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Neuronal correlates and serotonergic modulation of behavioural inhibition and reward in healthy and antisocial individuals

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ABSTRACT

Individuals with antisocial personality disorder (ASPD) are impulsive and show impairment in reinforcement processing. There is increasing evidence for a neurobiological basis of psychopathy, which shares some of the characteristics of ASPD, but research on the neuronal correlates of neuropsychological processes in ASPD remains limited. Furthermore, no research has examined the effects of serotonergic manipulation on brain activations in antisocial groups. In this study, 25 male participants with ASPD (mean age 42.1) and 32 male control participants (mean age 30.5; 25 participants providing usable scans) were randomly allocated to receive the 5-HT_{2C}-agonist mCPP or placebo. Participants were scanned using functional magnetic resonance imaging (fMRI) during a behavioural inhibition (Go/NoGo) and a reward task. In comparison to healthy controls the ASPD group showed reduced task related activations in the dorsolateral prefrontal cortex (DLPFC) but increased signal in the pre/subgenual anterior cingulate cortex (ACC) in the Go/No-Go task and increased activation in OFC in the reward task. mCPP modulated brain responses in both tasks in the whole group. Interactions between group and drug occured in bilateral OFC, caudate and ventral pallidum during the reward task but no significant interactions were found in the Go/No-Go task. This suggests that ASPD involves altered serotonin modulation of reward, but not motor inhibition pathways. These findings suggest that ASPD involves altered DLPFC, ACC and OFC function. Altered serotonergic modulation of reward pathways seen in the ASPD group raises the possibility that targeting serotonin systems may be therapeutic.

1. Introduction

Antisocial personality disorder (ASPD) is characterised by a disregard for and violation of rights of others (APA, 1994) and is associated with increased rates of aggressive and criminal behaviour. There is increasing evidence for a neurobiological basis of ASPD, including genetic liability, aberrant serotonergic function, neuropsychological deficits and structural and functional brain abnormalities (reviewed in Pridmore et al. (2005)). Individuals with ASPD display behavioural symptoms, such as impulsivity, as well as affective impairment. Previous neuroimaging research has mainly focused on the affective component of the disorder; little work has been conducted investigating the neuronal correlates of impulsive responding in this group.

In healthy individuals neuronal correlates of behavioural inhibition, one aspect of impulsivity, include anterior cingulate (ACC), dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) (reviewed in Elliott (2005)). In antisocial groups abnormal brain activations during tasks requiring restraint of motor responding (Go/No-Go tasks) have been described (Völlm et al., 2004). Functional neuroimaging studies using reward tasks in healthy control groups (reviewed in O'Doherty (2004)) have implicated a number of brain regions mediating the behavioural and motivational effects of reward, including ventral striatum, dopaminergic midbrain, amygdala and orbitofrontal cortex. Amygdala, striatum and midbrain appear to be involved in the experience of reward while OFC is thought to mediate the integration of reward and punishment stimuli to inform future behaviour. Behavioural (Dolan and Park, 2002) and imaging (Völlm et al., 2007) studies in personality disordered groups have led to the proposal that deficits observed in behavioural choice involving reward and punishment may be related to prefrontal cortex dysfunction in Cluster B personality disordered patients.

An inverse relationship between impulsivity and 5-HT function has been demonstrated across a broad range of population samples

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(Dolan et al., 2001). 5-HT modulation has also been associated with alterations in behavioural choice following reward and punishment (Cools et al., 2005). Recently, neuroimaging research has investigated how 5-HT might exert its effect on these neuropsychological processes. In healthy individuals several studies have shown enhanced brain activations in prefrontal, particularly orbitofrontal, cortex during behavioural inhibition after administration of a range of different serontonergic drugs (Anderson et al., 2002; Del Ben et al., 2005; Völlm et al., 2006). Enhanced parietal cortex activations were identified during reward processing (Völlm et al., 2006).

In this study we used functional magnetic resonance imaging (fMRI) to identify brain areas associated with behavioural inhibition and reward in healthy and ASPD individuals and differences in activations between the two groups. We further investigated the effect of a serontonergic manipulation with the 5-HT_{2C}-agonist m-chlorophenylpiperazine (mCPP) on these activations. Due to the deficient baseline 5-HT function in ASPD individuals, we hypothesised that a drug enhancing postsynaptic 5-HT function would have a larger effect on task related signal change in the ASPD group compared to the healthy control group.

2. Method

2.1. Participants

Male ASPD participants were recruited from a variety of sources including a high security and a private sector medium security forensic psychiatric hospital and an open prison, all located in the North-West of England. Additional individuals were recruited via probation and from the general public using newspaper advertisements. Male healthy control participants were recruited from university staff (particularly non-academic staff) and the student population as well as from the general public. All participants underwent diagnostic interviews including the Structured Clinical Interview for DSM-IV Axis I (First et al., 2002) and Axis II (First et al., 1997). All patients met criteria for adult ASPD symptoms and all but four participants had a history of conduct disorder. None of the control participants met criteria for any DSM-IV personality disorder. None of the participants in either group had any current major mental illness including schizophrenia, schizoaffective disorder, bipolar disorder or major depression. Individuals fulfilling diagnostic criteria for any of these disorders in the past were also excluded except for depression. Substance abuse and dependence were currently absent in both groups, past drug dependence was also excluded. Further exclusion criteria included age over 60 years, IQ < 85, history of significant head injury, neurological illness/pathological MRI scan, abnormal ECG reading, use of any illicit substances in the past 2 months, current self-reported alcohol intake >20 U week, current psychotropic medication and any contraindication for MRI scanning. All individuals had a urine drug screen to identify any potential non-disclosed drug use. IQ was determined using the Quick Test (Ammons and Ammons, 1962). All but two control participants were right-handed.

Of the 35 ASPD participants initially invited, one had to be excluded due to contraindications for MR scanning, and one participant could not see the stimulus material in the scanner because of poor eye sight. Five further individuals were excluded due to low IQ. Three participants had been released from prison and were no longer contactable for the scanning visit. Therefore, 25 ASPD participants were scanned. Two scans had to be excluded from analysis in the reward task due to excessive movement. In the healthy control group 38 individuals were interviewed for participation. Of those three had to be excluded for low IQ, three were lost to follow up. Therefore, 32 participants were invited for scanning. Three individuals felt claustrophobic in the scanner and could not proceed. The scans of four participants had to be excluded due to movement artefacts providing scanning data on 25 controls.

The study was approved by the University of Manchester and Multi Centre Research Ethics Committees. Written informed consent was obtained from all participants.

2.2. Self-report impulsivity measures

Two self-report questionnaires were used to assess impulsivity: The Barratt Impulsivity Scale (BIS-11A; Barratt et al., 1985) and the Impulsivity Venturesomeness Empathy Scale (IVE; Eysenck and Eysenck, 1978). The BIS consists of 30 items answered on a 4-points scale and records three aspects of impulsivity: motor, non-planning and cognitive impulsivity. The IVE comprises of 54 forced choice questions of which 19 assess impulsivity.

2.3. Experimental design and drug administration

We used a double-blind parallel group design. Individuals were randomly allocated to receive an infusion of either mCPP or placebo (saline). Each participant underwent a 16 min fMRI scan receiving an infusion of either placebo (saline) or mCPP (0.08 mg/kg) via saline over 90 s starting at 8 min into the scan (results not reported here). Participants then performed four cognitive tasks in a pseudo-random order during fMRI scanning: A Go/No-Go task, a Reward/No-Reward task, a facial recognition task and an empathy task (results of the latter two are not reported here). After exclusion of non-usable scans 15 ASPD participants in the placebo group provided data for the Go-No-Go task and 23 for the reward task while 10 ASPD participants were included in the mCPP group. The corresponding numbers for the control group were 13 in the placebo group and 12 in the mCPP group for both tasks.

2.4. fMRI tasks

2.4.1. Go/No-Go task

The Go/No-Go task was a block design task comprising of four Go and four No-Go blocks, each of 45 s. duration, presented in an ABABABAB design. In each block participants were presented with 26 letters, each displayed for 500 ms, with a 1230 ms inter-stimulus interval. Participants responded to each letter with a right-handed button box but were required to withhold their response when the letter presented was a 'V'. In the Go blocks there were no 'V's', while in the No-Go blocks 50% of the letter were 'V's'. Reaction times and errors were recorded.

2.4.2. Reward task

The ABABAB block design reward task comprised three no-reward and three reward blocks lasting 6 min in total. In each block 33 coloured squares were successively displayed for 1164 ms each, with a 200 ms inter-stimulus interval. Participants were asked to respond to green and blue target squares, but not to other colours, using a button box. Reward blocks contained only blue targets, no-reward blocks only green squares as targets thereby matching the total number of motor responses between the blocks. Responses to the blue squares but not to the green squares produced a '£' symbol in a grey circle. Participants were told that every time they responded appropriately and saw a £ sign, money would be added to their winnings, so they believed that rewards were contingent on performance. In reality, however, the reward contingencies were fixed so that all participants received the same number of rewards per block as long as they made a motor response. A grey circle without '£' was displayed following all green squares.