Comparison of analysis techniques for direct pharmacological challenge-fMRI

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Introduction

Direct pharmacological challenge-fMRI (pMRI) is a method to study the dynamic effects of drugs on brain haemodynamics (Leslie & James 2000). One approach to analyzing the data is to use a pharmacokinetic model as a regressor, to identify brain voxels where the BOLD signal correlates significantly with the regressor One frequently used approach is to use self-ratings (Visual Analog Scales, VAS) to measure subject-specific changes while a drug is being infused. A standard fMRI analysis is then carried out, using the average response to the significant subjective ratings as a regressor (Anderson et al. 2002). However, there are several problems with this method: (1) The subjective rating being measured *e.g.* 'hot & sweaty', may be directly linked to a change in blood flow rather than a direct effect of the drug; (2) The BOLD signal in each brain area may react to the drug more slowly or faster than the subjective regressor; (3) The BOLD signal in each subject may differ from the average VAS shape being used as the regressor. (4) The drug may have no significant subjective effects so therefore no regressor can be modelled. Therefore, we have developed an alternative method to detect drug-induced BOLD signal changes without prior knowledge of pharmacokinetics or subjective effects.

Methods

Two psychiatric drugs were used, mCPP (a non-specific serotonin agonist) and ketamine (an NMDA receptor channel blocker):

- mCPP study – 24 healthy volunteers, aged 18-45, were recruited into a randomised, double-blind study. Each was given an infusion of either placebo or mCPP (0.08mg/kg) via saline.
- Ketamine study – 24 healthy volunteers, aged 18-45, were tested on two occasions receiving placebo (saline) or ketamine (bolus 0.26mg/kg over 1-minute, maintenance infusion 0.25mg/kg/hr for the rest of the scan) in a randomised, balanced order, double-blind fashion.

Each subject underwent a 9 minute fMRI scan during which they self-assessed their mental state using VAS. At 8 minutes the drug/saline was infused. Images were acquired on a 1.5T Philips scanner with a multi-slice, single shot EPI sequence to achieve whole brain coverage. Each volume comprised of 40 contiguous axial slices (TR = 5 s, TE=40 ms, 3.5 mm slice thickness with in-plane resolution 3.5x3.5 mm). Data were analysed using SPM2 (Friston, The Welcome Department of Cognitive Neurology, London, UK).

For the first analysis method (VAS analysis), a regressor was created for both drugs based on significant ratings from the VAS which was then used to locate areas that followed its time course. A random effects two-sample t-test was then applied to the resulting images. The second analysis method (block analysis) involved dividing the 9 minute (108 volume) infusion scan into 9 one-minute (12 volume) time-bins (T0 to T8). The average signal for each time-bin (Tn) was compared to the pre-infusion average (T0) using regression analysis. A random effects ANOVA was used to investigate significant signal changes over time.

Results

Both analysis methods resulted in the detection of similar areas for each drug, however more areas were present in the block analysis. The block analysis was also corrected for multiple comparisons (p(FWE)<0.05), making it more robust than the VAS method, which was not corrected but resulted in similar areas at a lower significance threshold (p(unc)<0.001).

Discussion

We have developed a method of detecting drug-induced BOLD signal changes without prior knowledge of the specific drug pharmacokinetics or subjective effects. Using subjective ratings results in the same areas being detected but at a lower significance level, this is thought to be due to individual differences in drug-induced BOLD signal shape as well as latency effects between different brain regions.

References

(1) Leslie & James 2000, Trends Pharmaco Sci, 21: 314-318

(2) Anderson *et al.* 2002, Neuroreport, 13: 1547-1551

Figure 1. Ketamine effect SPMs: VAS, p(unc)<0.001 (left) and block, p(FWE)<0.05 (right)