

Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours

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Impulsive-compulsive behaviours are a significant source of morbidity for patients with Parkinson's disease receiving dopaminergic therapy. The development of these behaviours may reflect sensitization of the neural response to non-drug rewards, similar to that proposed for sensitization to drug rewards in addiction. Here, by using ¹¹C-raclopride positron emission tomography imaging, we investigated the effects of reward-related cues and L-dopa challenge in patients with Parkinson's disease with and without impulsive-compulsive behaviours on striatal levels of synaptic dopamine. Eighteen patients (11 with and seven without impulsive-compulsive behaviours) underwent three ¹¹C-raclopride positron emission tomography scans. The impulsive-compulsive behaviours included hypersexuality, binge eating, punting, compulsive use of dopamine replacement therapy, compulsive buying and pathological gambling, with eight patients exhibiting more than one impulsive-compulsive behaviour. There were no significant differences in baseline dopamine D2 receptor availability between the Parkinson's disease groups. No differences were found when comparing the percentage change of raclopride binding potential between the two Parkinson's disease groups following L-dopa challenge with neutral cues. The group with Parkinson's disease with impulsive-compulsive behaviours had a greater reduction of ventral striatum ¹¹C-raclopride binding potential following reward-related cue exposure, relative to neutral cue exposure, following L-dopa challenge (16.3% compared with 5.8% in Parkinson's disease controls, $P = 0.016$). The heightened response of striatal reward circuitry to heterogeneous reward-related visual cues among a group of patients with different impulsive-compulsive behaviours is consistent with a global sensitization to appetitive behaviours with dopaminergic therapy in vulnerable individuals. Our findings are relevant for the broader debate on the relation between impulsive-compulsive behaviours and addictions and may have important implications with regards to advertisement legislation in an effort to prevent the onset of behavioural addictions.

Keywords: Parkinson's disease; impulse control disorders; addiction; functional imaging; impulsivity

Abbreviation: BP_{ND} = binding potential (non-displaceable)

Introduction

Impulsive-compulsive behaviours are an increasingly well-recognized adverse effect of dopaminergic medications used to treat Parkinson's disease. Impulsive-compulsive behaviours include the Diagnostic and Statistical Manual of Mental Disorders-IV impulse control disorder of pathological gambling, plus the putative impulse control disorders compulsive sexual behaviour, compulsive buying and binge eating (Grant, 2008), together with punding and the addiction-like compulsive use of dopamine replacement therapy, or dopamine dysregulation syndrome (Giovannoni *et al.*, 2000; Evans *et al.*, 2004). The prevalence of impulsive-compulsive behaviours was ~14% in a large ($n = 3031$) study undertaken in specialist movement disorder clinics (Weintraub *et al.*, 2010). Dopamine dysregulation syndrome is more associated with compulsive L-dopa use (O'Sullivan *et al.*, 2009), whereas other impulsive-compulsive behaviours are more linked with oral dopamine agonist use (Gallagher *et al.*, 2007; Weintraub *et al.*, 2010). The correlation between impulsive-compulsive behaviours and dopamine agonist dose is relatively weak, indicating that patients with Parkinson's disease and impulsive-compulsive behaviours have specific neurobiological vulnerabilities to the behavioural side-effects of these medications.

In a previous study (Evans *et al.*, 2006), we found that individuals with dopamine dysregulation syndrome showed an enhanced ventral striatal response to L-dopa, which was correlated with increased motivation to take the drug. This finding was consistent with the incentive sensitization theory of compulsive drug use, which posits that compulsive drug use arises from the excessive attribution of incentive salience or 'wanting' for drug rewards and their cues, due to progressive neuroadaptations in dopamine projections to ventral striatal motivation circuitry (Robinson and Berridge, 1993; Berridge *et al.*, 2009). In animal models, sensitization of ventral striatal circuitry by addictive drugs has been shown to enhance the pursuit of even natural rewards, including food and sexual incentives (Fiorino and Phillips, 1999; Nocjar and Panksepp, 2002), as a result of excessive incentive salience attribution to reward cues (Wyvell and Berridge, 2001). Such sensitized 'wanting' is greatly magnified by acute administration of dopaminergic drugs (Wyvell and Berridge, 2001). An important finding is that individual propensities for certain types of reward become selectively intensified, enhancing drug-seeking in some animals, while enhancing sexual pursuit, food-seeking or other appetitive behaviours in others (Nocjar and Panksepp, 2002). An enhanced incentive salience attribution to pre potent reward cues, especially in 'ON' dopaminergic states, could therefore lead to the compulsive pursuit of different rewards and may underpin the protean phenomenology of impulsive-compulsive behaviours in Parkinson's disease (Lawrence *et al.*, 2003; Berridge, 2007).

In this study, we investigate possible ventral striatal sensitization across a broad spectrum of Parkinson's disease associated impulsive-compulsive behaviours in relation to L-dopa and reward cues. We hypothesized that patients with impulsive-compulsive behaviours would demonstrate sensitization of their ventral striatal circuitry in response to diverse visual cues relating to reward. We further predicted that craving for non-drug rewards

would be related to L-dopa induced-striatal dopamine release and be responsive to reward-related visual cues.

Materials and methods

Patients

Eighteen L-dopa treated patients diagnosed with Parkinson's disease according to the Queen Square Brain Bank for Neurological Disorders clinical criteria underwent positron emission tomography (PET) scanning (Hughes *et al.*, 1992). All were assessed by the first author for the presence of impulsive-compulsive behaviours in a semi-structured interview, using proposed criteria (Lawrence *et al.*, 2003; Evans *et al.*, 2004; Voon and Fox, 2007; Grant, 2008). Eleven patients were identified as having impulsive-compulsive behaviours (Parkinson's disease with impulsive-compulsive behaviours) at the time of scanning, with eight exhibiting more than one impulsive-compulsive behaviour. The behaviours included compulsive sexual behaviour ($n = 5$), binge eating disorder ($n = 5$), punding ($n = 5$), dopamine dysregulation syndrome ($n = 5$), compulsive buying ($n = 5$), pathological gambling ($n = 5$) and reckless generosity ($n = 1$). The four patients with dopamine dysregulation syndrome and punding also exhibited other impulsive-compulsive behaviours. All participants gave informed written consent in accordance with the Declaration of Helsinki and the study received ethical approval from the Hammersmith, Queen Charlotte's and Chelsea research ethics committee. Permission to administer ^{11}C -raclopride was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC) of the Department of Health, UK.

Patients were screened using the Mini-Mental State Examination and those scoring <26 were excluded because of the requirement to complete self-report scales. Calculation of a daily L-dopa equivalent dose for each patient was based on theoretical equivalence of dopamine agonists to L-dopa (Evans *et al.*, 2004). After a clinic appointment, patients completed the Brief Sensation Seeking Scale-4 (Stephenson *et al.*, 2003), which consists of four questions regarding sensation seeking behaviours. The scale is reliable and has predictive value in alcohol, tobacco and other substance abuse (Stephenson *et al.*, 2003). Heightened impulsive sensation seeking has previously been found in a number of impulsive-compulsive behaviours (Lejoyeux *et al.*, 1998), and prospectively predicts development of impulsive-compulsive behaviours and addiction (Sher *et al.*, 2000; Cyders and Smith, 2008).

^{11}C -raclopride positron emission tomography scanning

All participants underwent three ^{11}C -raclopride PET scans on separate mornings after overnight drug withdrawal (at least 12 h) to study the effects of the pharmacological challenge and exposure to reward-related cues on endogenous dopamine levels. Patients were instructed not to eat from 11 p.m. the evening before each scan to control for state of hunger. ^{11}C -Raclopride is a specific D2 receptor radioligand, which binds receptors in competition with endogenous dopamine. Reductions in ^{11}C -raclopride binding potential (BP_{ND}) are considered an indirect measure of increased endogenous dopamine release, and this technique is well established in the Parkinson's disease and addiction functional imaging literature (Brooks and Piccini, 2006). One scan consisted of the patient 'OFF' medications, looking at neutral cues throughout the scanning. These images included landscapes and nature scenes, household objects and random patterns. Another scan consisted of patients being shown the same set of neutral cues after receiving

an oral dose of dispersible L-dopa/benserazide 200/50 mg 45 min prior to the scan starting. A third scan consisted of reward-related cues being shown to patients after receiving an oral dose of dispersible L-dopa/benserazide 200/50 mg 45 min prior to the scan starting.

We chose to look at response to reward cues as excessive reward pursuit following drug-induced sensitization, which is thought to result from excessive incentive salience attribution to reward cues (Wyvell and Berridge, 2001) and the design minimized cognitive and motor demands. Further, heightened cue reactivity has been reported not just in drug addiction (Carter and Tiffany, 1999), but in a number of impulsive-compulsive behaviours in the non-Parkinson's disease population, including pathological gambling (Sodano and Wulfert, 2010), compulsive buying (Youn and Faber, 2000) and binge eating (Sobik *et al.*, 2005).

The reward-related cues included equal proportions of those of appetizing foods, sexually themed pictures, gambling and money- and shopping-related images and pictures of familiar dopamine replacement therapies. The majority of neutral and reward-related cues were obtained from the well-validated International Affective Picture System (Lang *et al.*, 2008) and were supplemented by freely available images obtained from the internet. The variation of reward-related cue themes was used for several reasons. First, given ethical limitations on radiation exposure, we wanted to be able to sample as many distinct classes of impulsive-compulsive behaviour-related reward cues as possible (food, sex, drug cues, etc.). Second, we wanted to reduce habituation effects as sensitized responses are influenced by novelty (Crombag and Robinson, 2004). Third, there is evidence that cue reactivity is not necessarily focused on a single reward but can 'spill-over' to other rewards (Sodano and Wulfert, 2010), and several patients showed more than one impulsive-compulsive behaviour, consistent with the known comorbidity between impulsive-compulsive behaviours (Petry *et al.*, 2005; Grant, 2008; Kessler *et al.*, 2008; Yip *et al.*, 2010).

The order of the scanning conditions was randomized for each patient. All images were presented as a PowerPoint™ (Microsoft) presentation on a screen placed diagonally above patients' full field of view as they lay in the scanner. The picture presentation started 2 min prior to bolus injection of ¹¹C-raclopride and ran continuously until the end of the scan (60 min). Each image remained on the screen for 10 s. A total of 370 images were shown, without repetition. To control for levels of attention in participants, a 'rating slide' was shown at 10 pseudo-random intervals in all scans, and patients were asked to rate how much they liked the last slide seen into a recording dictaphone, using a scale of 1 (not at all) to 5 (extremely liked).

The PET data were acquired on an ECAT HR+ 962 scanner (CTI/Siemens) in 3D mode, with an axial field of view of 15.5 cm. A 10 min transmission scan (with a ¹³⁷Cs rotating point source) was performed before each emission scan for scatter and attenuation correction (Watson *et al.*, 1996). Head movement was monitored and minimised using a light head-strap. A mean dose of 256 MBq (± 1.90 MBq SEM) was administered as an intravenous bolus over 10 s. Dynamic data were collected over 60 min as 20 timeframes. ¹¹C-Raclopride was manufactured and supplied by GE Healthcare.

Assessments on days of positron emission tomography scanning

Participants undergoing PET scanning were asked to rate their drug and non-drug cravings on a visual analogue scale, anchored between 'the lowest ever' and 'the most ever'. Questions included: 'How do you rate your food cravings right now?'; 'How do you rate your libido/sex drive right now?'; 'How do you rate your desire to

gamble right now?'; 'How much do you like the effects of your medications?'; and 'How much do you feel you would like more of the medication?'. Similar single-item craving scales have been shown to be as reliable as longer several-item questionnaires (West and Ussher, 2010). Motor disability was assessed in a baseline 'OFF' medication state with the Unified Parkinson's disease Rating Scale part 3 and then again immediately before scanning to ensure patient has responded to the medication.

These assessments were performed in the morning before PET scanning or L-dopa administration, and then repeated immediately after the PET scan.

Analysis

The dynamic images were first summed to produce an ADD image. This consists of the integrated total emission data obtained from the whole brain between the start and finish of the 20 timeframes. The ADD image and region of interest object map was normalized to a ¹¹C-raclopride template which was on Montreal Neurological Institute space by using statistical parametric mapping software (SPM2; Wellcome Department of Cognitive Neurology, London). Regional time activity curves for the caudate, putamen, ventral striatum and cerebellum were obtained by defining regions of interest on normalised PET images. For each patient, the average left and right caudate, putamen and ventral striatum binding potential (BP_{ND}) reflecting B_{\max}/K_d were calculated using simplified reference tissue model with the cerebellum as a reference region; (Lammertsma and Hume, 1996; Gunn *et al.*, 1997).

Percentage change in ¹¹C-raclopride BP_{ND} related to the L-dopa challenge scan was calculated using the formula: $100 \times [(BP_{ND} \text{ value of 'OFF' L-dopa scan with neutral cues}) - (BP_{ND} \text{ value of 'ON' L-dopa scan with neutral cues})] / (BP \text{ value of 'OFF' L-dopa scan with neutral cues})$. Percentage change in ¹¹C-raclopride BP_{ND} related to reward cues was calculated using the formula: $100 \times [(BP_{ND} \text{ value of 'ON' L-dopa scan with neutral cues}) - (BP_{ND} \text{ value of 'ON' L-dopa scan with rewarding cues})] / (BP \text{ value of 'ON' L-dopa scan with neutral cues})$.

Percentage change in motor Unified Parkinson's Disease Rating Scale scores was calculated as follows: $100 \times [(value \text{ when 'OFF' L-dopa}) - (value \text{ when 'ON' L-dopa})] / (value \text{ when 'OFF' L-dopa})$. The percentage change in craving scores following various scan types was calculated as follows: $100 \times [(value \text{ after scan and L-dopa if relevant to that scan type}) - (value \text{ before scan and L-dopa if relevant to that scan type})] / (value \text{ before scan and L-dopa if relevant to that scan type})$.

Statistical analysis was performed using SPSS Version 16, SPSS Inc., Chicago, IL, USA. Medians/means were compared using Mann–Whitney U-test or Student 2-tailed *t*-tests where appropriate. Kolmogorov–Smirnov tests were undertaken to demonstrate that the data were normally distributed. Effect sizes for group differences were calculated using Cohen's *d*. Univariate correlations between percentage change in ¹¹C-raclopride BP_{ND} and variables such as sensation-seeking scores, percentage changes in cravings were made using Spearman's rho correlation tests separately on each Parkinson's disease group.

Results

Patients

Eighteen patients with Parkinson's disease (11 Parkinson's disease with impulsive-compulsive behaviours, seven Parkinson's disease

without impulsive-compulsive behaviours) who underwent PET scanning are described in Table 1. The patients without impulsive-compulsive behaviours were taking more dopamine agonists than the group with impulsive-compulsive behaviours at the time of scanning because of the need to discontinue agonists as part of the treatment of impulsive-compulsive behaviours. Apart from this, the groups were matched in terms of total daily dopamine replacement therapy used, age, gender, Unified Parkinson's disease rating scale measures and Parkinson's disease history.

Comparisons of absolute ¹¹C-raclopride binding levels and percentage change between scans

Using the *a priori* defined dorsal and ventral striatal regions of interest, we found no significant differences in the 'OFF medication + neutral images' scan baseline ¹¹C-raclopride-BP_{ND} between the Parkinson's disease groups (Table 2).

No differences were found when comparing the percentage change of ¹¹C-raclopride-BP_{ND} between the two Parkinson's disease groups following a L-dopa challenge when viewing neutral cues. The group of patients with impulsive-compulsive behaviours had a greater reduction of ventral striatum ¹¹C-raclopride-BP_{ND} following the 'reward images' scan, relative to the neutral cue scan, when 'ON' medication ($t = -2.7$, $P = 0.016$, Cohen's $d = 1.37$, $r = 0.56$). (See Table 3 and Fig. 1B and C for the percentage changes in ¹¹C-raclopride-BP_{ND} following L-dopa challenge or reward cue exposure and Fig. 2 for representative changes in ¹¹C-raclopride-BP_{ND} between Parkinson's disease groups). Excluding the four patients with dopamine dysregulation syndrome from analyses did not affect the differences between the other patients with Parkinson's disease with impulsive-compulsive behaviour and Parkinson's disease without impulsive-compulsive behaviour controls, with the seven remaining patients with Parkinson's disease with impulsive-compulsive behaviour

showing a greater reduction of ventral striatum ¹¹C-raclopride-BP_{ND} following the reward-related cues than the neutral scan, when on drug, $P = 0.011$.

Clinical assessments and craving measurements during positron emission tomography scanning

No differences were found between groups comparing absolute measures and percentage changes of self-reported cravings for medication, gambling, libido or food following L-dopa challenge or exposure to reward-related imagery. No differences were seen either between groups or between cue types (reward versus neutral) regarding the rating of how much they liked the particular images seen (data not shown). The rates of completing these ratings was similar between groups, with >90% response to the rating slides.

Correlations between psychological assessments, craving measures and change in ¹¹C-raclopride binding potentials between scan types

No correlations were found between sensation seeking measures and the percentage change in ¹¹C-raclopride-BP_{ND} of the three brain regions analysed following a L-dopa challenge with neutral images. No changes in measures of craving were found to correlate with changes on PET scanning, either in relation to L-dopa challenge or exposure to reward-related cues.

Sensation seeking measures positively correlated with percentage change in ¹¹C-raclopride BP_{ND} seen in the putamen (Spearman's correlation coefficient = 0.68, $P = 0.022$), and caudate (Spearman's correlation coefficient = 0.65, $P = 0.03$) following exposure to reward-related cues among patients with Parkinson's disease with impulsive-compulsive behaviour. No correlations were found between sensation seeking and ¹¹C-raclopride-BP_{ND}

Table 1 Clinical and psychological data

	Parkinson's disease without ICB	Parkinson's disease with ICB	Statistical test
<i>n</i> (%)	7 (39)	11 (61)	
Age (years)	57.7 ± 10.5	57.1 ± 7.7	$t = 0.1$, $P = 0.9$
Gender (male:female)	5:2	8:3	Chi sq = 0.95, $P = 1.0$
Age of Parkinson's disease onset	47.0 ± 8.8	45.1 ± 11.2	$t = 0.4$, $P = 0.7$
Parkinson's disease duration	10.7 ± 6.4	11.9 ± 11.3	$t = -0.3$, $P = 0.8$
L-dopa (mg/day)	708 ± 319	636 ± 325	$t = 0.5$, $P = 0.7$
DA LED (mg/day)	241 ± 143	62 ± 92	Mann-Whitney U = 10.5, $P = 0.007$
Total dopamine replacement therapy (mg/day)	949 ± 253	698 ± 337	$t = 1.8$, $P = 0.09$
UPDRS OFF medication	37.4 ± 11.4	43.3 ± 10.6	$t = -1.1$, $P = 0.3$
UPDRS ON medication	22.0 ± 8.2	24.1 ± 9.3	$t = -0.5$, $P = 0.6$
Percentage UPDRS change post-L-dopa	42.2 ± 4.5	46.1 ± 14.0	$t = -0.9$, $P = 0.4$
Sensation seeking	10.3 ± 2.0	12.6 ± 2.7	$t = -1.9$, $P = 0.08$

All values are mean ± SD. Comparisons are made using Student's *t*-test, except for Mann-Whitney U and Chi-square analyses where indicated. DA LED = daily L-dopa equivalent dose of dopamine agonists; ICB = impulsive-compulsive behaviour; UPDRS = Unified Parkinson's disease Rating Scale.

Table 2 Absolute levels of ^{11}C -raclopride binding potential comparative data

	Parkinson's disease without ICB	Parkinson's disease with ICB	Statistical test
OFF + neutral images			
Mean caudate raclopride binding potential	2.0 ± 0.47	1.73 ± 0.36	$t = -1.2, P = 0.25$
Mean putamen raclopride binding potential	2.66 ± 0.65	2.24 ± 0.36	$t = -1.7, P = 0.1$
Mean ventral striatum raclopride binding potential	2.16 ± 0.55	1.89 ± 0.4	$t = -1.2, P = 0.2$
ON + neutral images			
Mean caudate raclopride binding potential	1.89 ± 0.44	1.57 ± 0.26	$t = -1.8, P = 0.1$
Mean putamen raclopride binding potential	2.4 ± 0.55	1.96 ± 0.32	$t = -1.9, P = 0.08$
Mean ventral striatum raclopride binding potential	1.83 ± 0.44	1.56 ± 0.31	$t = -1.4, P = 0.17$
ON + reward images			
Mean caudate raclopride binding potential	1.73 ± 0.37	1.5 ± 0.21	$t = -1.6, P = 0.14$
Mean putamen raclopride binding potential	2.2 ± 0.47	1.89 ± 0.3	$t = -1.5, P = 0.15$
Mean ventral striatum raclopride binding potential	1.52 ± 0.32	1.46 ± 0.27	$t = -0.4, P = 0.7$

All values are mean \pm SD. Comparisons are made using Student's *t*-test.
ICB = impulsive-compulsive behaviour.

Table 3 Percentage changes in ^{11}C -raclopride binding potentials across scan types

	Parkinson's disease without ICB	Parkinson's disease with ICB	Statistical test
OFF neutral–ON neutral			
Mean caudate percent reduction	3.5 ± 3.5	8.4 ± 7.0	$t = 2.0, P = 0.061$
Mean putamen percent reduction	9.2 ± 6.7	12.4 ± 6.2	$t = 1.0, P = 0.3$
Mean ventral striatum percent reduction	14.4 ± 10.6	16.8 ± 9.4	$t = 0.5, P = 0.6$
ON neutral – ON reward			
Mean caudate percent reduction	8.2 ± 7.1	4.5 ± 4.7	$t = -1.2, P = 0.25$
Mean putamen percent reduction	7.8 ± 8.0	3.6 ± 2.9	$t = -1.3, P = 0.2$
Mean ventral striatum percent reduction	16.3 ± 9.3	5.8 ± 5.6	$t = -2.7, P = 0.016$

All values are mean \pm SD. Comparisons are made using Student's *t*-test.
ICB = impulsive-compulsive behaviour.

in the Parkinson's disease without impulsive-compulsive behaviour group.

Discussion

A range of impulse control and related 'disinhibitory' or compulsive disorders has been linked to dopamine therapies in Parkinson's disease. The central role of dopaminergic drug therapy in these disorders (Weintraub *et al.*, 2010) suggests that they may be different manifestations of the same underlying causal mechanism, but what this mechanism is remains unclear. This is the first study to use visual cues to investigate dopamine release in the striatum of non-substance addicted participants. Here, we show that medicated patients with Parkinson's disease with impulsive-compulsive behaviour exhibit greater decrease in ventral striatal ^{11}C -raclopride BP_{ND}, i.e. enhanced dopamine release, than patients with Parkinson's disease without impulsive-compulsive behaviour following exposure to a variety of reward-related cues, but not to L-dopa challenge alone.

While debate continues over the precise role of mesolimbic dopamine systems in reward, one prominent theory (Berridge, 2007) holds that dopamine motivates the pursuit of rewards by

attributing incentive salience to reward-related stimuli, triggering pursuit ('wanting'). Further, in the case of compulsive behavioural disorders, including addiction, reward cues may be attributed with pathological incentive salience (Robinson and Berridge, 2008). Our results are consistent with this hypothesis, showing exaggerated ventral striatal dopamine release to reward cues in medicated patients with Parkinson's disease with a variety of impulsive-compulsive behaviours in the absence of differences in hedonic ratings of the images themselves.

The Parkinson's disease with impulsive-compulsive behaviour group was heterogeneous in that it contained individuals who exhibited overlapping but different impulsive-compulsive behaviours, with the majority of individuals having more than one impulsive-compulsive behaviour. Given the limitations on PET imaging, and in order to match the heterogeneity of the sample, and the presence of more than one impulsive-compulsive behaviour in the majority of individuals, we exposed patients to a variety of reward cues. Functional MRI studies show that sex and money reward cues activate the same region of ventral striatum within individuals (Sescousse *et al.*, 2010) and ^{11}C -raclopride PET studies show that even abstract rewards like money lead to ventral striatal dopamine release (Koepp *et al.*, 1998; Zald *et al.*, 2004),

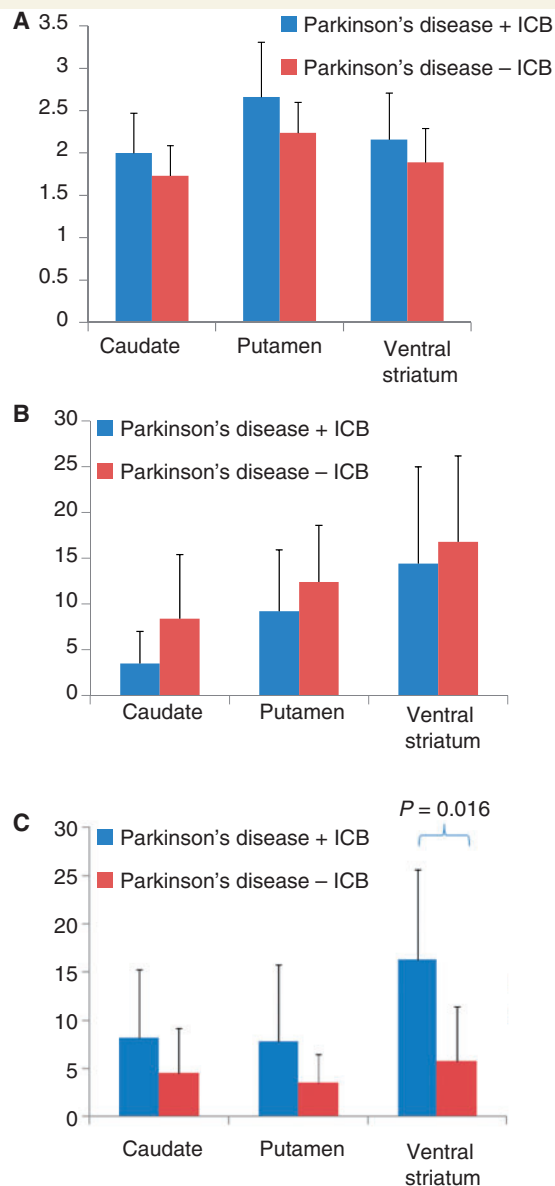


Figure 1 (A) Mean baseline ¹¹C-raclopride binding potential in 'OFF-medication' scan with neutral images. (B) Mean percentage reduction in ¹¹C-raclopride binding potential following L-dopa challenge. (C) Mean percentage reduction in ¹¹C-raclopride binding potential following exposure to reward-related cues. Error bars show standard deviation. ICB = impulsive-compulsive behaviour.

consistent with a general dopaminergic incentive salience reward system. Further, behavioural studies in healthy volunteers show that activation of this general reward circuit leads to non-specific effects on reward processing, such that both food and sex cues can instigate money craving (Van den Bergh *et al.*, 2008). Similarly, pathological gamblers show enhanced cue reactivity not just to gambling cues, but other reward-related cues (Sodano and Wulfert, 2010). Our results could thus be taken to support a relatively non-specific exaggerated reward 'wanting' of individuals with Parkinson's disease and impulsive-compulsive

behaviour, presumably resulting from dopaminergic drug induced sensitization of mesolimbic systems in certain vulnerable individuals. This is consistent with observations that impulsive-compulsive behaviours frequently coexist in treated parkinsonian patients, and that increased or new substance addictions (tobacco, alcohol or other recreational drugs) have also been reported in patients with Parkinson's disease displaying impulsive-compulsive behaviours (Evans *et al.*, 2009). This is also consistent with observations in non-Parkinson's disease addicts that addictive tendencies frequently cluster; such as the frequent co-occurrence of alcohol use disorders, pathological gambling and nicotine dependence (Grant and Kim, 2003; Petry *et al.*, 2005; Kessler *et al.*, 2008).

However, there are limits to the extent of such broad motivational 'wanting'. In animals models, amphetamine sensitization can make drugs more 'wanted' than natural rewards for some individuals, but for others make food and/or sex more 'wanted' than drugs (Nocjar and Panksepp, 2002). Thus, dopaminergic drugs used to treat Parkinson's disease potentially 'sensitize' a range of appetitive or repetitive behaviours in vulnerable individuals—and the nature of the behaviour that becomes compulsive depends on individual and contextual factors. This variability probably explains why, in contrast to our previous findings (Evans *et al.*, 2006), we did not find increased L-dopa induced dopamine release in the ventral striatum in patients with Parkinson's disease and impulsive-compulsive behaviours exposed to neutral cues compared with patients with Parkinson's disease without impulsive-compulsive behaviours. However, our Parkinson's disease with impulsive-compulsive behaviour group contained only 4 of 11 patients (36%) with dopamine dysregulation syndrome whereas all the patients studied by Evans *et al.* (2006) had dopamine dysregulation syndrome. Although dopamine dysregulation syndrome is frequently associated with other impulsive-compulsive behaviours, (with all four patients with dopamine dysregulation syndrome exhibiting other impulsive-compulsive behaviours in this study), there is an important difference between dopamine dysregulation syndrome and other impulsive-compulsive behaviours. The defining feature of patients with dopamine dysregulation syndrome is their initial craving and subsequent addictive tendencies towards their dopaminergic therapy (O'Sullivan *et al.*, 2009). The results of our study, taken together with those of Nocjar and Panksepp (2002) may explain why the strong associations between L-dopa use and development of dopamine dysregulation syndrome are not seen in the development of other impulsive-compulsive behaviours (Giovannoni *et al.*, 2000). The use of dopamine agonists has been strongly implicated in impulsive-compulsive behaviours, but their use is not necessarily associated with a craving for the medication (Weintraub *et al.*, 2010). Future studies in larger cohorts of patients will need to explore the extent to which exaggerated ventral striatal-dopamine release might be limited to specific impulsive-compulsive behaviours and specific or general reward cues.

A recent study restricted to patients with Parkinson's disease and pathological gambling performing a simulated gambling task also found exaggerated ventral striatal dopamine release in pathological gambling versus control patients with Parkinson's disease. However, that task involved both reward and loss outcomes, and

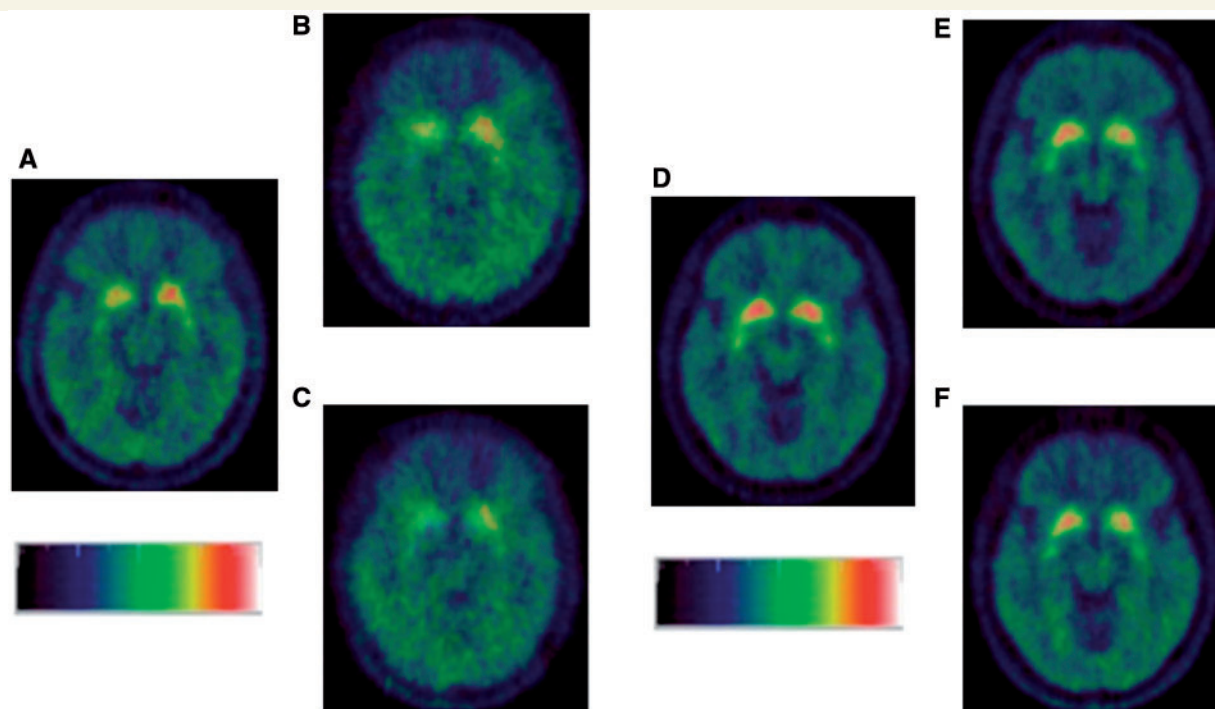


Figure 2 Representative changes in ^{11}C -raclopride binding potential between groups of patients with Parkinson's disease during scanning. (A) Parkinson's patient with ICB, off medication, neutral images. (B) Parkinson's patient with ICB, on medication, neutral images. (C) Parkinson's patient with ICB, on medication, reward images. (D) Parkinson's control patient, off medication, neutral images. (E) Parkinson's control patient, on medications, neutral images. (F) Parkinson's control patient, on medications, reward images.

a study in non-Parkinson's disease pathological gambling found that ventral striatal dopamine release was related to losing money in a simulated gambling task (Linnet *et al.*, 2010). Hence, our study is the first convincing demonstration of exaggerated responses to reward cues *per se* in individuals with Parkinson's disease and impulsive-compulsive behaviour. Four recent functional MRI and H_2^{15}O PET studies of Parkinson's disease and impulsive-compulsive behaviour have also been published although it is important to note that these techniques cannot measure dopamine release. Frosini *et al.* (2010) found increased ventral striatal activation to gambling-related cues on functional MRI in a small group of individuals with Parkinson's disease who did or did not exhibit pathological gambling, potentially consistent with our findings. Voon *et al.* (2010) studied a group of patients with Parkinson's disease who exhibited problem gambling and buying 'ON' and 'OFF' dopamine agonists, showing enhanced reward-related learning on dopamine accompanied by increased ventral striatal-related blood-oxygen level dependent activity to gain-specific outcomes (Voon *et al.*, 2010). While interpreted in terms of a role for dopamine in learning, the findings could be consistent with enhanced motivation rather than learning *per se* (Ranaldi *et al.*, 2009). Behavioural studies of reward-learning in individuals with Parkinson's disease and impulsive-compulsive behaviours have not been consistent (Djamshidian *et al.*, 2010; Housden *et al.*, 2010). van Eimeren *et al.* (2010) studied a group of individuals with Parkinson's disease that did or did not exhibit pathological gambling on a card selection task. They found that in individuals with Parkinson's

disease showing pathological gambling, dopamine medication resulted in a reduction of regional cerebral blood flow in lateral orbitofrontal cortex, rostral cingulate, amygdala and pallidum. However, in that study, medication status was not counterbalanced, response to financial reward *per se* (as opposed to task performance) was not examined and it was unclear whether there were performance differences between groups. Rao *et al.* (2010) reported reduced basal perfusion and diminished blood-oxygen level dependent activity during risk taking in a group of nine patients with Parkinson's disease and a variety of impulsive-compulsive behaviours (Rao *et al.*, 2010). Given that ventral striatal dopamine release to rewards is correlated with increased ventral striatal blood-oxygen level dependent response to rewards (Schott *et al.*, 2008), the findings of Rao *et al.* (2010) appear discrepant with ours. However, the difference may reflect fundamental differences in the processing of rewards versus risks in the ventral striatal in individuals with Parkinson's disease and impulsive-compulsive behaviours.

Some impulsive-compulsive behaviours, especially pathological gambling, have been labelled as behavioural addictions due to a presumed common underlying neurobiology (Grant, 2008). Volkow *et al.* (2009) have consistently shown that, during drug withdrawal, cocaine abusers show significant reductions in striatal dopamine D2 receptors and in amphetamine evoked dopamine release (Volkow *et al.*, 2009). They postulate that this hypodopaminergic state results in a decreased sensitivity to natural reinforcers perpetuating the use of the drug as a means to compensate for this deficit and contributing to the anhedonia and dysphoria

seen during withdrawal. Such a model has recently been applied to compulsive eating (Johnson and Kenny, 2010). Steeves *et al.* (2009) showed that patients with Parkinson's disease exhibiting pathological gambling had lower levels of baseline D2 binding than Parkinson's disease controls during a non-gambling card selection task (Steeves *et al.*, 2009). However, we found no difference between Parkinson's disease groups in the baseline ^{11}C -raclopride BP_{ND} in the 'off-medication and neutral cues' scan. Our current findings are instead consistent with our previous results comparing dopamine dysregulation syndrome patients with Parkinson's disease controls (Evans *et al.*, 2006) and demonstrates that reduced D2 receptor availability is not a necessary precondition to developing impulsive or compulsive behaviours. A relative strength of this study compared with previous studies that have associated addiction with reduced striatal dopamine function is that our study controls for drug use between groups, whereas previous human studies on drug addiction have largely compared healthy (non-users) controls with drug addicts (Volkow *et al.*, 2009). Our results thus appear more consistent with an incentive sensitization, hyperdopaminergic account than a 'reward-deficiency' hypodopaminergic account. It is likely that impulsive-compulsive behaviours and addictions are heterogeneous conditions, and the relative contributions of hyper- versus hypodopaminergic states is an important topic for future work.

Previous cue reactivity studies of drug addiction have shown increased striatal dopamine release to drug cues. In some studies these occur in ventral striatum, consistent with our findings (Boileau *et al.*, 2007), but in others they are limited to dorsal striatum and these increases correlated with craving (Volkow *et al.*, 2006; Wong *et al.*, 2006). Since the dorsal striatum is implicated in habit and stimulus-response learning, this association has been thought to reflect the strengthening of habitual control over drug seeking/taking as addiction takes hold (Everitt and Robbins, 2005; Volkow *et al.*, 2009). However, recent work shows that dorsal striatum is also implicated in incentive salience processes, notably in focusing enhancement of 'wanting' onto most preferred cues (Difeliceantonio and Berridge, 2010), which might suggest a reconciliation of our findings with studies of cue-reactivity in drug addiction. We did find that sensation seeking positively correlated with per cent change in dopamine release in caudate and putamen to reward cues, but only in patients with Parkinson's disease and impulsive-compulsive behaviours. This may reflect an underlying risk factor for addiction (Sher *et al.*, 2000), but alternatively could reflect a result of a pathological process leading to increased impulsivity in some individuals (Ersche *et al.*, 2010).

In the current study, heightened cue induced ventral striatal dopamine release was not accompanied by enhanced self-reported food cravings, sexual desire, urge to gamble or medication craving in the Parkinson's disease with impulsive-compulsive behaviour group. According to the incentive sensitization hypothesis, incentive salience 'wanting' is not directly experienced in conscious awareness (Berridge and Robinson, 1995). Nonetheless, it causes the perception or representation of a stimulus to become attractive and sought after, potentially leading to impulsive reward pursuit. Additional cognitive processes are required to transform preconscious 'wanting' into subjective desire (Berridge and Robinson,

1995). Indeed, numerous contextual influences, including perceived availability of reward (Wertz and Sayette, 2001) influence subjective craving ratings, and such influences were likely at work here. In our previous study (Evans *et al.*, 2006) we found that sensitized L-dopa evoked ventral striatal dopamine release in the dopamine dysregulation syndrome was correlated with enhanced ratings of 'want more drug' obtained following a priming dose of L-dopa in a separate testing session. Studies of alcohol craving suggest that such drug primed, immediate ratings of craving may more closely reflect the incentive motivational properties of drug rewards (Schoenmakers *et al.*, 2008) reconciling the current findings with our earlier ones.

In conclusion, we show that patients with Parkinson's disease and impulsive-compulsive behaviours ON medication have increased ventral striatal dopamine responses to reward-related cues. This is the first study to look at ventral striatal dopamine release to cues in impulsive-compulsive behaviours, and also the first test of the 'reward spillover' account of impulsive-compulsive behaviours, providing an important link between neurobiological models of drug addiction and developing models of impulse control disorders. The findings are consistent with the hypothesis that, as a result of neural sensitization in vulnerable individuals, reward-related cues are attributed with pathological incentive salience, leading to compulsive pursuit. Our findings also potentially have important implications for decision making policies relating to advertising, which has a powerful impact and relies strongly on reward-related imagery. For instance, 40% of British young adult online gamblers cited advertising as a primary stimulus in encouraging them to start gambling online (Griffiths and Barnes, 2007). Our data raise the possibility that individuals with behavioural addictions are likely to undergo almost constant activations of their aberrant reward circuitry from the sort of reward-related cues that are typically employed in advertising (such as pop-up internet advertisements), thus potentially maintaining the behaviour and making it more difficult for abstinence to occur.

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