of neural function more generally, based on its known coupling with changes in regional CBF. phMRI based on ASL has been used to monitor the effects of both acutely administered intravenous drugs[2, 3] and more recently chronically administered oral drugs[4]. Here we assessed the utility of ASL phMRI for detecting a single orally administered dose of citalopram, a selective serotonin uptake inhibitor used commonly in the treatment of major depression. Although SSRI medications require many days to develop their antidepressant effects, some psychoactive effects can be detected after a single dose[5] and a prior study demonstrated regional phMRI changes after an intravenous injection of citalopram using BOLD contrast[6].
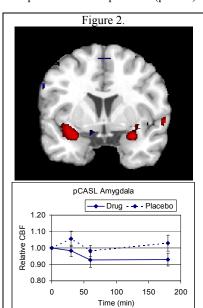
Methods

Twelve healthy subjects (8 females, mean age 29) were recruited for the randomized, placebo-controlled, double-blind, crossover study. Subjects were scanned on two different days, at least 1 week apart. All data were collected on a 3T whole-body Siemens scanner (Trio, Erlangen, Germany) with an 8-channel receive-only head coil. Each day consisted of three sessions: session one included structural MPRAGE images and two baseline pCASL and FAIR scans. Subjects then received either placebo or an oral dose of 20mg citalopram, and returned to the scanner 30 minutes after drug administration for session two, during which five pCASL and FAIR scans were collected. Three more pCASL and FAIR scans were collected during session three, which began 3 hours after drug administration. Imaging parameters for pCASL were: postlabeling delay=1s, tau=1.8s, 16 axial slices (5mm thick, 1mm gap), TR/TE=4s/17ms, gradient-echo EPI acquisition. For FAIR, TIs=700ms/1400ms. Blood samples were collected before session one and after session three on both days to assess plasma concentrations of prolactin, cortisol and citalopram.

CBF maps were calculated as previously described[7], averaged within each of the three scan sessions and normalized to standardized template in SPM5 (Wellcome Institute, UK). Support vector machine (SVM)[8] analysis was performed on relative CBF maps (defined as post-drug CBF map/baseline CBF map) to explore regional drug effects. CBF time-courses within regions-of-interest (ROIs) were generated using predefined ROIs in PickAtlas.
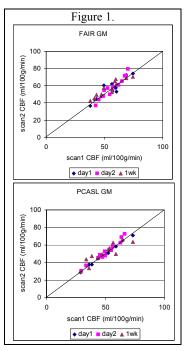
Results

Within-session and after 1 week test-retest reproducibility of gray matter CBF for both FAIR and pCASL are shown in Figure 1. Excellent reproducibility was observed for both methods, especially pCASL (within-subject coefficient of variation, wsCV = 2.4% within-session, 8.8% after 1 week). Figure 2 shows a coronal slice of the SVM map calculated from pCASL data, which shows decreased blood flow in the amygdala after citalopram compared to placebo (areas in red, $p<0.01$). Although SVM revealed significant drug effect in multiple areas, ROI analysis was focused on the amygdala. A plot of the time-course of CBF changes in a bilateral amygdala ROI for both citalopram and placebo is also shown in Figure 2. A significant difference between placebo and drug is visible for pCASL; no such distinction was observed with the FAIR data (not shown). Paired t-test on the plasma levels of prolactin ($p=0.35$) and cortisol ($p=0.75$) revealed no significant drug effect.

Figure 1.

Figure 2.

Discussion

Our results demonstrate that both FAIR and pCASL excellent reproducibility, with a 1 week wsCV of less than 10%. Results from the amygdala ROI indicate that pCASL has sufficient sensitivity to detect drug-induced regional CBF after a single dose of a psychoactive drug within a relatively small sample of n=12. These findings suggest that ASL phMRI may provide a valuable biomarker of changes in regional brain function produced by orally administered drugs in clinical trials. ASL phMRI may thus provide a translational pharmaco-dynamic biomarker bridging preclinical to clinical studies. The amygdala is a likely target for SSRI effects based on its known involvement in affect. A prior PET study demonstrated a positive correlation between metabolic abnormality and depression severity in the amygdala[9] and altered amygdala function has been demonstrated in individuals who are genetically prone to depression[10].

References

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