Acute Serotonergic Modulation of Neuronal Responses to Implicit Recognition of Facial Expressions, Behavioural Inhibition and Reinforcement

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Introduction

Serotonin (5-HT) is implicated in the aetiology and treatment of a variety of psychiatric disorders including depression, anxiety and implusivity. It also seems to be implicated in motivational, emotional and social functioning where recognition of external emotional information is crucial for social adaptation. Recently, it was shown that the infusion of the 5-HT_{2C} receptor agonist methyl-chlorophenylpiperazine (mCPP) provoked regional changes in BOLD signal corresponding to brain areas rich in 5-HT_{2C} receptors (Anderson et al. 2002). mCPP also modulated responses to cognitive challenge using a go/no-go test of behavioural inhibition. To further investigate the role of 5HT in social, emotional and motivational functions, the present study used a selective serotonin reuptake inhibitor, citalopram. This drug has been shown to be effective in the treatment of anxious (Bakker et al. 2000) and depressed patients (Keller 2000). By inhibiting reuptake of 5-HT, citalopram acutely enhances serotonin function at a pre-synaptic level. In this study, we assess the modulatory effect of citalopram on neural responses to a classic behavioural inhibition task, a reward task, a loss task and a face recognition task.

Materials and Methods

12 healthy male volunteers aged between 18 and 35 years (mean 24.7(5.8)) were tested on 2 occasions receiving saline (placebo) or citalopram (7.5 mg over 7.5 minutes) in a randomised, balanced order, single-blind fashion. The drug was administered 20 minutes before the battery of tasks. The four cognitive tasks were as follows:-

a: behavioural inhibition - go/no-go: subjects respond via a button press to a sequence of rapidly presented letters, to any letter apart from V. Two conditions were presented in which a response was required for all stimuli (Go) or to 50% of stimuli (NoGo).

b: reinforcement - reward/no-reward: subjects are shown a rapidly changing flow of coloured squares and are asked to respond via a button press to green and blue coloured targets only. Rewards are received after 65% of blue targets via a £1 symbol. Two conditions were presented: a response was required to green squares (no-reward) or to blue squares (reward).

c: reinforcement - loss/no-loss: same as reward task (above) but with punishment received after 65% of blue coloured targets via a crossed out £1 symbol.

d: face recognition: subjects were asked to judge the gender of the people in pictures from the International Affective Pictures Series. Four conditions were presented, neutral faces (A), angry faces (B), faces showing disgust (C) and fearful faces (D).

The fMRI data were acquired on a 1.5T Philips *Intera* scanner with a multi-slice, single shot EPI sequence to achieve whole brain coverage and analysed using SPM2 with a random effects model (SPM2, Friston, The Wellcome Department of Cognitive Neurology, London).

Results

Citalopram did not alter the subjects' performance of the tasks. Modulation of the go/no-go task by citalopram was observed in a number of right sided frontal areas including lateral orbital frontal cortex (OFC). Citalopram attenuated neuronal activation in the left OFC as well as the bilateral supramarginal gyrus and left thalamus. An interaction of the reward task with citalopram showed enhanced activation in the anterior cingulate bilaterally and attenuated activation in the left putamen. Modulation of responses to the loss task by citalopram showed attenuation of the activation of the right frontopolar cortex and right lateral OFC, left insula and thalamus bilaterally.

Citalopram attenuated activation in left parahippocampal gyrus when comparing negative to neutral faces. No effects of citalopram were observed on responses to angry faces. The neuronal response of the temporal cortex to disgusted faces was attenuated by citalopram whilst the right cingulate gyrus and right thalamus responses were enhanced. For fearful faces only the left amygdala response was attenuated by citalopram.

Conclusions

Citalopram enhanced the neuronal activation associated with go/no-go performance, confirming previous data indicating a role for serotonin in behavioural inhibition involving frontal lobe mechanisms. Haemodynamic responses to reward were significantly modulated by citalopram in areas that have been previously related to reward processing:- anterior cingulate and putamen. In addition, citalopram attenuated neuronal responses to punishment (loss). These results suggest a critical role for 5-HT in modulating incentive motivation. Finally, citalopram modulated the limbic response to implicit recognition of facial expressions, attenuating the activation to fearful faces in the amygdala and enhancing the activation of cingulate gyrus and thalamus to disgusted expressions. These results support the hypothesis that 5-HT acutely modulates incidental responses to emotional stimuli at a neuronal level and have implications for further understanding of disorders characterised by serotonergic dysfunction.

References

Anderson et al. 2002, Neurorep **13**, 1547-51; Bakker et al. 2000, Int Clin Psychopharm, **15**, S25-S30; Keller 2000, J Clin Psych, **61**, 896-908;