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

Birgit Völlm a,*, Paul Richardson b, Shane McKie c, Renate Reniers a, c, Rebecca Elliott c, Ian M. Anderson c, Steve Williams c, Mairead Dolan d, Bill Deakin c

a Sir Colin Alan Campbell Building, Institute of Mental Health, Section of Forensic Mental Health, University of Nottingham Innovation Park, Triumph Road, Nottingham NG7 2TU, UK
b Brain, Behaviour and Cognition Group, Sheffield Hallam University, UK
c Neuroscience and Psychiatry Unit, University of Manchester, UK
d Centre for Forensic Behavioural Science, Monash University, Australia

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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-HT2C-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 occurred 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.

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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
(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 serotonergic 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 serotonergic manipulation with the 5-HT2C-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 psychotrophic 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.
Table 1

Areas in which significant signal increases in No-Go compared to Go blocks were observed in all subjects (i.e. main effect of task, \(N = 50\)). Effects of group (ASPD \(N = 25\) vs. control \(N = 25\)) and drug (mCPP \(N = 22\) vs. placebo \(N = 28\)) are also shown.

<table>
<thead>
<tr>
<th>Brain area</th>
<th>BA</th>
<th>R/L</th>
<th>Main effect of task</th>
<th>ASPD &gt; control</th>
<th>Control &gt; ASPD</th>
<th>mCPP &gt; placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MNI coordinates</td>
<td>Cluster size</td>
<td>Z value</td>
<td>MNI coordinates</td>
</tr>
<tr>
<td>Lateral orbitofrontal cortex</td>
<td>47</td>
<td>R</td>
<td>36 51 -12</td>
<td>3.79'</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>-57 17 -6 203</td>
<td>3.42'</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>-27 16 -24</td>
<td>3.23'</td>
<td></td>
<td></td>
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<tr>
<td>Medial orbitofrontal cortex</td>
<td>11</td>
<td>R</td>
<td>24 54 -9</td>
<td>3.81'</td>
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<td></td>
</tr>
<tr>
<td>Pre/subgenual cingulate</td>
<td>32</td>
<td>R</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
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<td></td>
<td></td>
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<tr>
<td>Inferior frontal cortex</td>
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<td>R</td>
<td>21 63 0</td>
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<tr>
<td></td>
<td></td>
<td>L</td>
<td>-27 58 -5 65</td>
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<tr>
<td></td>
<td>44</td>
<td>R</td>
<td>51 12 24</td>
<td>4.22'</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>R</td>
<td>54 18 21</td>
<td>4.20'</td>
<td></td>
<td></td>
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<td>Dorsolateral prefrontal cortex</td>
<td>9</td>
<td>R</td>
<td>33 42 36</td>
<td>4.72'</td>
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<td></td>
<td></td>
<td>L</td>
<td>48 30 27</td>
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<tr>
<td>Medial frontal cortex</td>
<td>9</td>
<td>L</td>
<td>-3 54 27</td>
<td>3.17'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>10</td>
<td>R</td>
<td>36 57 3</td>
<td>4.63'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>6</td>
<td>R</td>
<td>15 9 69 4188</td>
<td>5.34'</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>L</td>
<td>-3 0 69</td>
<td>4.01'</td>
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<tr>
<td>Premotor cortex</td>
<td>8</td>
<td>R</td>
<td>48 9 48</td>
<td>4.25'</td>
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<td></td>
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<td>L</td>
<td>-6 24 54</td>
<td>3.73'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle cingulate</td>
<td>24</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>23</td>
<td>R</td>
<td>0 -33 24 122</td>
<td>4.20'</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>R</td>
<td>9 -24 39</td>
<td>3.90'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal cortex, including precuneus and supramarginal gyrus</td>
<td>7</td>
<td>R</td>
<td>36 -60 57 7439</td>
<td>5.67'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal lobe, including temporal pole</td>
<td>20</td>
<td>R</td>
<td>45 0 -27 39</td>
<td>3.48'</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>21</td>
<td>R</td>
<td>51 -30 -12</td>
<td>4.38'</td>
<td></td>
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<tr>
<td></td>
<td>22</td>
<td>R</td>
<td>56 -46 16</td>
<td>5.16'</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>-54 -48 3 71</td>
<td>3.94'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital lobe, including lingual and fusiform gyrus</td>
<td>38</td>
<td>R</td>
<td>54 18 -9 73</td>
<td>3.89'</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>R</td>
<td>-6 -81 -27</td>
<td>4.79'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>19</td>
<td>R</td>
<td>-21 -75 -27</td>
<td>4.02'</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>R</td>
<td>9 -18 6</td>
<td>3.84'</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>L</td>
<td>33 21 0</td>
<td>3.22'</td>
<td></td>
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<tr>
<td>Caudate</td>
<td></td>
<td>L</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Midbrain</td>
<td></td>
<td>R</td>
<td>3 -24 -18</td>
<td>3.84'</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>-3 -24 -6</td>
<td>3.69'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raphe nuclei</td>
<td></td>
<td>R</td>
<td>0 -27 -21 192</td>
<td>3.96'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
<td>L</td>
<td>-42 -66 -33 643</td>
<td>5.17'</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BA, Brodmann area; R/L, right/left.

\( p_{FDR} < 0.05 \) across the whole brain.

All other regions are thresholded at \( p < 0.001 \), uncorrected.

*Cluster size:* Where no cluster size is reported, responses in this region were part of a larger cluster the most significant voxel of which was in a different anatomical region.
2.5. Imaging data acquisition

Functional magnetic resonance (fMRI) images were acquired using a 1.5 T Philips Gyrosan ACS NT (Philips, Best, NL) scanner. In each task, 72 volumes were acquired, each comprising 40 T2*-weighted contiguous axial slices (slice thickness = 3.5 mm), acquired using a single shot echo planar (EPI) pulse sequence (TR = 5 s; TE = 40 ms; in-plane resolution 3.5 mm × 3.5 mm).

2.6. Data analysis

Sociodemographic, questionnaire and behavioural task data were analysed using SPSS 11.5. An independent samples t-test was used to compare means for age, IQ and impulsivity measures. A repeated measure ANOVA with group (control vs. personality disordered) and condition (placebo vs. mCPP) as between group factors and block (Go vs. No-Go block or reward vs. no-reward block) as within subject factor was used to analyse differences in reaction times. A Mann–Whitney U test was used to compare means of error rates. All tests were two-tailed and an alpha level of \( p < 0.05 \) was used to determine statistical significance. fMRI data were processed using Statistical Parametric Mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm) with a random effects model. Individual scans were realigned using the first scan as a reference and normalized into the Talairach and Tournoux stereotactic space (Talairach and Tournoux, 1988) using Montreal Neurological Institute (MNI) templates. Spatial smoothing with a 10 mm Gaussian kernel was applied.

Statistical analysis of imaging data was carried out using the general linear model to model blood oxygenation level dependent (BOLD) signal changes to the No-Go relative to the Go and the reward relative to the no-reward blocks. The statistical parametric maps from each individual dataset were entered into second-level, random effects analyses. A 2 × 2 factorial design was used to identify the main task effects, effects of group (ASPD vs. controls) and drug condition (mCPP vs. placebo) and interactions between group and drug. Age was used as covariate of no interest in all imaging analyses.

Task, group and drug effects on BOLD signal were deemed statistically significant if they survived correction for multiple comparisons across the whole brain at \( p_{FDR} < 0.05 \). We also report responses significant at \( p < 0.001 \), uncorrected in regions about which we had an a priori hypothesis. For the Go/No-Go task, these regions were orbitofrontal cortex (OFC; BA 11/47), dorsolateral prefrontal cortex (DLPFC; BA 9/10/44/46), inferior frontal cortex (BA 45), motor cortex (BA 6), cingulate cortex (BA 24/30/31/32), inferior parietal cortex (BA 39/40) and basal ganglia (putamen, caudate, globus pallidus; Elliott, 2005; Casey et al., 1997). For the reward task, these were ventral and medial prefrontal cortices (including ventral anterior cingulate cortex and orbitofrontal cortex), amygdala, striatum and midbrain (Elliott et al., 2003). For effect of mCPP, regions which have previously been identified as having high density of 5-HT2C receptors were also included (choroid plexus, substantia nigra, amygdala, caudate, globus pallidus and hypothalamus (Anderson et al., 2003). Significant correlations between impulsivity scores and BOLD signal changes in the placebo condition are reported. Some subthreshold activations of interest at \( p < 0.005 \) and >0.001 are discussed in the text. Only clusters of five or more contiguous voxels are reported.

3. Results

3.1. Sociodemographic and behavioural data

Control participants were significantly younger than those with ASPD (mean controls 30.5, range 18–55; mean ASPD 42.1, range 29–56; \( p < 0.001 \)). Individuals with ASPD and healthy control participants differed in years of education (12.3 vs. 16.4; \( p < 0.001 \)). However, IQ scores were not significantly different between the two groups (mean controls 103.9, range 89–130; mean ASPD 99.4, range 89–113; \( p = 0.077 \)).

ASPD participants had higher total BIS scores compared to control individuals which just missed statistical significance (mean
ASPD 51.1, range 21–96; mean controls 39.8, range 17–63; 
$P = 0.05$). None of the three BIS subscores were significantly different 
between the two groups. ASPD participants scored higher on 
the IVE questionnaire for impulsivity (mean ASPD 9.4, range 0– 
19; mean controls 5.3, range 0–14; $P = 0.001$).

3.2. Task performance

The repeated measures ANOVA revealed no significant 

3.2.1. Task-evoked BOLD responses (No-Go vs. Go)

Table 1 and Fig. 1 show significant BOLD responses in No-Go 
compared to Go blocks in the whole group (main effect of task), 
including orbitofrontal, inferior and dorsolateral prefrontal cortex, 
precentral gyrus, cingulate and parietal cortex. Significant signal 
increase was also identified in the raphe nuclei and habenulae.

3.2.2. Effect of group (ASPD vs. control group)

Control participants had greater responses than the ASPD group 
in left DLPFC, precentral gyrus and right parietal cortex. Increased 
signal in the ASPD group was detected in right pre/subgenual (per- 
genual) cingulate (Table 1 and Fig. 2a) and at $P < 0.005$ in areas 
associated with emotional processing about which we had no a 

3.2.3. Effect of drug (mCPP vs. placebo)

Whole brain analysis comparing the mCPP to the placebo condition 
across both groups revealed significantly increased activations in 
middle cingulate gyrus and caudate (see Table 1 and Fig. 2b) and 

3.3. Imaging results: Go-No-Go task

3.3.1. Task-evoked BOLD responses (No-Go vs. Go)

No significant positive interactions of group (ASPD and control) 
and drug (mCPP and placebo) were observed. However, at $P < 0.005$
mCPP and ASPD interacted to enhance responses in left 
inferior frontal cortex (centre $–57$, $27$, $6$) and a caudate cluster extending to 
chondr cortex (centre 15, 12, 18). A negative interaction was 
observed in premotor cortex (centre $–48$, 6, 51).

3.3.5. Correlations between impulsivity scores and signal

We investigated inverse correlations between total BIS scores 
and brain signal in regions of interest in the placebo condition. 
No such correlations were found in the whole group or control 
group only. However, in the ASPD we found significant negative 
correlations in DLPPC (centre, 39; 39; 28, $z = 3.25$; cluster size 
44) and inferior frontal cortex (centre 15; 55; –8; $z = 3.23$; cluster 
size 36).

3.4. Imaging results: reward task

3.4.1. Task-evoked BOLD responses (reward – no-reward)

Reward blocks were associated with BOLD responses in extras- 
triate cortex and fusiform gyrus but no responses were seen in pred- 
edicted areas associated with reward processing (Table 2).

3.4.2. Effect of group (ASPD vs. control group)

Increased BOLD responses were seen in the ASPD group in a re- 

gion of right OFC and in the pregenual cortex. No significantly in- 
creased signal in the control group was observed in the 

3.4.3. Effect of drug (mCPP vs. placebo)

Whole brain analysis showed greater responses to reward after 
mCPP than after placebo in bilateral OFC (BA 11/47) and ventral 
tegmental area. A trend to greater response was also seen in right 

Fig. 2. Effect of diagnosis (a) and mCPP (b) on signal during behavioural inhibition. Areas with significant BOLD signal increases were overlaid on standard T1-weighted slices. 
Axial (slice numbers given in the z plane) and sagittal (slice numbers given in the x plane) slices are shown. Height threshold $T = 3$. (a) Greater No-Go – Go responses in the ASPD compared to the control group in right and left pre/subgenual cingulate (left two figures). Subthreshold ($P < .005$) activations of interest (right two figures) in left posterior hypothalamus and left precuneus and [far right] anterior right hippocampus are also shown. (b) Greater No-Go responses at subthreshold significance ($P < .005$) in the mCPP group compared to the placebo group in bilateral subgenual cingulate (two left figures) and putamen (right figure).
**Table 2**

<table>
<thead>
<tr>
<th>Brain area</th>
<th>BA</th>
<th>R/L</th>
<th>MNI coordinates</th>
<th>Cluster size</th>
<th>Z value</th>
<th>MNI coordinates</th>
<th>Cluster size</th>
<th>Z value</th>
<th>MNI coordinates</th>
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<tr>
<td>Orbitofrontal cortex</td>
<td>11</td>
<td>R</td>
<td>27</td>
<td>38</td>
<td>-4</td>
<td>3.38</td>
<td>39</td>
<td>3.37</td>
<td>21</td>
<td>3.15</td>
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<tr>
<td>Ventral pallidum</td>
<td>29</td>
<td>L</td>
<td>-12</td>
<td>0</td>
<td>6</td>
<td>3.08</td>
<td>6</td>
<td>3.42</td>
<td>68</td>
<td>3.08</td>
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<tr>
<td>Pregenual cingulate</td>
<td>10</td>
<td>L</td>
<td>9</td>
<td>45</td>
<td>6</td>
<td>3.31</td>
<td>36</td>
<td>3.31</td>
<td>21</td>
<td>3.15</td>
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<tr>
<td>Temporal lobe</td>
<td>20</td>
<td>L</td>
<td>-62</td>
<td>-30</td>
<td>-16</td>
<td>4.08</td>
<td>30</td>
<td>5.72</td>
<td>300</td>
<td>3.86</td>
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<td>Occipital lobe, includ-</td>
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<td>ing lingual and</td>
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<td></td>
<td>18</td>
<td>-30</td>
<td>-96</td>
<td>3.38</td>
<td>36</td>
<td>3.38</td>
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<td>3.15</td>
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<tr>
<td>fusiform gyrus</td>
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<td></td>
<td>19</td>
<td>-45</td>
<td>-65</td>
<td>3.42</td>
<td>27</td>
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<td>68</td>
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<tr>
<td>Vertical lamina</td>
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<tr>
<td>Brainstem</td>
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**Note:** BA, Brodmann area; R/L, right/left.

**Z value:** FDR < 0.05 across the whole brain. All other regions are thresholded at p < 0.001, uncorrected.

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**3.4.4. Interactions between drug and group effects**

A number of positive interactions between group (ASPD and control) and drug (mCPP and placebo) were observed in hypothesised regions including left bilateral caudate (centre -12; 27; 6 and 18; 29; 9), ventral pallidum (centre 12, 0, -6; see Fig. 3). No negative interactions were observed.

**4. Discussion**

In this study we examined two neuropsychological processes proposed to be impaired in antisocial individuals: impulsivity and reward processing. We investigated task performance on a Go/No-Go and a reward task and used fMRI to identify brain activations associated with performing these tasks in antisocial personality disordered individuals and in a healthy control group. We further explored whether a serotonergic drug challenge (mCPP) modulated task related neuronal activations. Our results suggest that the ASPD group was more impulsive than the control group on two self-rated measures of impulsivity. Although there were no differences in performance, we identified subtle differences between personality disordered and healthy individuals in the neuronal correlates associated with behavioural inhibition and reward and in the effect mCPP had on these brain activations. Our findings complement previous data suggesting a neurobiological basis for ASPD and highlight brain areas which may be involved in the deficits observed in this patient group.

**4.1. Brain activations associated with behavioural inhibition**

Go/No-Go tasks have been widely used to assess impulsive responding, i.e. the inability to withhold motor responses to certain stimuli, both as behavioural tasks and in the context of imaging experiments. Studies examining performance of antisocial individuals on such tasks have produced inconsistent findings. Lapiere et al. (1995) and Dolan and Park (2002) have provided evidence for significant task impairment in psychopathic and anti-social individuals while Dinn and Harris, (2000) and Kiehl et al. (2000) failed to find such differences. In our study, reaction times and error rates were also not significantly different between the two groups. This may be due to a ceiling effect in task performance as the Go/No-Go task was relatively undemanding with low overall error rates. It is also possible that our patient group was less impulsive than groups in some previous studies. In our group, there was only a non-significant trend for ASPD participants to be more impulsive than controls (on the BIS-11A), although it is important to note that self-report scales may be less reliable in forensic populations, such that impulsivity was underreported.

The Go/No-Go task evoked the well-known pattern of BOLD responses in predominantly right-sided OFC, inferior frontal cortex and parietal cortex (Elliott, 2005; Garavan and Ross, 1999; Horn et al., 2003). An intriguing finding in this study was the significant activation in the midline raphe of the brain stem and pons during behavioural inhibition. The raphe nuclei contain serotonin neurons that innervate the forebrain with serotonin terminals. In view of the extensive evidence for a key role of serotonin in behavioural restraint, we propose that raphe BOLD responses in the No-Go condition are the result of increased serotonin neuronal activity evoked by the requirement to suppress the pre-potent Go response. We did not observe impaired raphe activation in the ASPD group as might have been expected for the low serotonin hypothesis of impulsivity. However, this is not a decisive negative finding since the raphe BOLD responses were only detectable in the full sample but were not seen in either group alone.
Few studies so far have investigated differences in neuronal correlates of behavioural inhibition between personality disordered and healthy control groups. Kiehl et al. (2000) used event-related potentials (ERPs) during a Go/No-Go task and identified a reduction in the frontal N275 ERP component thought to reflect neuronal activity associated with response inhibition, in psychopaths. We have previously described (Völlm et al., 2004) increased brain activations in fronto-temporal regions in a group of Cluster B personality disordered patients. However, OFC and DLPFC activity was only found in the control but not in the PD group. Consistent with this previous observation, the current study identified enhanced signal in DLPFC and parietal cortex in the control compared to the ASPD group.

In the present study, reduced left DLPFC BOLD responses in the ASPD group might reflect an impaired recruitment of frontal executive mechanisms as suggested by the neuropsychological findings of Dolan & Park in ASPD (Dolan and Park, 2002). Although right prefrontal responses in the ASPD group were similar to those in controls, they did correlate inversely with total BIS impulsivity self-ratings in DLPFC and IFC in the ASPD group whereas no correlations were seen in the controls. This suggests that altered right frontal function may be relevant to trait impulsivity in ASPD in a way not revealed by the Go/No-Go task. For example, the task may have been too easy to reach the limit of neural resource in ASPD.

Diminished parietal cortical engagement in No-Go compared to Go blocks in the ASPD group raise the possibility that impulsivity in ASPD may have a visuo-spatial attentional component – a lack of selection and attention to targets for action. Greater No-Go BOLD responses occurred in bilateral pre/subgenual cingulate gyrus in the ASPD group. Anterior cingulate has been implicated in allocating attentional resource under conditions of conflicting cognitive and emotional demands and in regulating negative emotional responses (Bush and Luu, 2000). Failure of cingulate responses to negative information may be an important cognitive mechanism of depression (Elliott et al., 2002; Mannie et al., 2008). Increased signal in this area has been observed in a number of emotional tasks involving, e.g. sadness or fear and in the monitoring of internal states (reviewed in Drevets (2008)). Subgenual cingulate cortex has strong connections with brain areas involved in emotional and autonomic function, such as amygdala and hypothalamus where evidence of enhanced activation was also seen in the ASPD group (see Fig. 2). A tentative hypothesis is that the No-Go condition is experienced as frustrating. In debriefing, participants typically report that they felt annoyed with themselves when they make an error on what should be a very simple task. It is possible, though admittedly speculative, that this frustration may be experienced more strongly in ASPD individuals than in controls, associated with enhanced pre/subgenual cingulate response.
4.2. Brain activations associated with reward processing

Contrary to previous evidence using similar tasks (Elliott et al., 2003), we failed to identify significant signal change during reward processing in hypothesised reward areas. This task may have been too simple and the winnings too small relative to total study reimbursement (up to £120, £30 of which could be earned through performance on the different tasks which formed part of this study) to elicit reward system activations. In particular, there was no uncertainty associated with receipt of reward, and studies suggest that rewards that are fully expected and predictable elicit less response with dopaminergic reward systems than rewards that are less predictable (O’Doherty, 2004).

Neuropsychological studies have provided evidence for dysfunctional responses to reinforcing stimuli in antisocial and impulsive individuals, e.g. discounting of delayed rewards, increased responsiveness to reward and decreased sensitivity to punishment. In the present study, the APSD group showed activations in mid OFC and pregenual cingulate relative to the control group and this is compatible with the idea that reward may be more salient in ASPD. In contrast, using a similar reward task, we found reduced rather than increased medial prefrontal reward activations in nine individuals with both borderline and antisocial personality disorder (Völlm et al., 2007). Clearly, further research is needed to investigate the neurobiology of reward in different personality disorders.

4.3. Effect of mCPP on task related brain activations

The inverse relationship between central nervous system 5-HT function and aggressive/impulsive behaviour is one of the most robust findings in biological psychiatry. Behavioural studies in healthy individuals have demonstrated that manipulation of 5-HT availability, e.g. following tryptophan depletion, altered performance on a continuous performance task (Walderhaug et al., 2002) and behavioural choice in a reward task (Cools et al., 2005) although not all studies have identified such effects. How 5-HT exerts its effects on these functions on a neuronal level is not yet understood.

In the present study the 5-HT2C receptor agonist mCPP modulated brain activations observed during performance of both, the behavioural inhibition and the reward task. In the Go/No-Go task, mCPP was associated with middle cingulate gyrus and caudate activation. Both these regions are involved in motor control and the caudate is rich in 5-HT2C receptors (Pasqualetti et al., 1999). However, we did not replicate our previous finding that mCPP increased right IFC responses in the Go/No-Go task (Völlm et al., 2007). The reasons are not obvious since the procedures were closely similar. It is of interest that mCPP, like ASPD, was associated with greater activation in bilateral subgenual cingulate although at P < 0.005 (Fig. 2b and c). Our results suggest ASPD may involve dysregulation of emotion and that mCPP, like ASPD, enhances an emotional component of the No-Go condition that is minimal in controls. We did not find evidence that mCPP modulation was greater in ASPD participants than controls but further studies, using affective tasks, are needed to determine whether ASPD subjects have altered 5-HT modulation of emotion.

In the reward task, mCPP increased brain activations in part of the reward circuit, namely OFC, putamen and a focal midbrain activation including the ventral tegmentum which contains dopamine cells projecting to mesolimbic structures. The reward task was apparently not sufficiently engaging to elicit reward system activations in the absence of drug and it is therefore particularly striking that mCPP enhanced reward system response to this task to a detectable threshold. The psychopharmacological basis for this is unclear since in experimental animals 5HT2C agonists suppress spontaneous mesolimbic dopamine cell firing probably by activating local GABA interneurones (Di Matteo et al., 2001). One possibility is that mCPP suppressed background dopamine function allowing a stronger contrast between the reward and the control blocks. It is of interest that this effect of mCPP was greater in the ASPD group in OFC, caudate and ventral pallidum. This would suggest that altered reward sensitivity in ASPD involves altered 5HT2C function, possibly a supersensitivity due to impaired presynaptic serotonin function.

4.4. Limitations

While we have tried to exclude many confounding factors that may account for differences between the two groups, we did not match for age or years of education. Instead we used age as a covariate of no interest in the analysis. Even though no significant differences between IQ were found, our IQ measure was rather crude and we cannot therefore rule out more subtle cognitive differences between the two groups, particularly as the groups differed in terms of years of education. It is also possible that our patient group was not comparable to ASPD groups used in some previous studies; in particular it is striking that their impulsivity scores did not differ significantly from controls. This may reflect the use of a forensic population which may be less reliable on self-report scales. Alternatively, it is possible that this was a genuinely atypical sample in terms of impulsivity scores.

It is of note that there were no significant behavioural differences between groups on either of the tasks used. This may suggest performance at ceiling level in both groups. Therefore, if more challenging tasks had been chosen, we might have been able to observe greater differences in task related brain activations between the two groups.

A further limitation of our findings is that group comparisons did not survive corrections for multiple comparisons. Given that we had a priori hypothesis with regards to these comparisons, we would argue that our findings still make a valuable contribution to the limited literature on ASPD. However, they should be interpreted cautiously particularly as the sample sizes were relatively small. It is also important to consider whether the effects of mCPP we observed could be a result of global changes in blood flow. However, we would not expect non-specific changes to account for the regional effects we saw and our finding of distinct drug effects depending on group and task.

5. Conclusions

In conclusion, in this study we demonstrated reduced task related brain activations in prefrontal and parietal regions during performance of a behavioural inhibition task as well as increased engagement of parts of the reward circuit during a reward task in a group of individuals with ASPD. This may reflect deficits in executive function and a possible attentional component to impulsivity in ASPD. We also found evidence that the restraint condition engaged pre/subgenual cortex and other emotion processing regions in ASPD but not in controls possibly suggesting that emotional dysregulation may contribute to impulsivity in ASPD. Serotonergic challenge significantly affected brain activations in the whole group but interactions with patient group were only observed in the reward task. The positive interaction between ASPD and mCPP in reward related areas may suggest increased sensitivity to serotonin, possibly due to a supersensitivity following reduced 5-HT release. Future research should examine in more detail how neurobiological deficits in ASPD relate to the clinical presentation of this patient group and whether serotonergic intervention might have a role in improving underlying neurocognitive deficits in this difficult to treat patient group.
Role of funding source

Funding for this study was provided by the Medical Research Council; the MRC had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

B.V., P.R., R.E., I.A., S.W., M.D. and B.D. were involved in the design of the study; B.V., P.R., R.E., I.A., S.W., M.D. and B.D. wrote the protocol. B.V. and P.R. collected the data; B.V. and P.R. managed data collection and databases; B.V., P.R., S.M. and R.R. analysed the data; B.V. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest statement

None declared.

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