

A distributed network of cerebral blood flow changes accurately discriminates methylphenidate and atomoxetine: A Gaussian process pattern recognition approach

A. Marquand¹, S. De Simoni², O. O'Daly², F. Zelaya², and M. Mehta²

¹Centre for Neuroimaging Sciences, Institute of Psychiatry, London, United Kingdom, ²Institute of Psychiatry

Introduction

Methylphenidate and atomoxetine are two psychoactive drugs routinely used for treatment of attention deficit/hyperactivity disorder (AD/HD), but little is known about their differential brain physiology in humans. We sought to directly discriminate between the cerebral effects of methylphenidate and atomoxetine in healthy volunteers at rest by applying exploratory pattern recognition methods to regional cerebral blood flow (rCBF) brain images derived from arterial spin labelling (ASL) MRI. ASL provides quantitative measures of rCBF and is thus well suited to detect blood flow changes resulting from the ingestion of psychotropic medication. Although discriminating the effects of drugs with similar pharmacological profiles can be a difficult problem for conventional (univariate) analysis methods, pattern recognition (PR) techniques are known to furnish greater sensitivity than voxel-wise analysis methods owing to their sensitivity to spatial correlation between brain voxels (1). Whole-brain PR also demonstrates good exploratory power and is well suited to applications where the underlying functional neuroanatomy is poorly understood.

Methods

Fifteen healthy male volunteers were recruited and scanned on three occasions. On each visit, each subject received an oral dose of 30mg of methylphenidate, 60mg of atomoxetine or a placebo according to a double-blind, randomised Latin square design. On each visit, between 90 minutes and 135 minutes post dose, six quantitative resting rCBF scans were acquired using a pulsed-continuous arterial spin labelling (cASL) sequence (2) with a 3D-spiral FSE readout, ETL=64, TR=4s. CASL images had a spatial resolution of 1 x 1 x 3mm and acquisition time of 6minutes. Data were preprocessed using SPM5 and a mask was applied to select intracerebral voxels. A multivariate PR algorithm based on Gaussian process classification (GPC) was applied (3,4) to each pair-wise combination of conditions (atomoxetine vs. placebo (AxP), methylphenidate vs. placebo (MxP) and methylphenidate vs. atomoxetine (MxA)). A leave-one-out cross-validation framework was used to assess generalisability (i.e. prediction accuracy) and a multivariate representation of the discriminating pattern was generated for each contrast (4).

Results

For each contrast, GPC achieved accuracy significantly better than would be expected by chance ($p < 0.017$; Figure 1). Multivariate maps revealed that in each contrast, classification was driven by a distributed network of cortical and subcortical regions. In the AxP contrast, the network with high positive coefficients (suggestive of an increase in rCBF for atomoxetine relative to placebo, or favouring atomoxetine) encompassed the cerebellum, anterior cingulate cortex and parietal regions. A network with negative coefficients (i.e. favouring placebo) was also observed which encompassed dorsomedial prefrontal cortex, superior temporal gyrus and lateral fronto-polar regions. For MxP, a network of positive coefficients (favouring methylphenidate) was observed in cerebellum, anterior cingulate cortex, temporal poles, thalamus and putamen, while negative coefficients (favouring placebo) were observed in a diffuse bilateral network comprising frontal and parietal cortices. In the MxA contrast, positive coefficients (favouring methylphenidate) were observed in the putamen, temporal poles and anterior cingulate cortex. Negative coefficients (favouring atomoxetine) were observed in fronto-parietal cortex and cerebellum.

Discussion

Using a multivariate PR technique we have shown that methylphenidate and atomoxetine have differential effects on resting rCBF in a number of regions, including the putamen, anterior cingulate and temporal poles. The effects of atomoxetine and methylphenidate also overlap in some areas (e.g. cerebellum). Although discrimination was achieved using the whole input pattern, multivariate GPC brain maps provide an indication of the relative importance of different brain regions underlying the prediction and can be understood as providing a representation of the direction along which experimental classes differ the most (4). The strong fronto-parietal changes in rCBF also seem to be restricted to the methylphenidate condition and changes in the cerebellum may be stronger for atomoxetine than methylphenidate. Exploratory multivariate PR techniques may be a suitable approach for discrimination of psychotropic drug profiles where discriminating information is weak but diffusely distributed and where the underlying neuro-pharmacology is poorly understood.

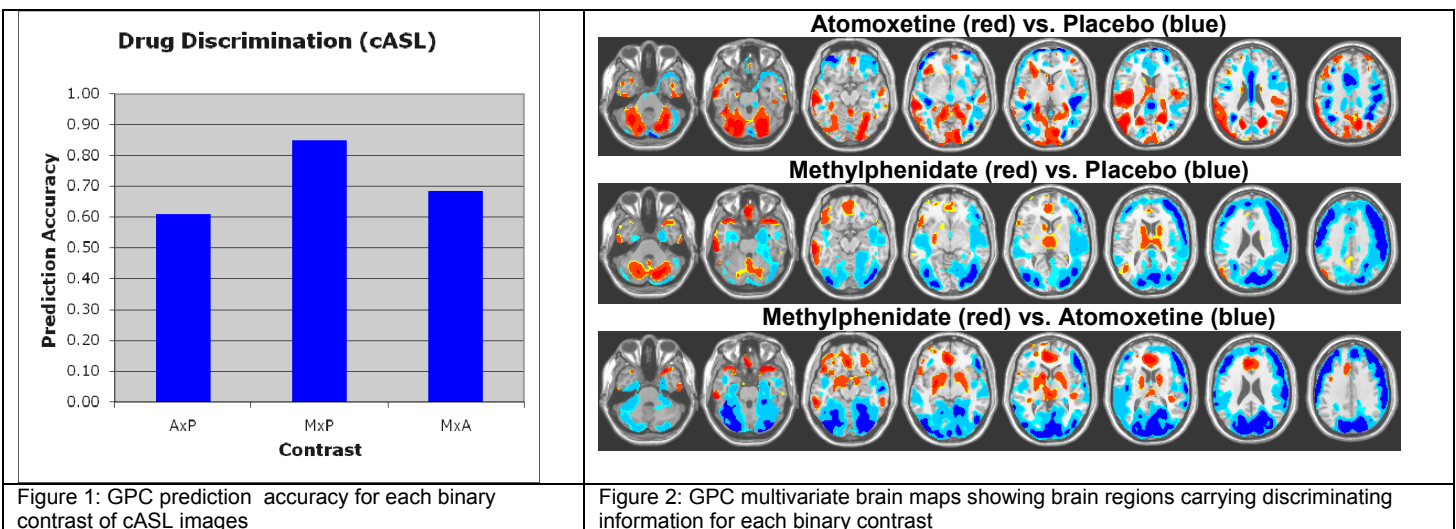


Figure 1: GPC prediction accuracy for each binary contrast of cASL images

Figure 2: GPC multivariate brain maps showing brain regions carrying discriminating information for each binary contrast

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