Impairment of prefrontal cerebral attentional networks by intravenous D-fenfluramine challenge measured using fMRI

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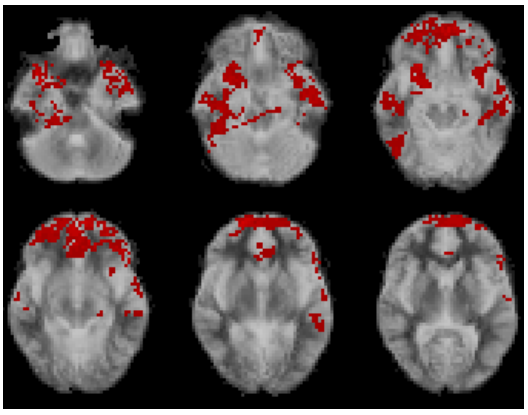
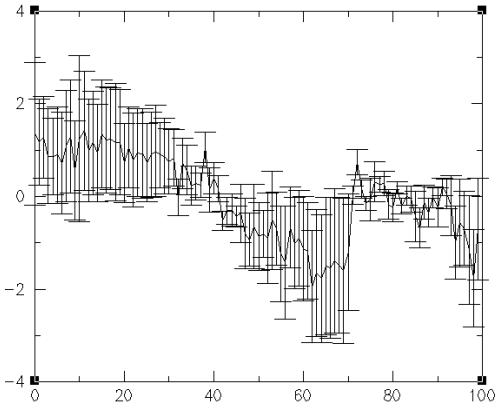
Introduction: Cerebral 5-hydroxytryptamine (5HT, serotonin) neurotransmission in the reticular activating system has a recognised role in the maintenance of alertness and has been implicated in the pathophysiology of a variety of psychiatric disorders. However, research into the relationship between abnormal 5HT-function and these disorders has been impeded by the lack of direct methods to determine endogenous 5HT function, and by poor knowledge of the role of 5HT in normal cerebral function. D-fenfluramine (DFEN) is an indirect agonist of 5HT with an amphetamine-like action to release 5HT from nerve terminals, which in pilot studies from our group have been shown to produce decreases in subjective awareness. We examined the acute effect of intravenous DFEN on activity within distributed neural networks, measured using BOLD functional magnetic resonance imaging (fMRI), with the aim of identifying networks associated with subjective alertness.

Methods: Healthy subjects (n = 8) attended twice, separated by at least seven days, and received intravenous DFEN (0.5 mg/kg) or placebo (saline) administered over a 1 minute period in a single-blind, placebo-controlled randomised crossover design. Subjects were scanned over a 15 minute period and placebo or DFEN administered after the first 5 minutes. Subjects were able to rate subjective alertness using an interactive keypad following visual display of the rating scale at 30 second intervals. Gradient-echo echoplanar MR images were acquired using a 1.5 Tesla GE Signa System (General Electric, Milwaukee, WI, USA) fitted with Advanced NMR hardware and software (ANMR, Woburn, MA, USA) at the Maudsley Hospital, London. In each of 7 non-contiguous planes parallel to the inter-commissural (AC-PC) plane, 100 T2*-weighted MR images depicting BOLD contrast were acquired with TE = 40ms, TR = 9000ms. After motion correction the resulting time-series was analysed by regression modelling and non-parametric hypothesis testing of correlation with a specified input function.

Results: Subjective rating of alertness during fMR scanning monitored by interactive visual analogue recording demonstrated significant decrement in alertness with intravenous DFEN ($p < 0.001$ repeated measures ANOVA), one subject did not reattend for the paired scan and this data is not shown. The figure shows, on the left, the group brain activation map displaying three dimensional clusters showing significant correlation with the initial analysis using a step input function (cluster threshold $p < 0.01$; voxel threshold $p < 0.05$). These clusters extend from anterior and medial temporal regions inferiorly, ventral striatum and medial prefrontal cortex and anterior cingulate. The figure on the right shows average cluster BOLD response, mean and standard deviation for the 7 subjects, demonstrating ~ 3% signal decrement following intravenous DFEN (no response seen in placebo condition, data not shown).





Discussion: The functional clusters identified following intravenous DFEN showed substantial decrement in BOLD signal in large contiguous regions involving bilateral medial temporal, ventral striate, medial prefrontal and anterior cingulate. These regions are recognised to be fundamental components of attention, motivation and interoception and hence corroborate subjects' reporting of decreased alertness with DFEN. This study suggests that involvement of the 5HT system in attentional processes is mediated via prefrontal projections. This approach may be used to examine the dynamic effects of 5HT modulation between subject and diagnostic groups, and may thus represent a useful *in vivo* measure of the functional capacity of the 5HT system, suitable for studies of the role of 5HT in psychiatric disorders.