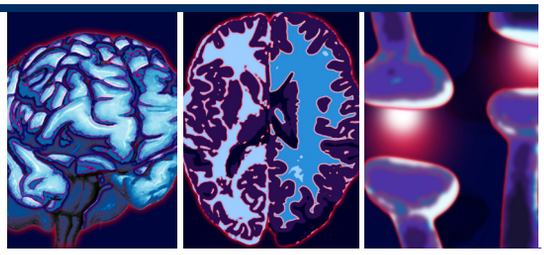
REVIEW



Impulse control disorders in Parkinson's disease: clinical characteristics and implications

Robert F Leeman[†] & Marc N Potenza[1]

Practice points

- Dopamine replacement therapies (DRTs), including levodopa (LD) and, particularly, dopamine agonists (DAs), have demonstrated efficacy in reducing motor and cognitive dysfunction in patients with Parkinson's disease (PD).
- There is also evidence from small case–control studies to support the effects of deep-brain stimulation in ameliorating symptoms of PD.
- Impulse control disorders (ICDs), related to excessive gambling, sex, shopping and eating, have been observed in PD patients.
- ICDs in PD have been associated with factors related to PD (e.g., age at PD onset) and its treatment (e.g., DAs and perhaps to a lesser extent LD), as well as factors seemingly unrelated to PD (e.g., impulsivity, ICDs prior to PD onset, familial or personal history of alcoholism, family history of a gambling problem, marital status and geographic location).
- Given the associations between DRTs and ICDs in PD, ICDs should be considered when discussing the potential risks, benefits and alternatives to DRTs in the treatment of PD.
- Given associations between ICDs and LD equivalent daily dose measures, DRT dosing magnitude should also be considered and discussed with patients.
- PD patients should be evaluated for possible ICDs. Brief self-report screening instruments (e.g., the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease) are available to aid in identifying PD patients with ICDs and other possibly related disorders or behaviors. Patients responding in a manner suggestive of possible ICDs can then be further evaluated and treated.
- For PD patients exhibiting features of an ICD, reductions in DA dose, potentially accompanied by an increase in LD, may help to reduce impulse control behaviors, although controlled trials are currently lacking.
- Given neurobiological similarities between ICDs with and without PD, treatments found to be efficacious in ICD patients in the general population (e.g., opiate antagonists and cognitive behavioral therapy) may help PD patients with ICDs. However, the potential impact of PD on treatment outcome for these approaches has not yet been tested.

[1]Departments of Psychiatry, Neurobiology & Child Study Center, Yale University School of Medicine, CMHC, Room S104, 34 Park Street, New Haven, CT 06519, USA
[†]Author for correspondence: Department of Psychiatry, Yale University School of Medicine, CMHC, Room S200, 34 Park Street, New Haven, CT 06519, USA; Tel.: +1 203 974 7373; Fax: +1 203 974 7606; robert.leeman@yale.edu

part of future medicine fsg

SUMMARY Impulse control disorders (ICDs), specifically those related to excessive gambling, eating, sex and shopping, have been observed in a subset of people with Parkinson's disease (PD). Although some initial case reports claimed that dopamine replacement therapies, particularly dopamine agonists, cause ICDs, more recent, larger and better controlled studies indicate a more complicated picture. While dopamine replacement therapy use is related to ICDs, other vulnerabilities, some related to PD and/or its treatment directly and others seemingly unrelated to PD, have also been associated with ICDs in PD. This suggests a complex etiology with multiple contributing factors. As ICDs occur in a sizable minority of PD patients and can be associated with significant distress and impairment, further investigation is needed to identify factors that can predict who may be more likely to develop ICDs. Clinical implications are discussed and topics for future research are offered.

The relatively high rate of impulse control disorders (ICDs) among Parkinson's disease (PD) patients is an issue that has gained considerable clinical and research attention in the past decade. While ICDs are observed in a minority of PD patients, a considerable number of patients are affected and the disorders can have a profound impact [1,2]. Furthermore, many patients may not reveal the existence of an ICD to care providers for reasons of shame, denial, motivations to continue the behavior or other reasons. As such, the true prevalence might be higher than existing estimates. Over the past decade, progress has been made in understanding the clinical, cognitive and neurobiological correlates of ICDs in PD. The primary focus of this article is to review recent findings (from 2006 to 2010) in the literature. While we will touch upon earlier research, prior review articles have addressed findings published prior to 2006 [3,4].

Overview of PD & ICDs

Parkinson's disease is a condition characterized by progressive degeneration of dopamine production in the substantia nigra, particularly in the ventrolateral and caudal areas of the substantia nigra pars compacta, adversely affecting dopaminergic projections from these areas to the dorsal striatum [5–7]. Dopaminergic pathways that project to the striatum not only are involved in motoric behaviors, but have also been implicated in the prediction of rewarding situations and outcomes [8]. PD is characterized by various neuropsychiatric, cognitive, motor and autonomic impairments, and these may result from depleted dopaminergic activity [4,9].

Impulse control disorders are a heterogeneous class of disorders that are characterized by repeated and excessive performance of typically or initially hedonic behaviors [10]. ICD behaviors may begin as more hedonically motivated actions during initial engagement and become less driven by pleasurable motivations over time. ICDs are grouped in a category called 'ICDs not elsewhere classified' in the *Diagnostic and Statistical Manual, 4th Edition* (DSM-IV) [11]. Specific ICDs described in the DSM-IV include intermittent explosive disorder and pathological gambling (PG), arguably the most well-studied ICD both in the general population and among PD patients [10]. The category of ICDs in the DSM-IV also includes a 'not otherwise specified' subcategory. The ICD not otherwise specified subcategory can be used to diagnose several conditions that have been noted in PD, including hypersexuality (possibly the earliest identified ICD in PD patients) and compulsive shopping [10]. Research in PD has investigated other conditions and patterns of behavior [12] that, like ICDs, involve repeated excessive activities, may share common neurobiologies and may result from similar underlying vulnerabilities as ICDs [13]. One such condition is dopamine dysregulation syndrome (DDS), which is defined as compulsive use of dopaminergic medication, particularly levodopa (LD) [9,13]. DDS demonstrates similarities with drug addiction, including withdrawal syndromes following medication cessation or reduction [9,14]. Punding, which is defined as the frequent performance of repetitive, stereotyped behaviors, such as collecting or hording, internet use, and sorting and reordering of items, is an example of another pattern of behaviors possibly related to ICDs [4,10].

There is overlap in the diagnostic criteria [11] for ICDs and addictions, consistent with ICDs being described as 'behavioral addictions' [15]. For example, individual inclusionary criteria for both drug dependence and PG exist that target continued engagement despite negative consequences, tolerance, withdrawal and repeated unsuccessful attempts to cut back or quit [11,15]. Evidence has also shown parallels

in the neurotransmitter dysfunction and patterns of limbic and cortical activity typified by addictions and ICDs such as PG [15,16]. For these reasons, PG and possibly other ICDs (e.g., problematic internet use or internet addiction) are being considered for reclassification as addictive disorders in the forthcoming DSM-V [17].

Impulse control disorders may occur more commonly among PD patients than in the general public. In a sample of 554 consecutive PD patients at an outpatient movement disorders clinic in Turkey, 5.9% were found to have an ICD [1]. In a larger, multisite study, a significant percentage of PD patients (13.6%) met criteria for an ICD [2]. Regarding specific disorders, 2.9% met criteria for PG and 5.7% met criteria for compulsive buying in this study. While the compulsive buying frequency is comparable to the rate in the US general population (i.e., 5.8%; [18]), the PG frequency is higher than in the US general population, where the prevalence is approximately 1% in adults [19]. However, elevated frequencies of PG have been observed in association with multiple medical conditions. For example, among a sample of 389 medical and dental patients, over 15% met study criteria for PG and approximately another 10% met criteria for having a gambling problem [20]. Thus, in addition to the specific factors associated with PD, multiple more generalized factors (e.g., the impact of having a significant medical condition and the associated stressors) should be considered when investigating the etiologies of ICDs in PD.

Possible etiologies of ICDs in PD

It has been hypothesized that dopamine deficiencies occurring during the progression of the disease [5,6] may lead PD patients to be less responsive to reward and more responsive to punishment [8,21]. Such a lack of reward responsiveness related to disease progression may lead to a loss of pleasure, which may in turn lead some PD patients to seek extrinsic stimulation, in some cases in the form of impulsive behaviors [9]. Similar neurobiological dysfunction has been described in substance dependence. Continued drug seeking and use may be perpetuated, in part, by reduced numbers of dopamine D2-like receptors in the brain (particularly in the striatum), and these alterations may influence dopamine signaling, feelings of reward or pleasure, reinforcement of behaviors and reward-based learning [22].

Aspects of cognitive decline associated with PD progression (e.g., decrements in working memory [23]) may also predispose PD patients toward impulsive behavior. Tendencies toward response perseveration, a feature sometimes associated with ICDs and addictions, have been found in PD patients and may not be closely linked to anti-Parkinson's medications [23]. Utilizing functional MRI, Rowe *et al.* found with patients both on and off anti-Parkinson's medication that there was less intense anterior cingulate activation during the prospect of reward in a continuous performance task among those with more severe PD [24]. By contrast, activation in response to actual rewards increased with disease severity. These findings suggest that lack of reward responsiveness in more severe PD patients may be associated specifically with weaker anticipation of reward rather than a lack of responsiveness to actual reward receipt. This pattern of response may be related to greater delay discounting (i.e., a preference for more immediate, smaller rewards rather than delayed, larger rewards [25]), which is considered to be an aspect of impulsivity [26].

These findings suggest that disease progression may lead to impulsive tendencies. Data also suggest that dopamine replacement therapies (DRTs), including LD (a biochemical precursor to dopamine) [27] and particularly dopamine agonists (DAs; e.g., pramipexole and ropinirole) are associated with ICDs [2,3]. Another anti-Parkinson's treatment that has been discussed as a possible risk factor for impulsive behavior and ICDs is deep-brain stimulation (DBS) of the subthalamic nucleus [28,29].

Clinical studies

■ Factors associated with ICDs in PD

Dopamine replacement therapies improve motor function and may influence cognitive flexibility [8,30,31]. ICDs in PD have been associated with DRTs [2,32–35]. In an international study involving over 3000 PD patients, 17.1% of patients taking DAs had ICDs compared with 6.9% of PD patients not taking a DA [2]. LD use was also associated with ICDs in this study, although the association was not as strong as for DAs. Of the small minority of PD patients in this sample who received neither LD nor DA treatments (n = 59), only 1.7% met criteria for an ICD.

The relationship between medication use and ICD does not appear to be straightforward and may reflect an underlying vulnerability. While a considerable number of PD patients are affected,

those who develop an ICD nonetheless represent a minority of the PD patients who take medication [36]. Several factors may influence the likelihood of developing an ICD **(Table 1)** [3,4]. ICDs in PD have been associated with factors related directly to PD (e.g., age at PD onset and functional impairment related to PD) and its treatment (e.g., DBS, DAs, LD and amantadine). In addition, ICDs in PD have been associated with factors seemingly unrelated to PD, including mental health disorders (e.g., personal and/or familial histories of alcoholism, gambling problems and

Table 1. Factors associated with impulse control disorders in Parkinson's disease patients.

Factor	Author (year)	Ref.
Amantadine treatment	Weintraub *et al.* (2010)	[63]
Trait anxiety	Voon *et al.* (In Press)	[60]
Deep-brain stimulation	Ballanger *et al.* (2009)	[28]
	Frank *et al.* (2007)	[72]
	Lim *et al.* (2009)	[29]
Depression	Gallagher *et al.* (2007)	[13]
	Voon *et al.* (In Press)	[60]
Dopamine agonist treatment	Ardouin *et al.* (2006)	[32]
	Bostwick *et al.* (2009)	[73]
	Driver-Dunckley *et al.* (2003)	[33]
	Gallagher *et al.* (2007)	[13]
	Giladi *et al.* (2007)	[74]
	Pontone *et al.* (2006)	[75]
	Voon *et al.* (2006)	[34]
	Weintraub *et al.* (2006)	[35]
	Weintraub *et al.* (2010)	[2]
Family history of gambling problems	Weintraub *et al.* (2010)	[2]
High functional impairment related to Parkinson's disease	Voon *et al.* (In Press)	[60]
Impulse control disorders history before onset of dopamine agonist treatment	Weintraub *et al.* (2006)	[35]
Impulsivity	Voon *et al.* (In Press); motor and rapid decision	[60]
	Voon *et al.* (2007); nonplanning	[38]
Levodopa equivalent daily dose	Voon *et al.* (In Press)	[60]
Levodopa treatment	Weintraub *et al.* (2010)	[2]
Male sex	Gallagher *et al.* (2007)	[13]
	Giladi *et al.* (2007)	[74]
	Kenangil *et al.* (2010)	[1]
Medication-induced hypomania	Voon *et al.* (2007)	[38]
Novelty/sensation seeking	Bodi *et al.* (2009)	[8]
Obsessive–compulsive symptoms	Voon *et al.* (In Press)	[60]
Personal or family history of alcoholism	Voon *et al.* (2007)	[38]
	Weintraub *et al.* (2010)	[2]
Residing in the USA	Weintraub *et al.* (2010)	[2]
Tobacco smoking	Weintraub *et al.* (2010)	[2]
Unmarried	Weintraub *et al.* (2010)	[2]
Younger age/younger age of Parkinson's disease diagnosis/onset	Gallagher *et al.* (2007)	[13]
	Giladi *et al.* (2007)	[74]
	Voon *et al.* (2006)	[34]
	Voon *et al.* (2007)	[38]
	Weintraub *et al.* (2006)	[35]
	Weintraub *et al.* (2010)	[2]

ICDs prior to PD onset), personal features or tendencies (e.g., impulsivity, obsessionality–compulsivity, anxiety and depression), and socio-demographic characteristics (e.g., unmarried and living in the USA vs Canada).

■ Clinical characteristics

As it has been suggested that PD patients may be relatively inhibited [37,38], especially when not taking medications [4,8], a low threshold may be important for identifying ICDs, particularly given their potential negative impact [3]. Given the lack of longitudinal data it is uncertain the extent to which high inhibition/low disinhibition may be a precursor to the development of PD, relate to dopamine depletion in PD or reflect some other phenomena [37].

Clinical conditions and behavior patterns possibly associated with ICDs have been identified in PD and are listed in **Table 2** along with citations for recent studies. Although these conditions and behaviors involve repetition, some are hedonic-like, at least at their onset (e.g., compulsive eating/weight gain, compulsive shopping and hypersexuality), while others consist of typically nonhedonic, stereotyped behaviors (e.g., walkabout, which is defined as a persistent restlessness that may lead to a strong urge to walk or travel [10]). Health professionals and researchers seeking ideographic descriptions of ICDs in PD patients can refer to brief case histories in recent published reports [1,32].

Neurobiological & neurocognitive studies

■ Background

When evaluating neurobiological and neurocognitive research on ICDs in PD, researchers and clinicians should consider multiple factors. Some of these factors (e.g., the medication use status of PD patients in the sample) are described in **Table 3**. Although the list includes many important questions it is not exhaustive, and additional considerations specific to individual studies are likely to be relevant. Key aspects of the methods and results of studies discussed in this section are presented briefly in **Table 4**.

■ Responsiveness to reward & punishment

Dopamine deficiencies occurring during PD progression [5,6] may lead patients to become more responsive to punishment and less responsive to reward [8,21]. Recent neurocognitive research has suggested that DRT use may be implicated in a reversal of this pattern (i.e., greater reward responsiveness and lesser responsiveness to punishment) in some PD patients [8,21]. Recent studies have also shown similarly altered contingencies in PD patients with ICDs and that their tendencies to respond more strongly to reward than punishment may be amplified with DRT use [27].

Recent studies have compared non-medicated PD patients with healthy controls and medicated PD patients with healthy controls regarding their responsiveness to reward and punishment. In accordance with the dopamine deficiency hypothesis, Bodi *et al.* found that relatively young, previously unmedicated PD patients (ICD status not reported) showed impairment in reward processing and enhanced learning from punishment in a feedback-based probabilistic classification task [8]. By contrast, recently medicated PD patients did not differ significantly from healthy controls on reward learning, but performed significantly worse than healthy controls and never medicated PDs on punishment learning. Prospective findings from a 12-week follow-up conducted as part of this study paralleled the cross-sectional findings. DA use in the previously unmedicated group was associated with enhanced reward learning and disrupted punishment learning. Kobayakawa *et al.* [39] found that primarily older adult PD patients without ICDs (tested while on their regular medication regimen of LD or DAs) were more likely to draw from disadvantageous decks in the Iowa Gambling Task [40] than matched healthy controls. Pagonabarraga *et al.* also found that PD patients without ICDs tested when taking their normal DA regimen performed worse than matched healthy controls on the Iowa Gambling Task, making more choices from disadvantageous decks as the task continued [41]. This pattern of drawing from disadvantageous decks suggests hypersensitivity to reward and/or hyposensitivity to punishment in individuals with PD who take DRTs.

Other studies have pursued within-subjects comparisons of PD patients on and off medication. Frank *et al.* compared matched healthy controls with PD patients (ICD status not reported) on and off their regular DRT regimen (all were on LD and some were also taking DAs) [21]. Participants performed probabilistic and deterministic procedural learning tasks. The authors found that, when medicated, PD patients were more effective at learning from positive (i.e., information that a choice was correct) than negative (i.e., information that a choice was

Table 2. Recent studies concerning clinical conditions and behavior patterns possibly associated with impulse control disorders in Parkinson's disease patients.

Condition/behavior	Author (year)	Ref.
Compulsive eating/weight gain	Kenangil *et al.* (2010)	[1]
	Nirenberg and Waters (2006)	[76]
	Weintraub *et al.* (2009)	[12]
Compulsive shopping	Kenangil *et al.* (2010)	[1]
	Weintraub *et al.* (2006)	[35]
	Weintraub *et al.* (2009)	[12]
Dopamine dysregulation syndrome (i.e., compulsive use of anti-Parkinson medications, particularly levodopa)	Evans *et al.* (2006)	[56]
	Lawrence *et al.* (2003)	[77]
Drug use	Kenangil *et al.* (2010)	[1]
Hobbyism	Weintraub *et al.* (2009)	[12]
Hypersexuality	Kenangil *et al.* (2010)	[1]
	Weintraub *et al.* (2006)	[35]
	Weintraub *et al.* (2009)	[12]
Problem/pathological gambling	Ardouin *et al.* (2006)	[32]
	Avanzi *et al.* (2006)	[78]
	Driver-Dunckley *et al.* (2003)	[33]
	Grosset *et al.* (2006)	[79]
	Lu *et al.* (2006)	[80]
	Voon *et al.* (2006)	[34]
	Weintraub *et al.* (2006)	[35]
	Weintraub *et al.* (2009)	[12]
Punding	Evans *et al.* (2006)	[56]
	Kenangil *et al.* (2010)	[1]
	Weintraub *et al.* (2009)	[12]
Walkabout	Weintraub *et al.* (2009)	[12]

wrong) feedback with the reverse observed when not medicated. Healthy controls showed no such performance disparity between positive and negative feedback. Positive feedback could be thought of as analogous to reward and negative feedback analogous to punishment. Thus, these findings parallel results from the between-subjects comparisons discussed earlier. By contrast, van Eimeren *et al.* [42] found no significant differences in performance on the Balloon Analogue Risk Task (BART) [43], a computerized task of risk-taking propensity, between medication administration conditions (i.e., no medication, LD and an equivalent dose of the DA pramipexole) in a sample of early-stage PD patients without ICDs. Hamidovic *et al.* found similar negative results on a battery of impulsivity measures in healthy adult subjects following administration of pramipexole, a DA utilized in PD treatment [44].

Some studies have tested differences between PD patients with and without ICDs. On a stimulus reinforcement learning task, medicated PD patients without ICDs rated stimuli with a high probability of reinforcement to be significantly less likely to yield reward than both healthy controls and medicated PD patients with ICDs [7]. In the same study, PD patients with ICDs indicated a preference for immediate over delayed rewards on the Kirby delay discounting questionnaire [45]. This response pattern may indicate a dampened response to reward among PD patients without ICDs and heightened responsiveness to immediate rewards among PD patients with ICDs, possibly indicative of impulsive response [7]. Voon *et al.* found that PD subjects with ICDs had faster reaction times on the experiential discounting task (EDT) [46], a naturalistic intertemporal choice task examining real-time temporal discounting, as compared with PD subjects without ICDs [27], which may also suggest heightened reward responsiveness and/or response impulsivity among PD patients with ICDs. However, Rao *et al.* found no significant differences in risk-taking as assessed by performance on the BART between PD patients with and without ICDs (all but one of whom were taking DAs) [47].

In addition to between-subjects comparisons among PD patients with and without ICDs and matched normal controls, the Voon *et al.* study also included within-subjects comparisons of the PD patient groups on and off DA [27]. DA use was associated with increased impulsive choices on the EDT among PD patients with ICDs, but not in those without, and the aforementioned main effect of faster EDT reaction times by PD patients with ICDs was more pronounced in patients on DAs compared with off. While on DA, PD patients with ICDs also made more errors on a spatial working memory task than those without ICDs, suggesting that PD patients with ICDs may also have impaired executive function [27]. In a recent study utilizing a computerized trust game, PD patients with and without ICDs were compared with healthy controls. In an additional between-subjects comparison, PD patients were tested either on or off their regular LD medication regimen. Regardless of medication condition, PD patients without ICDs punished computerized opponents they believed were real people in cases when monetary resources were not shared to a greater extent than healthy controls. PD patients with ICDs punished more than controls on medication, but were similar to controls off medication [48]. While the nature of the relationship is not entirely clear, ICD and medication status appeared to have influenced task performance in this study.

In summary, cognitive impairments potentially linked to PD progression rather than medication use may put patients at risk for impulsive behaviors, and DRTs may influence responses to reward and punishment. Data also suggest possible differences in reward responsiveness based on ICD status, although negative findings were reported with a risk-taking task. As many studies have employed relatively small samples, investigations with larger and well-characterized samples should help to further identify neurocognitive contributions to ICDs in PD.

■ Possible ventral striatal & cortical involvement

Recent research suggests that the ventral striatum and the prefrontal cortex are two key regions with regard to alterations in responsiveness to reward and punishment observed in PD patients. ICD behaviors in PD patients have been proposed to reflect 'dopamine overdosing' in the ventral striatum, resulting from DRTs [4,23,49]. While dopaminergic loss in PD initially involves the dorsal striatum, the ventral striatum is left relatively intact in the early stages. As such, it has been hypothesized that over-stimulation of the ventral striatum may occur in DRTs. Given the role of the ventral striatum in regulating reward responsiveness and motivational drives, DRTs may influence responsiveness to reward [42] and motivational values of stimuli [50].

Table 3. Some factors to consider when evaluating results of neurobiological and neurocognitive work related to Parkinson's disease and impulse control disorders.

Factor	Some questions to consider
General issues regarding nature of PD patient sample	What level of disease severity/progression is evidenced by the patients? What age group (e.g., middle-aged, older adults)?
Types of comparisons between groups	Does the study compare PD patients with and without ICD or with specific ICDs (e.g., pathological gambling)? Is the comparison between PD patients versus healthy controls? Is a within-subject comparison being conducted?
Pre-PD/premedication ICD status	Is the patient sample limited to those who report that their onset of ICD was after PD onset or the beginning of anti-Parkinson's medication use or does the sample include those whose onset of ICD may have predated their PD?
Patient medication status clinically and for study design	Is the patient sample taking anti-Parkinson's medications and, if so, what type (e.g., DAs, LD, combinations)? Is a comparison in the study between patients taking a particular type of medication versus those who are not? For study purposes, are patients taking medication being asked to abstain before study sessions and, if so, for how many hours beforehand?
Medication challenge	Will patients be administered DRTs as part of the study? If so, which type of medication (e.g., DAs, LD)?
For cognitive task studies: nature of task	What type of task is being utilized? Is it a task to assess some aspect of impulsivity (e.g., delay discounting) or compulsivity (e.g., response perseveration), is it a risk-taking/gambling task or some other task?
Assessment instruments	How were assessments of ICDs or other possibly related behaviors made? Were self-report measures or clinical interviews utilized? Have these instruments been established in the literature as being reliable and valid?

DA: Dopamine agonist; DRT: Dopamine replacement therapy; ICD: Impulse control disorder; LD: Levodopa; PD: Parkinson's disease.

Table 4. Summary of neurobiological and neurocognitive studies concerning impulse control disorders and related behaviors in Parkinson's disease patients (papers listed in the order in which they are first described in the manuscript).

Author (year)	Sample/group comparisons	Task(s) utilized	Medication manipulation	fMRI or PET	Key results	Ref.
Bodi *et al.* (2009)	▪ Never medicated PD (PD-no-med) ▪ Recently medicated PD (PD-med) ▪ HC	▪ Feedback-based probabilistic classification task, with reward and punishment learning aspects	During follow-up period, previously unmedicated patients began taking DA	NA	PD-no-med group showed impairment in reward processing and enhanced learning from punishment PD-med group did not differ from HC group on reward learning, but was worse than HC and PD-no-med groups on punishment learning In a 12-week follow-up, DA use in PD-no-med group was associated with enhanced reward learning and disrupted punishment learning	[8]
Kobayakawa *et al.* (2010) Pagonabarraga *et al.* (2007)	▪ PD-no-ICD ▪ HC	▪ IGT	PD patients tested while on DRT	NA	PD-no-ICD group more likely than HC group to draw from disadvantageous decks in the IGT	[39,41]
Frank *et al.* (2004)	▪ PD ▪ HC	▪ Probabilistic and deterministic procedural learning tasks	Within-subject, PD patients tested on and off DRT	NA	PD patients on DRT more effective than PD patients off DRT and HC group at learning from positive feedback PD patients off DRT better than PD patients on DRT and HC group at learning from negative feedback HC group showed no performance disparity with positive versus negative feedback	[21]
van Eimeren *et al.* (2009)	▪ PD-no-ICD	▪ BART ▪ Roulette-style probabilistic reward task	Within-subject, PD tested on LD, DA and no medication, following overnight abstinence	fMRI	No significant difference in BART performance by condition On DA, enhanced activity in the OFC in response to feedback in general in roulette task compared with LD and no-medication group On DA or LD, altered response deactivation in ventral striatum during negative error trials On DA, altered response deactivation in OFC during negative error trials	[55]
Housden *et al.* (2010)	▪ PD–ICD ▪ PD-no-ICD ▪ HC	▪ A stimulus reinforcement learning task ▪ Kirby DDT	PD tested on DRT	NA	PD-no-ICD group rated stimuli with a high probability of reinforcement to be less likely to yield reward than both HC and PD–ICD groups PD–ICD group indicated a preference for immediate over delayed rewards on the Kirby DDT	[7]
Voon *et al.* (2010)	▪ PD–ICD ▪ PD-no-ICD ▪ HC	▪ EDT ▪ Executive function tasks	Within-subject, PD tested on EDT both on and off DA Executive function tasks conducted in PD patients only, while on DA	NA	PD–ICD group showed faster reaction times on EDT than the PD-no-ICD group Tendency more pronounced in the PD–ICD group when on DA DA use associated with impulsive choice on the EDT among the PD–ICD group but not among the PD-no-ICD group On DA, the PD–ICD group showed more working memory errors	[27]

BART: Balloon Analogue Risk Task; DA: Dopamine agonist; DDT: Delay discounting task; DRT: Dopamine replacement therapy; EDT: Experiential Discounting Task; fMRI: Functional MRI; HC: Healthy control; ICD: Impulse control disorder; IGT: Iowa Gambling Task; LD: Levodopa; NA: Not applicable; OFC: Orbitofrontal cortex; PD: Parkinson's disease; PD-no-ICD: Parkinson's disease patients without impulse control disorders; PD-no-PG: Parkinson's disease patients without pathological gambling; PG: Pathological gambling.

Table 4. Summary of neurobiological and neurocognitive studies concerning impulse control disorders and related behaviors in Parkinson's disease patients (papers listed in the order in which they are first described in the manuscript) (cont.).

Author (year)	Sample/group comparisons	Task(s) utilized	Medication manipulation	fMRI or PET	Key results	Ref.
Rao *et al.* (2010)	▪ PD–ICD ▪ PD-no-ICD (all but one PD patient taking DA, all but two PD patients taking LD)	▪ BART	No medication manipulation	fMRI	No group differences on BART Reduced perfusion in ventral striatum at rest and reduced activation during BART in PD–ICD group relative to PD-no-ICD group PD-no-ICD group also showed activation in other relevant regions during the BART At a similar significance threshold, individuals with ICDs showed no activation in these structures	[47]
Djamshidian *et al.* (2011)	▪ PD–ICD ▪ PD-no-ICD ▪ HC	▪ Computerized trust game	Between-subjects, PD patients tested on or off LD	NA	On or off LD, PD-no-ICD group administered punishment more often than the HC group Off LD, the PD–ICD group administered punishment equivalent to the HC group, but PD–ICD patients tested while on LD administered punishment more than HC group	[48]
Steeves *et al.* (2009)	▪ PD–PG ▪ PD-no-PG	▪ Computerized gambling/card task and a control task	PD group tested off DRT after overnight abstinence	PET	Raclopride-binding levels in the ventral striatum at baseline were lower in PD–PG group than in PD-no-PG group PD–PG group showed greater reduction than PD-no-PG group in raclopride-binding potential in the ventral striatum during gambling task performance	[50]
Cilia *et al.* (2010)	▪ PD–PG ▪ PD-no-PG ▪ HC	▪ NA	PD group tested off DRT after overnight abstinence	PET	PD–PG group showed greater reductions in striatal dopamine transporter binding in the ventral striatum than the PD-no-PG group	[36]
van Eimeren *et al.* (2010)	▪ PD–PG ▪ PD-no-PG	▪ Probabilistic feedback card task	DA after overnight abstinence	PET	PD–PG group showed reduced brain activity in regions associated with impulse control and response inhibition during the card game DA administration increased activity in these areas in the PD-no-PG group	[55]

BART: Balloon Analogue Risk Task; DA: Dopamine agonist; DDT: Delay discounting task; DRT: Dopamine replacement therapy; EDT: Experiential Discounting Task; fMRI: Functional MRI; HC: Healthy control; ICD: Impulse control disorder; IGT: Iowa Gambling Task; LD: Levodopa; NA: Not applicable; OFC: Orbitofrontal cortex; PD: Parkinson's disease; PD-no-ICD: Parkinson's disease patients without impulse control disorders; PD-no-PG: Parkinson's disease patients without pathological gambling; PG: Pathological gambling.

Regarding the role of the prefrontal cortex, dopamine stimulation from DRTs may disrupt gating mechanisms. These cortical gating mechanisms help to distinguish stimuli to which one should react to from stimuli one should ignore. Greater distractability may occur as a result of this disruption [23]. Receipt of rewards, particularly those that were not anticipated, is associated with phasic dopamine release and signaling, whereas the nonreceipt of expected rewards is associated with a pause in dopamine-related neuronal firing. The enhanced dopaminergic activity resulting from DRTs has been proposed to disrupt these pauses that may normatively lead to response inhibition [42].

Recent findings have provided empirical support for these proposed roles for the prefrontal cortex and ventral striatum. After a medication abstinence period, early-stage PD patients without ICDs displayed enhanced activity in the orbitofrontal cortex in response to feedback in general in a roulette-style probabilistic reward task when tested after DA administration, compared with LD or no medication [42]. The authors also observed impaired response deactivation in the ventral striatum during negative error trials following LD or DA administration and in the orbitofrontal cortex following DA administration only [42].

Relevant to the roles of the ventral striatum and prefrontal cortex, parallels may exist between ICDs in PD patients and ICDs in the general population. The ventral striatum and parts of the prefrontal cortex including the ventromedial prefrontal cortex have been implicated in addictions and ICDs, such as PG in the general population [16]. Substance-dependent individuals have been found to release dopamine in the ventral striatum in response to their drugs of choice [51–53]. Individuals with PG have shown diminished activity in the ventral striatum during simulated gambling [54], similar to findings during a risk-taking task in PD/ICD patients [47].

Given this type of evidence for the involvement of the ventral striatum and prefrontal cortex in ICDs, such as PG in the general population, some investigators have explored whether dysfunction in these regions may be observable in PD patients with ICDs. Following overnight medication abstinence, PD patients with PG compared with PD patients without PG showed greater reductions in raclopride (a D2-like dopaminergic ligand) binding potential in the ventral striatum during gambling task performance, which could be suggestive of greater dopamine release in the ventral striatum in the group with PG. Levels of raclopride binding in the ventral striatum at baseline were also lower in the group with PG, suggesting differences not directly related to gambling participation *per se* [50]. In a separate publication, reduced striatal dopamine transporter binding in the ventral striatum was observed in PD patients with PG as compared with PD patients without PG. The authors reported that this finding may be explained by increased synaptic dopamine among PD patients with PG [36].

Regarding cortical activity, after DA administration following overnight abstinence, PD patients with PG showed reduced brain activation in regions associated with impulse control and response inhibition (e.g., lateral orbitofrontal cortex and rostral cingulate) while engaged in a probabilistic feedback card game during PET scans. By contrast, DA administration increased activity in these areas among PD patients without PG [55].

A recent functional MRI study addressed activation in both the ventral striatum and prefrontal cortex in PD patients with and without ICDs. The investigators found reduced activation in the ventral striatum at rest and during a risk-taking task in individuals with ICDs and PD as compared with those with PD alone [47]. Individuals with PD and ICDs were compared with PD subjects without ICDs while performing the BART. In addition to ventral striatal differences, subjects without ICDs showed activation in other areas relevant to risk/reward decisions and impulse control during the BART, including the dorsolateral prefrontal cortex and anterior cingulate cortex/medial frontal cortex. At a similar significance threshold, individuals with ICDs showed no activation in these structures [47].

Activity in the striatum has also been found to be altered among PD patients with conditions and behavior patterns possibly related to ICDs. In a PET study, Evans *et al.* compared PD meeting criteria for DDS to PD patients without DDS [56]. After LD administration following medication abstinence, PD patients with DDS showed a greater reduction in raclopride binding in the ventral striatum than PD patients without DDS, suggestive of greater ventral striatal dopamine release following LD administration in the DDS group. Reduction in the percentage binding of raclopride was related to punding behavior in the DDS patients, who were also more likely to work for small financial rewards while on LD.

To summarize, individuals with PD and ICDs show differences in brain function from those with PD alone while at rest and during risk-taking and decision-making tasks. The ventral striatum and prefrontal cortex appear to be two key regions with regard to these functional differences. DRTs may influence decision-making and impulsive responding. While a considerable number of PD patients develop ICDs, these patients represent a minority of the PD population taking medication. Therefore, individual differences are relevant as some patients may be at elevated risk for developing these disorders **(Table 1)**.

Clinical implications

Clinicians should discuss the potential for ICDs with their patients as early as possible following diagnosis. This type of discussion is especially pertinent when clinicians advise patients on treatment options, given data associating DRTs and DBS with ICDs in PD **(Table 1)**. As features of PD are often distressing and may be disabling, risks and benefits of the possible treatments should be considered and discussed with patients (see [57] for discussion of these issues). Clinicians can also assess patients for factors that have been associated with ICDs in PD **(Table 1)**. This information may have an impact on treatment recommendations. For instance, for individuals with several factors associated with ICDs, LD may be a better option than DA. While LD use has been associated with ICDs [2,58], odds ratios for ICDs in PD associated with LD were lower than those associated with DAs in a large cross-sectional study [2]. These findings are in accordance with results from small, uncontrolled studies, also suggesting stronger associations between ICDs and DAs than between ICDs and LD [33,34,59]. Nonetheless, as individuals on DAs may also be on LD, it may be challenging to disentangle fully the influence of medication. With respect to DAs, studies have found no differences with respect to specific DAs (e.g., ropinirole or pramipexole) and their associations with ICDs [8,13,34,35]. However, evidence suggests that DRT dose is an important factor to consider with regard to ICDs. Results from a recent multicenter case–control study showed that PD patients with ICDs had significantly higher LD equivalent daily doses of DRT than PD patients without ICDs [60], although this relationship has not been found in all studies [34].

Clinicians can assess patients for ICDs. There is now a brief, self-report screening measure entitled the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease (QUIP) [12]. Individuals who screen positive for one or more ICD may be identified and can thus be treated directly and/or referred for additional evaluation and care.

Dopamine agonist dose reductions, or outright discontinuation, have been suggested to ameliorate ICD symptoms in small uncontrolled studies [13,35,59,61]. Reductions in DA dosing in response to ICD symptoms are sometimes accompanied by increases in LD dosing [59]. Alternative treatments may also be considered, however, there is relatively little evidence-based data available regarding the efficacy of these treatment options. A recent, small, double-blind crossover trial showed evidence for the efficacy of amantadine (a drug influencing glutamatergic function utilized to treat early PD motor symptoms [62]) compared with placebo in treating recent-onset PG in PD [62]. However, these findings should be approached with caution, given the small sample size, potential for adverse effects and possible psychosis induction. Furthermore, recent data from a large, multisite, cross-sectional study [2] have linked amantadine use with ICDs [63]. Speculatively, amantadine's prodopaminergic properties may underlie its association with ICDs and its antiglutamatergic properties may underlie possible therapeutic effects. Further research is needed to investigate these issues and to explore possible individual differences that may be associated with positive and negative treatment response [63]. There is evidence suggesting efficacy of non-medication treatments such as DBS in the enhancement of motor function and overall quality of life in PD patients, although there is a lack of randomized, controlled studies in this area [64]. DBS has also been associated with impulsive behavior [21,28], and ICDs [29], although there have also been negative findings with regard to an association with ICDs [2] and the relationship between DBS and ICDs may be influenced by the specific location of the stimulation [65].

Evidence suggests that there are neurobiological similarities among addictions and ICDs with and without PD. For instance, diminished ventral cortical activations have similarly been observed in association with ICDs with and without PD [16,55] and in drug addictions [16]. Given this evidence of neurobiological similarity, treatments found to be efficacious in ICD patients without PD may be helpful for ICDs in PD patients, although direct testing of this hypothesis is warranted given the potential influences of neuropathology associated

with PD. Medications that have been found to demonstrate efficacy in the treatment of specific ICDs may be considered. While there are not yet any US FDA-approved medications for ICDs, multiple randomized clinical trials (e.g., [66]) have found opioid antagonists to be superior to placebo, particularly for PG [3]. Additionally, self-help groups (e.g., Gamblers Anonymous [67]) or professionally delivered behavioral therapies (e.g., cognitive behavioral therapy [68,69]) may be helpful.

Conclusion & future perspective

Although we have learned a great deal from recent studies, there are multiple areas that would benefit from additional research. Molecular investigations into the pathophysiology of ICDs in PD are at an early stage. However, the recent development of animal models of gambling [70,71], in conjunction with those in existence for PD, should aid in this area. Longitudinal studies are needed to identify predictors of, or risk factors for, ICDs in PD. These studies would likely have to be large to provide statistical power to yield generalizable results, which would be ambitious given that the development of PD and the development of an ICD in PD are each low probability occurrences. While there are findings suggesting parallels between ICDs with and without PD [55,47], conclusions are speculative until studies are conducted in which ICD patients with and without PD are included in the same research protocols. This type of research might inform not only our understanding of ICDs in PD, but also suggest additional treatment options. Several recent studies [27,36,41,42,47,50,56] have enrolled only PD/ICD patients who reported ICD features since PD onset or the onset of PD-related pharmacotherapy. Given evidence that a prior history of ICD may represent a risk factor for ICDs in PD [35], excluding such patients may limit the external validity of studies. Future research is needed that incorporates patients with PD and ICDs with a history of an ICD prior to PD onset. A potentially important aspect of research design is the severity of disease progression, as PD severity has been related to cognitive function [23]. While most investigators report average ratings of disease severity in their samples, and often match samples accordingly, results involving relationships between PD disease severity and ICDs are infrequently reported (see [24] for an exception). Dissecting changes in reward responsiveness and impulsive behaviors that may occur owing to disease progression versus medication use versus other possible factors is an important area of additional research focus, with important clinical ramifications. Such research could inform the development of novel and more efficacious treatment approaches for ICDs in PD. Testing behavioral, pharmacological and other treatments in large, carefully controlled randomized clinical trials will be important in identifying safe and efficacious therapies for individuals with ICDs and PD.

Acknowledgements

The authors would like to thank C Nogueira for editorial assistance with the manuscript.

Disclosure

The contents of the manuscript are solely the responsibility of the authors and do not necessarily represent the official views of any of the funding agencies.

Financial & competing interests disclosure

This work was supported in part by the NIH (K01 AA 019694, R01 DA019039, P20 DA027844 and RC1 DA028279), the VA VISN1 MIRECC, the Connecticut Department of Mental Health and Addiction Services (Hartford, CT, USA) and a Center of Research Excellence Award from the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders (Washington, DC, USA). MN Potenza has received financial support or compensation for the following: MN Potenza has consulted for and advised Boehringer Ingelheim; has consulted for and has financial interests in Somaxon; has received research support from the NIH, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories, Ortho-McNeil, Oy-Control/Biotie and GlaxoSmithKline pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the NIH and other agencies; has guest edited journal sections; has given academic lectures in grand rounds, continuing medical education events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Kenangil G, Özekmekçi S, Sohtaoglu M *et al.*: Compulsive behaviors in patients with Parkinson's disease. *Neurologist* 16(3), 192–195 (2010).

2 Weintraub D, Koester J, Potenza MN *et al.*: Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch. Neurol.* 67(5), 589–595 (2010).

▪▪ **The initial results of the DOMINION study are presented in this article. Given the size (n = 3090) and multisite nature of this study, which took place in two countries, it offers important results regarding the frequencies of different types of impulse control disorders (ICDs) in Parkinson's disease (PD) as well as factors associated with ICDs in PD.**

3 Potenza MN, Voon V, Weintraub D: Drug insight: impulse control disorders and dopamine therapies in Parkinson's disease. *Nat. Clin. Pract. Neurol.* 3(12), 664–672 (2007).

4 Voon V, Potenza MN, Thomsen T: Medication-related impulse control and repetitive behaviors in Parkinson's disease. *Curr. Opin. Neurol.* 20(4), 484–492 (2007).

5 Bernheimer H, Birkmayer W, Hornykiewicz O *et al.*: Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. *J. Neurol. Sci.* 20(4), 415–455 (1973).

6 Fearnley J, Lees AJ: Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* 114(Pt 5), 2283–2301 (1991).

7 Housden CR, O'Sullivan SS, Joyce EM *et al.*: Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive–compulsive spectrum behaviors. *Neuropsychopharmacology* 35(11), 2155–2164 (2010).

8 Bodi N, Keri S, Nagy H *et al.*: Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinsons patients. *Brain* 132(9), 2385–2395 (2009).

▪▪ **Involves recently medicated and never medicated PD patients who were compared with healthy controls in their performance on a feedback-based probabilistic classification task and in a subsequent follow-up, the previously unmedicated patients were treated with a dopamine agonist and then retested. The reward and punishment response tendencies of the group first medicated during follow-up appeared to shift such that they paralleled the patterns observed in the recently medicated patients in the first part of the study.**

9 Linazasoro G: Dopamine dysregulation syndrome and levodopa-induced dyskinesias in Parkinson disease: common consequences of anomalous forms of neural plasticity. *Clin. Neuropharmacol.* 32(1), 22–27 (2009).

10 Evans AH, Strafella AP, Weintraub D *et al.*: Impulsive and compulsive behaviors in Parkinson's disease. *Mov. Disord.* 24(11), 1561–1570 (2009).

11 American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*. American Psychiatric Association, Washington, DC, USA (1994).

12 Weintraub D, Hoops S, Shea JA *et al.*: Validation of the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease. *Mov. Disord.* 24(10), 1461–1467 (2009).

▪ **The Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease (QUIP) was introduced in this article. Given that this is the first comprehensive instrument devoted specifically to screening for ICDs and other repetitive behaviors in PD, it represents an important contribution to the literature.**

13 Gallagher DA, O'Sullivan SS, Evans AH *et al.*: Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation. An analysis of published case series. *Mov. Disord.* 22(12), 1757–1763 (2007).

14 Thobois S, Ardouin C, Lhommee E *et al.*: Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain* 133(Pt 4), 1111–1127 (2010).

15 Holden C: 'Behavioral' addictions: do they exist? *Science* 294(5544), 980–982 (2001).

16 Potenza MN: The neurobiology of pathological gambling and drug addiction: an overview and new findings. *Philos. Trans. R Soc. Lond. B Biol. Sci.* 363(1507), 3181–3189 (2008).

17 Holden C: Behavioral addictions debut in proposed DSM-V. *Science* 327(5968), 935 (2010).

18 Koran L, Faber R, Aboujaoude E *et al.*: Estimated prevalence of compulsive buying in the United States. *Am. J. Psychiatry* 163(10), 1806–1812 (2006).

19 Alegria A, Petry N, Hasin D *et al.*: Disordered gambling among racial and ethnic groups in the US: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *CNS Spectr.* 14(3), 132–142 (2009).

20 Ladd GT, Petry NM: Disordered gambling among university-based medical and dental patients: a focus on internet gambling. *Psychol. Addict. Behav.* 16(1), 76–79 (2002).

21 Frank MJ, Seeberger LC, O'Reilly RC: By carrot or by stick: cognitive reinforcement learning in Parkinsonism. *Science* 306(5703), 1940–1943 (2004).

22 Volkow ND, Fowler JS, Wang GJ: The addicted human brain: insights from imaging studies. *J. Clin. Invest.* 111(10), 1444–1451 (2003).

23 Price A, Filoteo JV, Maddox WT: Rule-based category learning in patients with Parkinson's disease. *Neuropsychologia* 47(5), 1213–1226 (2009).

▪ **Review of rule-based category learning deficiencies in PD, which provides substantial information on cognitive decrements in PD that may be related to disease progression and treatments for PD.**

24 Rowe JB, Hughes L, Ghosh BCP *et al.*: Parkinson's disease and dopaminergic therapy – differential effects on movement, reward and cognition. *Brain* 131(8), 2094–2105 (2008).

▪ **A functional MRI study that assesses neural function in PD patients during a continuous performance task. Its analyses relate disease severity to neural function during a cognitive task.**

25 Bickel W, Marsch L: Toward a behavioral economic understanding of drug dependence: delay discounting processes. *Addiction* 96(1), 73–86 (2001).

26 Dick DM, Smith G, Olausson P *et al.*: Understanding the construct of impulsivity and its relationship to alcohol use disorders. *Addict. Biol.* 15(2), 217–226 (2010).

27 Voon V, Reynolds B, Brezing C *et al.*: Impulsive choice and response in dopamine agonist-related impulse control behaviors. *Psychopharmacology* 207(4), 645–659 (2010).

▪ **This study includes both between- and within-subject comparisons in its design. PD patients with and without ICDs were compared with matched controls in their**

performance on a probabilistic inter-temporal choice task and on executive function tasks. The two PD patient groups were also compared on and off dopamine agonists.

28 Ballanger B, van Eimeren T, Moro E *et al.*: Stimulation of the subthalamic nucleus and impulsivity: release your horses. *Ann. Neurol.* 66(6), 817–824 (2009).

29 Lim SY, O'Sullivan SS, Kotschet K *et al.*: Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease. *J. Clin. Neurosci.* 16(9), 1148–1152 (2009).

30 Cools R, Barker RA, Sahakian B *et al.*: Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb. Cortex* 11(12), 1136–1143 (2001).

31 Cools R, Barker RA, Sahakian B *et al.*: L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia* 41(11), 1431–1141 (2003).

32 Ardouin C, Voon V, Worbe Y *et al.*: Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. *Mov. Disord.* 21(11), 1941–1946 (2006).

33 Driver-Dunckley E, Samanta J, Stacy M: Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology* 61(3), 422–423 (2003).

34 Voon V, Hassan K, Zurowski M *et al.*: Prospective prevalence of pathologic gambling and medication association in Parkinson disease. *Neurology* 66(11), 1750–1752 (2006).

35 Weintraub D, Siderowf AD, Potenza MN *et al.*: Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Arch. Neurol.* 63(7), 969–973 (2006).

36 Cilia R, Ko JH, Cho SS *et al.*: Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. *Neurobiol. Dis.* 39(1), 98–104 (2010).

37 Evans AH, Lawrence AD, Potts J *et al.*: Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 77(3), 317–321 (2006).

38 Voon V, Thomsen T, Miyasaki JM *et al.*: Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. *Arch. Neurol.* 64(2), 212–216 (2007).

39 Kobayakawa M, Tsuruya N, Kawamura M: Sensitivity to reward and punishment in Parkinson's disease: an analysis of behavioral patterns using a modified version of the Iowa gambling task. *Parkinsonism Relat. Disord.* 16(7), 453–457 (2010).

40 Bechara A, Damasio A, Damasio H *et al.*: Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50(1–3), 7–15 (1994).

41 Pagonabarraga J, García-Sánchez C, Llebaria G *et al.*: Controlled study of decision-making and cognitive impairment in Parkinson's disease. *Mov. Disord.* 22(10), 1430–1435 (2007).

42 van Eimeren T, Ballanger B, Pellecchia G *et al.*: Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease. *Neuropsychopharmacology* 34(13), 2758–2766 (2009).

■■ **This functional MRI study compares patients' performance and neural activations during a probabilistic reward task within subjects, while off medication and following administration of dopamine replacement therapies.**

43 Lejuez C, Read J, Kahler C *et al.*: Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *J. Exp. Psychol. Appl.* 8(2), 75–84 (2002).

44 Hamidovic A, Kang UJ, De Wit H: Effects of low to moderate acute doses of pramipexole on impulsivity and cognition in healthy volunteers. *J. Clin. Psychopharmacol.* 28(1), 45–51 (2008).

45 Kirby KN, Petry NM, Bickel WK: Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J. Exp. Psychol. Gen.* 128(1), 78–87 (1999).

46 Reynolds B, Schiffbauer R: Measuring state changes in human delay discounting: an experiential discounting task. *Behav. Processes* 67(3), 343–356 (2004).

47 Rao H, Mamikonyan E, Detre JA *et al.*: Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. *Mov. Disord.* 25(11), 1660–1669 (2010).

48 Djamshidian A, O'Sullivan SS, Doherty K *et al.*: Altruistic punishment in patients with Parkinson's disease with and without impulsive behaviour. *Neuropsychologia* 49(1), 103–107 (2011).

49 Cools R, Lewis S, Clark L *et al.*: L-Dopa disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. *Neuropsychopharmacology* 32(1), 180–189 (2007).

50 Steeves TDL, Miyasaki J, Zurowski M *et al.*: Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [^{11}C] raclopride PET study. *Brain* 132(5), 1376–1385 (2009).

51 Everitt B, Robbins T: Neural systems of reinforcement for drug addiction: from addiction to habits to compulsion. *Nat. Neurosci.* 8(11), 1481–1489 (2005).

52 Volkow N, Wang G, Telang F *et al.*: Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J. Neurosci.* 26(24), 6583–6588 (2006).

53 Volkow N, Fowler J, Wang G *et al.*: Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. *Arch. Neurol.* 64(11), 1575–1579 (2007).

54 Reuter J, Raedler T, Rose M *et al.*: Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nat. Neurosci.* 8(2), 147–148 (2005).

55 van Eimeren T, Pellecchia G, Cilia R *et al.*: Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. *Neurology* 75(19), 1711–1716 (2010).

56 Evans AH, Pavese N, Lawrence AD *et al.*: Compulsive drug use linked to sensitized ventral striatal dopamine transmission. *Ann. Neurol.* 59(5), 852–858 (2006).

57 Antonini A, Tolosa E, Mizuno Y *et al.*: A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. *Lancet Neurol.* 8(10), 929–937 (2009).

58 Molina JA, Sainz-Artiga MJ, Fraile A *et al.*: Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Mov. Disord.* 15(5), 869–872 (2000).

59 Sohtaoglu M, Demiray DY, Kenangil G *et al.*: Long term follow-up of Parkinson's disease patients with impulse control disorders. *Parkinsonism Rel. Disord.* 16(5), 334–337 (2010).

60 Voon V, Sohr M, Lang AE *et al.*: Impulse control disorders in Parkinson disease: a multicenter case–control study. *Ann. Neurol.* (2011) (In Press).

61 Mamikonyan E, Siderowf AD, Duda JE *et al.*: Long-term follow-up of impulse control disorders in Parkinson's disease. *Mov. Disord.* 23(1), 75–80 (2008).

62 Thomas A, Bonanni L, Gambi F *et al.*: Pathological gambling in Parkinson disease is reduced by amantadine. *Ann. Neurol.* 68(3), 400–404 (2010).

63 Weintraub D, Sohr M, Potenza MN *et al.*: Amantadine use associated with impulse control disorders in Parkinson disease in cross-sectional study. *Ann. Neurol.* 68(6), 963–968 (2010).

64 Kleiner-Fisman G, Herzog J, Fisman DN *et al.*: Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov. Disord.* 21(Suppl. 14), S290–S304 (2006).

65 Rodriguez-Oroz MC, López-Azcárate J, Garcia-Garcia D *et al.*: Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinsons disease. *Brain.* 134(Pt 1), 36–49 (2010).

66 Grant JE, Kim SW, Hartman BK: A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. *J. Clin. Psychiatry* 69(5), 783–789 (2008).

67 Petry NM: Patterns and correlates of Gamblers Anonymous attendance in pathological gamblers seeking professional treatment. *Addict. Behav.* 28(6), 1049–1062 (2003).

68 McCloskey MS, Noblett KL, Deffenbacher JL *et al.*: Cognitive-behavioral therapy for intermittent explosive disorder: a pilot randomized clinical trial. *J. Consult. Clin. Psychol.* 76(5), 876–886 (2008).

69 Petry NM, Ammerman Y, Bohl J *et al.*: Cognitive-behavioral therapy for pathological gamblers. *J. Consult. Clin. Psychol.* 74(3), 555–567 (2006).

70 Winstanley CA, Cocker PJ, Rogers RD: Dopamine modulates reward expectancy during performance of a slot machine task in rats: evidence for a 'near-miss' effect. *Neuropsychopharmacology* (2011) (Epub ahead of print).

71 Zeeb FD, Robbins TW, Winstanley CA: Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. *Neuropsychopharmacology* 34(10), 2329–2343 (2009).

72 Frank MJ, Samanta J, Moustafa AA *et al.*: Hold your horses: impulsivity, deep brain stimulation, and medication in Parkinsonism. *Science* 318(5854), 1309–1312 (2007).

73 Bostwick JM, Hecksel KA, Stevens SR *et al.*: Frequency of new-onset pathologic compulsive gambling or hypersexuality after drug treatment of idiopathic Parkinson disease. *Mayo Clin. Proc.* 84(4), 310–316 (2009).

74 Giladi N, Weitzman N, Schreiber S *et al.*: New onset heightened interest or drive for gambling, shopping, eating or sexual activity in patients with Parkinson's disease: the role of dopamine agonist treatment and age at motor symptoms onset. *J. Psychopharmacol.* 21(5), 501–506 (2007).

75 Pontone G, Williams JR, Bassett SS *et al.*: Clinical features associated with impulse control disorders in Parkinson disease. *Neurology* 67(7), 1258–1261 (2006).

76 Nirenberg M, Waters C: Compulsive eating and weight gain related to dopamine agonist use. *Mov. Disord.* 21(4), 524–529 (2006).

77 Lawrence AD, Evans AH, Lees AJ: Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? *Lancet Neurol.* 2(10), 595–604 (2003).

78 Avanzi M, Barratti M, Cabrini S *et al.*: Prevalence of pathological gambling in patients with Parkinson's disease. *Mov. Disord.* 21(12), 2068–2072 (2006).

79 Grosset K, MacPhee G, Pal G *et al.*: Problematic gambling on dopamine agonists: not such a rarity. *Mov. Disord.* 21(12), 2206–2208 (2006).

80 Lu C, Bharmal A, Suchowersky O: Gambling and Parkinson disease. *Arch. Neurol.* 63(2), 298 (2006).