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Dopamine agonists and risk: impulse control disorders in Parkinson's disease

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Impulse control disorders are common in Parkinson's disease, occurring in 13.6% of patients. Using a pharmacological manipulation and a novel risk taking task while performing functional magnetic resonance imaging, we investigated the relationship between dopamine agonists and risk taking in patients with Parkinson's disease with and without impulse control disorders. During functional magnetic resonance imaging, subjects chose between two choices of equal expected value: a 'Sure' choice and a 'Gamble' choice of moderate risk. To commence each trial, in the 'Gain' condition, individuals started at $0 and in the 'Loss' condition individuals started at −$50 below the 'Sure' amount. The difference between the maximum and minimum outcomes from each gamble (i.e. range) was used as an index of risk ('Gamble Risk'). Sixteen healthy volunteers were behaviourally tested. Fourteen impulse control disorder (problem gambling or compulsive shopping) and 14 matched Parkinson's disease controls were tested ON and OFF dopamine agonists. Patients with impulse control disorder made more risky choices in the 'Gain' relative to the 'Loss' condition along with decreased orbitofrontal cortex and anterior cingulate activity, with the opposite observed in Parkinson's disease controls. In patients with impulse control disorder, dopamine agonists were associated with enhanced sensitivity to risk along with decreased ventral striatal activity again with the opposite in Parkinson's disease controls. Patients with impulse control disorder appear to have a bias towards risky choices independent of the effect of loss aversion. Dopamine agonists enhance sensitivity to risk in patients with impulse control disorder possibly by impairing risk evaluation in the striatum. Our results provide a potential explanation of why dopamine agonists may lead to an unconscious bias towards risk in susceptible individuals.

Keywords: Parkinson's disease; dopamine; gambling; decision making; risk

Abbreviations: BOLD = blood oxygen level dependent; ICD = impulse control disorders

Introduction

The impulse control disorders (ICDs) associated with dopaminergic therapy are common in Parkinson's disease and occur in 13.6% of patients with Parkinson's disease (Weintraub *et al.*, 2010). Behaviours such as pathological gambling and compulsive shopping can be characterized by an attraction towards risk taking. Risk taking behaviour is defined as the 'choice of an act (which)

may be construed as the acceptance of a gamble that can yield various outcomes with different probabilities' (Kahnemann and Tversky, 2000). Thus, pathological behavioural choices are associated with acts with a chance of yielding a potentially rewarding outcome but also with a probability of negative financial, social and occupational outcomes. This gamble is selected in favour of the status quo, or the choice to save money, stay at work or spend time with one's family. In this study, we use a pharmacological manipulation and a novel risk taking functional MRI task to ask how dopamine agonists affect risk taking in patients with Parkinson's disease with and without ICDs. The study of this Parkinson's disease population with ICDs on chronic dopamine agonists allows for a unique insight into effects of chronic dopamine agonists and the interaction between dopamine agonists and susceptibility.

Most people tend to be risk-averse, conservative and overestimate the chance of rare events. Following Bernouilli's classic example, given the choice between a sure $850 or a gamble with an 85% chance of winning $1000, most people choose the sure option despite equivalent mathematical expectation of the sure and gamble choices (Kahnemann and Tversky, 2000). This occurs as the evaluation depends on the subjective value of possible outcomes rather than the value of the expectation itself. Prospect Theory describes the value function for gains as a concave function of the actual outcome magnitude with subjective value levelling off with increasing gain (Kahnemann and Tversky, 2000). As a result of this concavity, behaviour in the gain domain is risk-averse as the subjective value of the 'Gamble' gain (i.e. subjective value of $1000) when weighted by probability (i.e. 85%) is lower than the subjective value of the certain 'Sure' gain (i.e. subjective value of $850). In contrast, the value function for losses is convex as disutility levels off with increasing losses. For example, the disutility of losing $50 is more than half the disutility of losing $100, which contributes to the preference for gambling versus opting for a sure loss. Thus, behaviour in the loss domain is risk-seeking with greater preference for loss gambles than a sure loss with matched expected values. Prospect theory also emphasizes the asymmetry of the gain and loss functions, suggesting that the loss function is much steeper than the gain function leading to the concept of loss aversion. Loss aversion also leads to risk aversion for mixed gambles; for example, most people will reject a 50–50 chance to gain $100 or lose $100. Guided by these perspectives on risk, we developed a novel task that assesses choices between a 'sure outcome' and a 'gamble without loss' versus a 'mixed gamble with loss'.

The neural representation of risk is associated with anterior insula, anterior cingulate, ventromedial prefrontal cortex, orbitofrontal cortex and striatum (Critchley et al., 2001; Kuhnen and Knutson, 2005; Preuschoff et al., 2006, 2008, Tobler et al., 2007). Medicated patients with Parkinson's disease with ICDs compared to medicated patients with Parkinson's disease without ICDs have lower ventral striatal activity to uncertainty (i.e. unknown probability) but not to risk (i.e. known probability) (Rao et al., 2010). Here, we focus on risk taking and ask whether manipulation of dopamine agonists affects risk taking in patients with Parkinson's disease with ICDs compared to Parkinson's disease controls. We hypothesized that dopamine agonists would be associated with greater risk taking and lower ventral striatal activity in patients with ICD relative to Parkinson's disease controls.

Materials and methods

The inclusion criteria have been described in previous publications (Voon et al., 2010a, b). Healthy controls were recruited from the National Institutes of Health (NIH) healthy volunteer database. Patients with Parkinson's disease with problem gambling or compulsive shopping and Parkinson's disease controls were recruited from the Parkinson Disease clinic at the National Institute of Neurological Disorders and Stroke, National Institutes of Health. Inclusion criteria for patients with ICD included (i) idiopathic Parkinson's disease (Queen Square Brain Bank criteria); (ii) either a problem gambling [Research Definition Criteria of the Diagnostic and Statistical Manual of Mental Disorders, Version IV (DSM IV), 1994], or compulsive shopping (McElroy criteria) (McElroy et al., 1994); (iii) behaviour onset after the initiation of dopamine agonists; and (iv) on the same dopamine agonists that resulted in their behavioural symptoms. Inclusion criteria for Parkinson's disease controls included idiopathic Parkinson's disease, no history of problem gambling, shopping, hypersexuality, punding or compulsive medication use (definitions reviewed in Voon and Fox, 2007) and matched for gender, age ($\pm$10 years), dopamine agonists type, dopamine agonists dose ($\pm$1 mg pramipexole and $\pm$4 mg ropinorole) and presence or absence of levodopa. Exclusion criteria included the presence of dementia, major depression or mania (DSM IV criteria) and MRI contraindications. Subjects were assessed using the Structured Clinical Interview for the Diagnosis of DSM IV psychiatric disorders and for the presence of visual hallucinations or illusions. The study was approved by the NIH Research Ethics Board and all subjects consented to the study.

Healthy volunteers underwent behavioural testing to validate the task and were not matched to the patients with ICD. Patients with ICD and Parkinson's disease controls underwent testing and functional MRI scanning ON and OFF dopamine agonists in a counterbalanced order.

Task

The risk task had a 'Gain' and 'Loss' condition (Fig. 1). In the 'Gain' condition, participants are given a starting amount of $0. They are then presented with the choice between a 'Gamble' with probabilities represented by a pie chart (e.g. $210 with $P = 0.4$ versus $0 with $P = 0.6$) and a 'Sure' amount with matched expected value (e.g. $210 \times 0.4 + $0 \times 0.6 = 85). In the 'Loss' condition, participants started with a loss or a negative starting amount (e.g. of $-$135). They are then presented with the exact same risk gamble of $+$210/$0 ($P = 0.4/0.6$) and the sure amount. However, because of the loss starting amount, the same risk gamble results in a combined outcome of $+$75/$-$135 ($P = 0.4/0.6$) and the alternative matched sure choice results in $-$50. Thus, 'Gain' and 'Loss' choices were matched in terms of equivalence in expected value between gamble and sure options. Thus, the effect of 'Gamble Risk' (i.e. choices for gambles with different ranges) is dissociated from the effect of Valence (i.e. choices for gambles with different valences but equivalent ranges). This means that different choice profiles between the gain and loss conditions can be attributed to an effect of loss. Subjects first saw a Start amount of either $0 ('Gain' condition) or $50 below the amount of the following 'Sure' choice
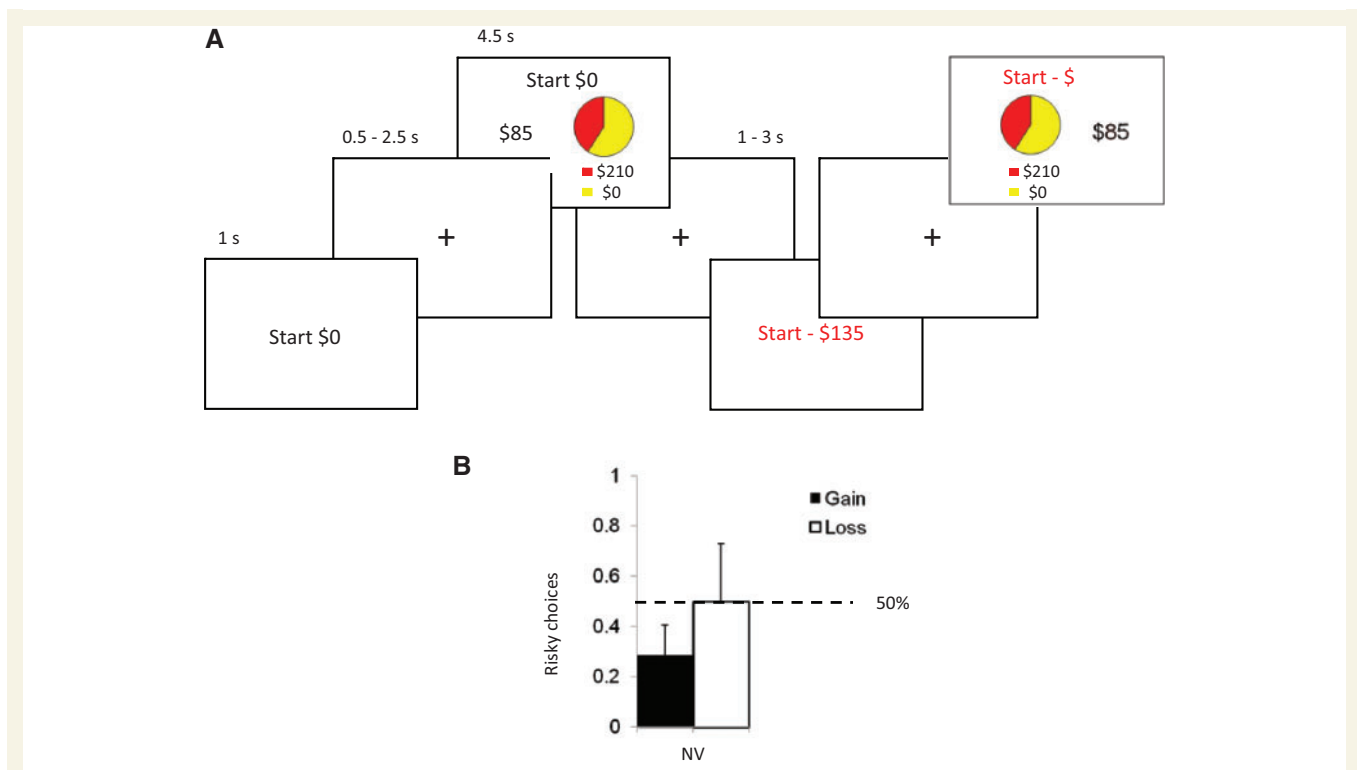
Figure 1 Risk task and normal volunteer outcomes. Risk task and choices—(**A**) Risk task: subjects first saw a start amount for 1 s of either $0 ('Gain' condition: in black) (e.g. 'Start $0') or $50 below the amount of the following 'Sure' choice ('Loss' condition: in red) (e.g. 'Start − $135). This was followed by a jitter of 0.5–2.5 s. Subjects then chose between two choices of equal expected value (4.5 s): a 'Sure' choice (e.g. $85) and a risky 'Gamble' choice. For the 'Gain' condition, the red colour in the pie chart of the 'Gamble' choice represented the likelihood ($P = 0.40$), they could win the amount indicated below the pie chart (e.g. $210) and the yellow indicated the likelihood they could win $0. For the 'Loss' condition, the 'Gamble' choice would result in the following possible outcomes: + $75/− $135 ($P = 0.4/0.6$) and the 'Sure' choice in − $50. Each trial was followed by an intertrial interval of 1–3 s. There was no associated feedback. Subjects were exposed to the same 'Sure' and 'Gamble' choices but modified by different starting amounts. (**B**) Proportion of risky choices in normal volunteers (NV) comparing the 'Gain' and 'Loss' conditions. Error bars represent standard deviation, *$P = 0.001$.

('Loss' condition). The 'Sure' choice had a range of $50–170 and the 'Gamble' choice probability of win 0.35–0.45. The 'Sure' choice was divided into five mean amounts (in $: 50, 70, 90, 150, 170), randomly distributed by ±$5 around these means. There was no associated feedback. Subjects were told that each start amount was new on each trial and unrelated to previous trials or choices, and that they would be paid in proportion to the total winnings accumulated from their choices. We included catch trials, which were state-wise dominated decisions where the gamble option was always worse than the sure option (e.g. Gamble expected value was 25% of the 'Sure' expected value: $P = 0.40$ of win $52 versus 'Sure' choice of $85) to ensure subjects were paying attention to and understood the task. The duration of each trial was 9 s with 45 trials per run for each condition and 10 catch trials per run. There were 4 runs lasting 15 min (total 180 trials per condition and 40 catch trials). Subjects practiced outside of the scanner for 10 min prior to scanning.

Range as a measure of risk

The difference between the maximum and minimum outcomes from each gamble (i.e. range) was used as an index of risk ('Gamble Risk'). Risk can been quantified by the spread of possible outcomes (Markowitz, 1952) measured as either variance, standard deviation or range, which are all correlated indices (Glimcher, 2008). In this

study, we manipulated risk by varying the range of two possible outcomes while holding probability relatively constant ($P = 0.35$–0.45). For a lottery with N potential outcomes ($m_1, m_2, \ldots, m_n$) with associated probabilities ($P = P_1, P_2, \ldots, P_n$), the expected value (EV) and variance (Var) of the outcome distribution are calculated as follows:

$$EV = \sum_{n=1}^{N} m_n p_n$$

$$Var = \sum_{n=1}^{N} (m_n - EV)^2 p_n$$

In this study, for each gamble trial, there are two possible outcomes per gamble of different magnitudes (m_1, m_2) and approximately constant probability ($P, 1 - P$):

$$EV = m_1 P + m_2 (1 - P)$$

$$Variance = (m_1 - EV)^2 P + (m_2 - EV)^2 (1 - P)$$
$$= (m_1 - m_2)^2 (1 - P) P$$

As $m_1 - m_2$ = range or Gamble Risk, if P is constant, then the variance is proportional to (range)^2 and standard deviation (SD) is proportional to range. Thus, the measure of range used here is proportional to the standard deviation of the gamble. In this study, the measure of the difference between gamble outcomes for each trial

was strongly correlated with variance (regression analysis: $R^2 = 0.94$) and standard deviation (regression analysis: $R^2 = 0.97$) supporting similarities between measures.

Statistics

We analysed the proportion of risky choices (risky/total choices). To assess task validity, 'Gain' and 'Loss' conditions in healthy volunteers were compared with paired t-test. Healthy volunteers were not compared to the patient with ICD and Parkinson's disease control groups. We used mixed measures ANOVA to assess risk choices with Group (patients with ICD and Parkinson's disease controls) as a between-subjects factor and Medication (ON and OFF dopamine agonists), Valence ('Gain' and 'Loss') and Gamble Risk (i.e. the maximum – minimum values of the gamble) as within-subjects factor. $P < 0.05$ was considered significant. Statistics were conducted using Statistical Package for the Social Sciences (SPSS) Version 16.0.

Imaging

MRI scanning was performed on a 3T General Electric scanner with an 8 channel head coil. Thirty-eight continuous axial slices (slice thickness = 3 mm, gap 1 mm) were acquired using T_2*-weighted echo planar images at a temporal resolution of 2.66 s, echo time 33 ms, flip angle 90°, matrix 64 × 64 with interleaved acquisition. The first four echo planar image volumes were discarded from analysis as dummy scans to allow for magnetization to reach steady state. The imaging data were preprocessed using SPM5 (www.fil.ion.ucl.ac.uk/spm). The data were adjusted for slice timing, realigned to the first image of the first run, normalized to the Montreal Neurological Institute atlas and smoothed using an 8-mm Gaussian kernel. Head motion parameters were used as regressors of no interest in the first level analysis.

The decision phase was modelled as a box car function convolved with the haemodynamic response function based on the time of onset of the decision phase with a 4-s duration. A trial-by-trial estimate of 'Gamble Risk' was included as a parametric regressor in the first level analysis, calculated as the difference between possible gain and loss of the gamble. Expected value (i.e. amount × probability, which was the same for both the sure and gamble choice) was included as a parameter of no interest, thus removing the variance associated with changes in expected value over the course of the task. The parameter of 'Gamble Risk' thus represented the specific estimate of blood oxygen level dependent (BOLD) response to risk. Catch trials were not included in the analysis. We used a flexible factorial imaging

analysis comparing the parameter of Δ for all choices for the within-subject factors of Medication, Valence and the between subject factor of Group. $P < 0.05$ false discovery rate corrected was considered significant (Genovese, et al., 2002).

Results

Behavioural results

Subject characteristics of 14 patients with ICD and 14 Parkinson's disease controls have been reported previously (Voon et al., 2010a, b). Eleven patients with ICD and 11 Parkinson's disease controls underwent the functional MRI study. Sixteen healthy volunteers were also behaviourally tested once. The data from one healthy volunteer who chose the higher expected values in <60% of the Catch trials were discarded. All other subjects chose the higher expected value in more than 85% of the Catch trials.

Behavioural outcomes: patients with ICD versus Parkinson's disease controls

In the mixed measures ANOVA comparing patients with ICD versus Parkinson's disease controls, there was a Medication effect ($F = 18.58$, $P < 0.0001$) in which medicated subjects took more risks than non-medicated subjects. There was a Valence effect ($F = 7.29$, $P = 0.01$) in which greater risks were associated with 'Gain' rather than 'Loss' condition. There was also a 'Gamble Risk' effect ($F = 4.38$, $P = 0.009$) with risky choices decreasing with increasing 'Gamble Risk'. There was no 'Group' effect ($F = 0.002$, $P = 0.96$).

In the following interaction effects, given our hypothesis, we focus only on interactions with 'Group' as a factor. All interaction effects are shown in Table 2. With respect to two-way interactions, there was a 'Group' by 'Valence' interaction ($F = 12.32$, $P = 0.002$): in the 'Gain' condition, patients with ICD compared to Parkinson's disease controls made more risky choices with the opposite in the 'Loss' condition. There was no interaction between 'Group' and 'Medication' or 'Group' and 'Gamble Risk' ($P > 0.05$). There was a three-way interaction of 'Group' by 'Valence' by 'Gamble Risk' ($P < 0.0001$) in which patients with ICD were more likely to make risky choices in the 'Gain' compared to 'Loss' conditions at all 'Gamble Risk' values, whereas there were

Table 1 Subject characteristics

	Patients with ICD	Parkinson's disease controls
No. of subjects	14	14
Gambling: shopping in no. of subjects	9:5	9:5
Gender (male)	10	10
Age (years)	51.52 (8.33)	54.51 (12.52)
Pramipexole: ropinorole in no. of subjects	9:5	9:5
Total dopamine agonists dose in LEDD mg/d*	161.53 (43.35)	155.47 (57.35)
Dopamine agonists monotherapy in no. of subjects	4	4
Total LEDD dose in mg/d[a]	589.32 (301.25)	609.55 (298.22)
Hoehn and Yahr score	1.91 (0.45)	2.35 (0.56)

There were no statistically significant differences. Standard deviations are reported in brackets. LEDD = levodopa daily dose equivalent; no. = number.
[a]Levodopa daily dose equivalents.

no differences between 'Valence' in patients with Parkinson's disease. There was also a 'Group' by 'Medication' by 'Gamble Risk' ($P < 0.0001$) in which patients with ICD on dopamine agonists compared to off dopamine agonists made more risky choices when Gamble Risk was small, whereas the opposite was observed in Parkinson's disease controls. There was no overall effect of 'Group' by 'Medication'; however, this is because patients with ICD treated small versus large risks in the opposite way to patients with Parkinson's disease, as evidenced by a significant 'Group' by 'Medication by 'Gamble Risk' interaction. There was no interaction between 'Group', 'Medication' and 'Valence' ($P > 0.05$).

Table 2 Behavioural outcomes

Effect	F	P-value
Main		
Medication	18.58	<0.0001
Valence	7.29	0.01
Group	0.002	0.96
Interaction		
Two-way		
Group × Valence	12.32	0.002
Medication × Valence	11.75	0.002
Medication × Gamble Risk	13.14	<0.0001
Valence × Gamble Risk	8.84	<0.0001
Group × Medication	1.79	0.19
Group × Gamble	2.58	0.06
Three-way		
Group × Valence × Gamble risk	387.82	<0.0001
Group × Medication × Gamble risk	16.16	<0.0001
Group × Medication × Valence	0.43	0.63
Four way		
Group × Medication × Valence × Gamble Risk	12.03	<0.0001

There was a four-way interaction between 'Group', 'Medication', 'Valence' and 'Gamble Risk' ($P < 0.0001$) (Fig. 2). *Post hoc* comparisons of 'Group' show that patients with ICD on dopamine agonists made more risky choices at lower 'Gamble Risk' ($P < 0.05$) compared to Parkinson's disease controls. *Post hoc* comparisons of 'Medication' show that patients with ICD ON dopamine agonists made more risky choices at lower 'Gamble Risk' ($P < 0.05$) and fewer risky choices at higher 'Gamble Risk' ($P < 0.05$) compared to OFF dopamine agonists (i.e. increased sensitivity to increasing risk but with higher baseline risk-taking at low 'Gamble Risk' levels). In contrast, Parkinson's disease controls on dopamine agonists demonstrate the opposite with fewer risky choices at lower 'Gamble Risk' ($P < 0.05$) compared to off dopamine agonists.

Healthy volunteers

Figure 1B shows that the healthy volunteers [$n = 15$; 9 male; mean age 49.62 years (SD 9.65)] chose the risky choice 28.22% (SD 12.45%) of the time in the 'Gain' condition suggesting a conservative risk preference. As expected, in the 'Loss' condition, healthy volunteers were more risk-seeking and chose the risky choice 50.18% (SD 22.79%) of the time (paired *t*-test: $t = 3.97$ $df = 19$ $P = 0.001$) [mean difference -21.49 (95% confidence interval -33.48 to -9.71)].

Imaging results

In the imaging analysis, we assessed the parameter of 'Gamble Risk' of the decision phase focusing on neural regions previously reported in the representation of risk. This measure of risk is consistent with the use of variance as an index of risk (Glimcher, 2008). All imaging findings and statistics reported in Table 2 focus on the parametric regressor of 'Gamble Risk'. BOLD activity
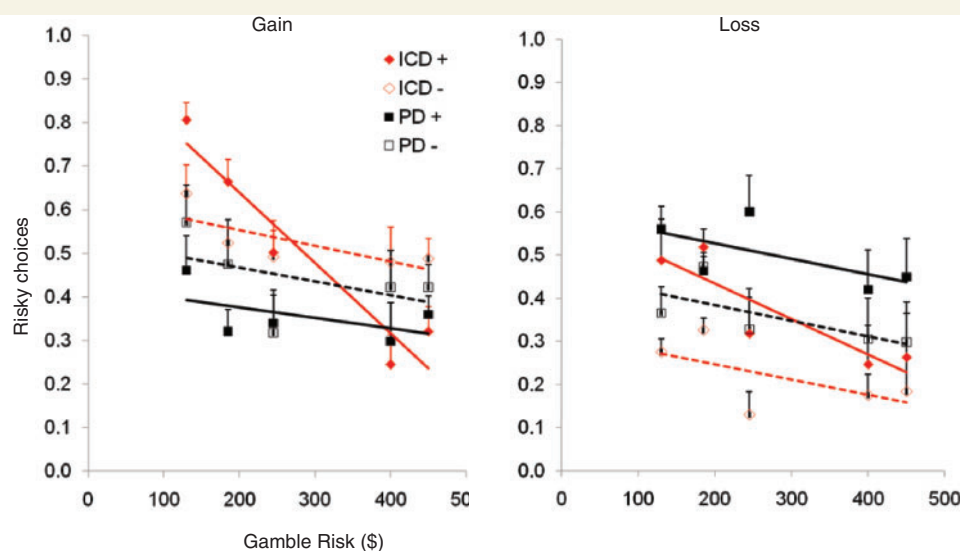
Figure 2 Risk taking choices. Proportion of risky choices during the 'Gain' and 'Loss' conditions in patients with Parkinson's disease (PD) with problem gambling or compulsive shopping (ICD) compared to Parkinson's disease controls ON (+) and OFF (−) dopamine agonists as a function of reward magnitude of the risky choice. The error bars represent standard error of the mean.
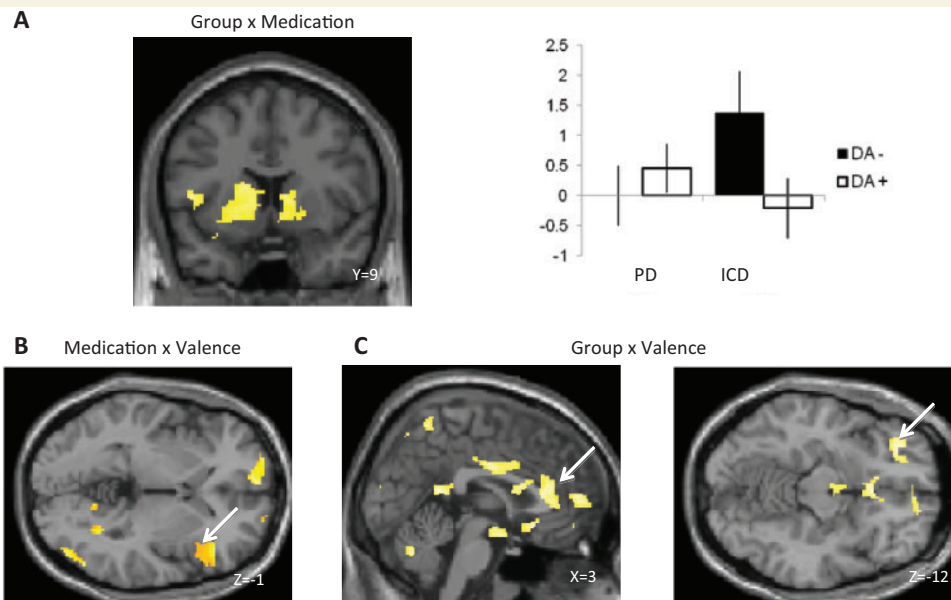
Figure 3 Imaging outcomes. The SPM image and contrast estimate demonstrate the 'Interaction' effects in the comparison of patients with Parkinson's disease with problem gambling or compulsive shopping (ICD) relative to Parkinson's disease (PD) controls ON and OFF dopamine agonists (DA). The SPM images are shown at $P < 0.005$ uncorrected. The error bars represent standard deviation.

corresponding to the 'Gamble Risk' parameter represents the correlation between neural activity and 'Gamble Risk', allowing us to draw direct comparison between the imaging findings and the relevant behavioural interaction effects with 'Gamble Risk' in each group and condition. We observed a 'Valence' effect with lower left ventral striatal and bilateral ventromedial prefrontal cortex sensitivity to risk in the 'Gain' than 'Loss' condition. We also showed a 'Group' effect with greater correlation between BOLD activity and risk in patients with ICD compared to Parkinson's disease controls in bilateral anterior cingulate and caudate, and left orbitofrontal cortex. There was no 'Medication' effect.

There was a 'Group' by 'Medication' effect in which dopamine agonists were associated with lower bilateral ventral striatal activity compared to OFF dopamine agonists in patients with ICD with the opposite in Parkinson's disease controls (Table 2, Fig. 3A). This means that patients with ICD ON dopamine agonists had lower correlation between BOLD activity and risk compared to OFF dopamine agonists relative to Parkinson's disease controls. There was also an interaction between 'Medication' and 'Valence': dopamine agonists were associated with greater right anterior insular activity during 'Loss' as compared to 'Gain' with the opposite observed OFF dopamine agonists (Fig. 3B). There was also an interaction between 'Group' and 'Valence': patients with ICD had lower orbitofrontal cortex and bilateral anterior cingulate activity during 'Gain' relative to 'Loss' with the opposite in Parkinson's disease controls (Fig. 3C). There were no other interactions observed in the imaging outcomes. There were no significant findings associated with the starting amount phase despite decreasing to a more liberal threshold of uncorrected $P < 0.01$.

Discussion

We demonstrate a pharmacological manipulation of risk taking in a susceptible population of subjects with ICD with underlying vulnerability such as problem gambling or compulsive shopping. Compared to Parkinson's disease controls, patients with ICD demonstrate an overall bias towards riskier choices in the 'Gain' relative to 'Loss' condition associated with lower correlation between risk and neural activity in the orbitofrontal cortex and anterior cingulate. As expected, all subjects showed a general sensitivity to increasing risk, choosing to gamble less as the 'Gamble Risk' (the range of possible outcomes) increased. In particular, dopamine agonists in patients with ICD enhanced sensitivity to 'Gamble Risk' with an opposite effect in Parkinson's disease controls, promoting a bias towards increased risk-taking for gambles at equivalent low-risk levels, compared to OFF dopamine agonists and Parkinson's disease controls. Compared to Parkinson's disease controls, dopamine agonists in patients with ICD were also associated with lower ventral striatal activity to Gamble Risk. Thus, overall patients with ICD have an increased risk-taking bias compared to Parkinson's disease controls when there is only the prospect of gain but not where there are both prospects of gain and loss. Crucially, all subjects (both ICD and Parkinson's disease controls) showed a general sensitivity to increasing risk, choosing to gamble less as the 'Gamble Risk' increased. Taken together, this suggests that rather than a sensitivity to a specific effect of loss or a non-specific decreased sensitivity to risk, patients with ICD have a specific change in attitude to risky situations. Dopamine agonists appear to alter a pre-potent or unconscious bias towards 'Gamble Risk' rather than simply affecting conscious risk estimation or evaluation, moreover with a potentially opposite effect in ICD

Table 3 Imaging statistics

Effect		Region	x, y, z	Cluster size	Z	P (FDR corrected)
Group	ICD–PD	Bilateral dorsal anterior cingulate	12, 38, 22	514	3.74	0.02
		Bilateral caudate	12, 6, 18	219	3.70	0.02
		Left lateral OFC	−34, 40, −12	173	3.84	0.01
Medication						
Valence	'Loss' − Gain	Bilateral vmpfc	−6, 40, −6	153	3.67	0.04
		LVS	−8, 10, −10	27	3.83	0.04
Group × Valence	[PD Gain − PD 'Loss'] − [ICD Gain-ICD 'Loss']	Left lateral OFC	−32, 40, −12	132	3.71	0.03
		Bilateral dorsal anterior cingulated / Left lateral and medial OFC	0, 32, 14 / −20, 40, −12	766	3.78	0.03
Medication × Valence	[dopamine agonists + 'Loss' − dopamine agonists + Gain] − [dopamine agonists − 'Loss' − dopamine agonists − Gain]	Right AI	34, 26, 2	263	4.46	0.05

AI = anterior insula; FDR = false discovery rate; LVS = left ventral striatum; OFC = orbitofrontal cortex; PD = Parkinson's disease; vmpfc = ventromedial prefrontal cortex.

and Parkinson's disease controls (i.e. dependent on underlying vulnerability).

We have previously demonstrated that patients with ICD ON dopamine agonists compared to OFF dopamine agonists learn faster from gain outcomes using a probabilistic reward learning task along with greater ventral striatal activity to unexpected rewards (Voon *et al.*, 2010*a*). Patients with ICD ON dopamine agonists compared to OFF dopamine agonists also make more impulsive choices, preferring smaller immediate rewards over larger delayed rewards, and make faster decisions during high conflict choices (Voon *et al.*, 2010*b*). These studies focused on learning from outcomes and assessment of impulsivity. Our current findings suggest a potential mechanism whereby dopamine agonists may influence risk-taking choices leading towards pathological behaviours. As the current risk task is not associated with outcomes, these findings focus on risk anticipation without the influence of gain or loss outcomes and the consequent effects of dopamine on outcome prediction error. The neural findings concur with a recent study demonstrating that medicated patients with Parkinson's disease with ICDs compared to medicated patients with Parkinson's disease without ICDs have lower ventral striatal activity in the Balloon Analogue Risk Task (Rao *et al.*, 2010), a measure of ambiguity in which the probability is not explicitly known. The authors did not demonstrate any behavioural difference between groups and subjects were only evaluated on medication. Similarly, in a task assessing impulsive choice, with dopamine agonists manipulation, patients with ICD ON compared to OFF dopamine agonists relative to Parkinson's disease controls had a trend towards a higher indifference point when choosing between a varying deterministic choice versus a fixed probabilistic choice (P = 0.35 of gaining $0.30) with real-time feedback compared to OFF dopamine agonists (Voon *et al.*, 2010*b*). This study focused on impulsive choice with feedback and was not designed to evaluate risk; the calculation of the single indifference point was used as a baseline measure to control for the effects of probabilistic learning. A behavioural study assessing patients with

Parkinson's disease on medications (levodopa and dopamine agonists) with and without pathological gambling along with compulsive medication use demonstrated impairment in the Iowa Gambling Task but not the Game of Dice Task, suggesting impairment in decisions under ambiguity but not risk (Rossi *et al.*, 2010). Another behavioural study did not demonstrate an effect of levodopa manipulation on a risk-taking task in patients with Parkinson's disease with mixed ICD symptoms compared to OFF levodopa (Djamshidian *et al.*, 2010). A subanalysis of the pathological gambling group compared to the control group did demonstrate a difference between groups. The study assessed the effects of levodopa rather than dopamine agonists on mixed gambles with both gains and losses and did not include an imaging arm. These current findings uniquely evaluate the effect of specific manipulation of dopamine agonists on behavioural risk assessment, with simultaneous measurement of functional MRI BOLD activity, and furthermore assessed the influence of degree of risk anticipation without feedback along with separation of the gain and loss components of the task.

Dopamine agonists in patients with ICD appear behaviourally to not only enhance risk sensitivity but also promote baseline risk-taking. Neurally, this is associated with lower ventral striatal activity to 'Gamble Risk'. The ventral striatum is implicated in tracking risk and ventral striatal activity commonly increases with increasing risk (Preuschoff *et al.*, 2006). The lower activity in our study suggests that rather than tracking risk *per se*, dopamine agonists may decrease the coupling of ventral striatal evaluation of risk in patients with ICD, and lead to an altered evaluation of the presented gambles. According to the hypothesis of an inverted U-shaped function of dopaminergic activity, if baseline dopaminergic activity in the ventral striatum is elevated in patients with ICD, then additional dopaminergic activity may further shift function along the curve and impair ventral striatal function (Cools, 2006). A PET study using ^{11}C-raclopride suggests a potential finding of elevated dopaminergic activity at baseline in patients with ICD (Steeves *et al.*, 2009). Tonic dopamine has also been

implicated in representation of risk as measured using variance (Fiorillo *et al.*, 2003). Thus, one possible interpretation may be that dopaminergic modulation may influence risk-taking through the encoding of uncertainty via the midbrain dopaminergic neurons. Tonic dopamine has also been implicated in motivation (Niv *et al.*, 2007), which was not evaluated in this task. In healthy volunteers, levodopa increases risk-taking choices in subjects with a DRD4 polymorphism with at least one copy of a 7-repeat allele (Eisenegger *et al.*, 2010). Further studies may shed light on whether genetic polymorphisms may mediate risk taking behaviours in the ICD population.

We further demonstrate that patients with ICD make more risky choices to gambles without the specific effect of loss aversion accompanied by lower orbitofrontal and anterior cingulate activity. The orbitofrontal cortex and anterior cingulate are also commonly implicated in tracking risk and value (Critchley *et al.*, 2001; Tobler *et al.*, 2007). Again, our findings suggest that in patients with ICD, neural tracking of risk in the orbitofrontal cortex and anterior cingulate is decreased leading to a bias towards risky choices in the 'Gain' condition. The finding is consistent with a recent study demonstrating that dopamine agonists are associated with an inhibition of orbitofrontal cortex activity in patients with ICD (van Eimeren *et al.*, 2010). The lower effect size in neural activity can also be interpreted as greater signal to noise, which is also consistent with a lower correlation between risk and neural activity.

We also show that dopamine agonists are associated with greater risk-taking and greater anterior insular activity, specifically in mixed gambles with the prospect of gain or loss as compared to risk taking with only the prospect of gains. The anterior insula tracks risk, risk prediction (Preuschoff *et al.*, 2008) and is also implicated in the representation of negative states including loss anticipation, pain and loss prediction error (Seymour *et al.*, 2005; Craig, 2009). Since gamble risk is objectively similar in both conditions, the difference in anterior insular activity must reflect either the different representation of subjective risk or a specific feature of the gamble such as the probability of a loss. 'Loss' aversion is one mechanism believed to underlie an increase in risk-taking behaviour in the context of loss. Thus, dopamine agonists may increase anticipatory loss aversion represented by greater anterior insular activity leading towards greater risk-taking behaviour. However, as patients with ICD were more risk-seeking in the 'Gain' but not the 'Loss' condition, this dopamine agonist effect, while intriguing, is unlikely to be driving risk-taking in patients with ICD.

Conclusion

Patients with ICD appear to have a bias towards risky choices independent of the effect of loss aversion and dopamine agonists enhance the sensitivity to 'Gamble Risk'. Our findings suggest that dopamine agonists may enhance an unconscious bias towards risk in susceptible individuals. Decreased coupling of neural evaluation and risk in the ventral striatum, orbitofrontal cortex and anterior cingulate may underlie these behavioural findings. Understanding the mechanisms underlying ICD behaviours will assist in developing preventative and therapeutic strategies to ameliorate these potentially devastating behaviours. Our demonstration of a quantitative difference in the neural responses to risk induced by dopamine agonists in ICD and Parkinson's disease control patients raises the possibility of assaying an underlying susceptibility to these effects using functional MRI.

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