Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update

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Dopaminergic medications used in the treatment of patients with Parkinson's disease are associated with motor and non-motor behavioural side-effects, such as dyskinesias and impulse control disorders also known as behavioural addictions. Levodopa-induced dyskinesias occur in up to 80% of patients with Parkinson's after a few years of chronic treatment. Impulse control disorders, including gambling disorder, binge eating disorder, compulsive sexual behaviour, and compulsive shopping occur in about 17% of patients with Parkinson's disease on dopamine agonists. These behaviours reflect the interactions of the dopaminergic medications with the individual's susceptibility, and the underlying neurobiology of Parkinson's disease. Parkinsonian rodent models show enhanced reinforcing effects of chronic dopaminergic medication, and a potential role for individual susceptibility. In patients with Parkinson's disease and impulse control disorders, impairments are observed across subtypes of decisional impulsivity, possibly reflecting uncertainty and the relative balance of rewards and losses. Impairments appear to be more specific to decisional than motor impulsivity, which might reflect differences in ventral and dorsal striatal engagement. Emerging evidence suggests impulse control disorder subtypes have dissociable correlates, which indicate that individual susceptibility predisposes towards the expression of different behavioural subtypes and neurobiological substrates. Therapeutic interventions to treat patients with Parkinson's disease and impulse control disorders have shown efficacy in randomised controlled trials. Large-scale studies are warranted to identify individual risk factors and novel therapeutic targets for these diseases. Mechanisms underlying impulse control disorders and dyskinesias could provide crucial insights into other behavioural symptoms in Parkinson's disease and addictions in the general population.

Introduction

Chronic treatment with dopaminergic medications, such as those used to manage Parkinson's disease, is commonly associated with motor and behavioural side-effects that include dyskinesias and impulse control disorders. Involuntary movements (ie, chorea and dystonia) associated with chronic levodopa treatment, termed levodopa-induced dyskinesias, occur in up to 80% of treated patients. A multicentre study has shown that impulse control disorders, which include gambling disorder, compulsive shopping, compulsive sexual behaviours, and binge-eating, occur in about 17% of individuals on dopaminergic medications. Other addictive behaviours, such as compulsive medication use (dopamine dysregulation syndrome) and punding (repetitive non-goal-directed simple or complex behaviours, including hobbies), are associated with impulse control disorders. Compulsive medication use, particularly of levodopa and fast-acting dopamine agonists, is also associated with dyskinesias.

In this Review, we present updated evidence regarding the epidemiology and the cognitive dysfunction associated with these prevalent and disabling side-effects of dopamine replacement therapy. We will also describe and compare the mechanisms underlying motor (levodopa-induced dyskinesias) and non-motor (impulse control disorders) side-effects associated with dopamine agonists, and discuss potential treatments for patients with impulse control disorders.

Epidemiology and risk factors

In the largest multicentre study (n=3090) of impulse control disorders in patients with Parkinson's disease (DOMINION), these disorders were identified in 14% of patients on any dopaminergic medication and 17% of patients treated with a dopamine agonist (compulsive gambling in 5%, compulsive sexual behaviour in 3-5%, compulsive shopping in 6%, and binge-eating disorder in 4%), and were more common in patients treated with dopamine agonists than in patients who were treated with other medications, including other dopaminergic medications (17.1% vs 6-9%; odds ratio 2.72; 95% CI 2.08-3.5). Different prevalences have been reported by small studies, which might reflect different diagnostic criteria or subclinical manifestations. The prevalence did not differ between two commonly prescribed dopamine agonists, pramipexole and ropinirole (17.7% vs 15.5%). A post-hoc review of six studies assessing continuous transdermal rotigotine showed an overall prevalence of 9-0%, which was affected by exposure duration (lower prevalence with <30 months exposure; high prevalence peak with 54-60 months exposure). Although long-acting pramipexole and transdermal rotigotine were less likely to be associated with impulse control disorders than short-acting dopamine agonists, this finding is preliminary, because the exposure to dopamine agonists varied between disorders. Both dopamine agonist and levodopa use were independently associated with impulse control disorders in the DOMINION study; this association was dose-dependent for levodopa, but not for dopamine agonists. However, the DOMINION study was cross-sectional and therefore unable to capture clinical changes longitudinally. In a small study of patients with Parkinson's disease (n=46), the group with impulse control disorders had a higher peak dopamine agonists...
dose relative to the group without these disorders (median 300·0 vs 165·0 levodopa equivalents, p=0·03). Furthermore, longitudinal studies show that dopamine agonists discontinuation or dose reduction can improve impulse control disorders,8 supporting a dose-dependent association.

The DOMINION study3 reported that the following factors are associated with impulse control disorders: dopamine agonist treatment; levodopa treatment; age (≥65 years); being unmarried; living in the USA; a family history of gambling problems; and ongoing cigarette smoking. Other associated factors were functional impairment, depression, anxiety, obsessive-compulsive symptoms, impulsivity, and novelty seeking.4 A small study7 showed that high caffeine use and cigarette smoking were associated with impulse control disorders, and that the disorders occurred only in a subset of individuals exposed to dopamine agonists,7 indicating an underlying susceptibility. The identified risk factors are similar to those reported for drug misuse disorders and gambling disorders, indicating common neurobiological substrates.

After initial treatment with levodopa, patients with Parkinson’s disease experience a so-called honeymoon phase in which therapeutic benefits are observed without major side-effects. Levodopa-induced dyskiniesias develop progressively, with up to 80% of levodopa-treated patients developing involuntary movements after 4–6 years of treatment, and up to 90% after 10 years. Risk factors for developing levodopa-induced dyskiniesias include long treatment duration, high initial dose of levodopa, young age at onset, low bodyweight, female sex, high Unified Parkinson’s Disease Rating Scale II scores, and high anxiety scores.10

Two studies9,11 have identified an increased probability of impulse control disorder and levodopa-induced dyskiniesias co-occurrence. Punding or excessive non-goal-oriented repetitive behaviours, which fall within the spectrum of impulse control behaviours, and individuals with more than one impulse control disorder have higher dyskiniesia scores than those without.11 These data suggest that motor and non-motor side-effects of dopamine replacement therapy might be associated with a common underlying susceptibility.

The role of Parkinson’s disease
The susceptibility of patients with Parkinson’s disease to impulse control disorders might be due to a pre-existing biological predisposition towards addictions or might occur as a result of dopaminergic medications modulating the neurobiology of Parkinson’s disease. Notably, impulse control disorders also occur with chronic dopaminergic medications in patients with restless leg syndrome (however, their prevalence might be lower in patients with Parkinson’s disease, possibly related to lower medication doses).12 Therefore, although Parkinson’s disease pathology might be important, it might not be crucial for the expression of impulse control disorders.

The role of endogenous dopamine signalling in the healthy brain is summarised in figure 1. In patients with Parkinson’s disease, there is an imbalance between dopaminergic systems projecting to motor and limbic systems, which are differentially affected by dopamine agonist therapy. Several hypotheses are emerging regarding the role of the parkinsonian lesions: parkinsonian dopaminergic lesions can increase levodopa-treated D3 receptor (D3R) expression in dorsal striatal regions; relative sparing or aberrant neurodegeneration of dopaminergic limbic regions...
Pharmacological primate studies have shown that different regions in the striatum regulate different behaviours. Local dysfunction induced by microinjections with bicuculline, a GABA antagonist, within the putamen leads to dyskinesia and myoclonus, whereas local dysfunction within associative and limbic striatal territories evokes behavioural disorders. Specifically, the anterior caudate nucleus controls hyperactivity, whereas regions in the ventral striatum (nucleus accumbens) control behavioural disorders: the medial region is associated with compulsive sexual behaviours, the central region with repetitive grooming (eg, licking or biting fingers), and the lateral regions with hypoactivity linked to loss of food motivation. Within the ventral striatum, three distinct topographically-organised circuits were associated with cortical (orbitofrontal cortex and anterior cingulate cortex) and subcortical (caudal levels of the basal ganglia) regions. Sexual behaviours were associated with a circuit involving the orbitofrontal cortex, medial prefrontal cortex, and mesial ventral striatum. Compulsive behaviour was linked to a circuit involving the lateral orbitofrontal cortex and limbic parts of the basal ganglia, known to process aversive information related to anxiety. Apathy with loss of food motivation was associated with a circuit involving the orbital and medial prefrontal cortex, lateral prefrontal cortex, anterior insula, and the lateral parts of the medial output basal ganglia structures. Because these disorders of motivation were induced by bicuculline in moderately dopamine-depleted monkeys, dopamine might modulate their expression rather than be causal. Furthermore, chronic treatment with levodopa induces dyskinesia in severely lesioned monkeys and hyperactive and neuropsychiatric-like behaviours (agitation, hallucinatory-like responses, stereotypies, and compulsive grooming) in moderately lesioned monkeys. Thus, dopamine replacement therapies might have a differential effect depending on the pattern and severity of the dopaminergic lesion and associated receptor hypersensitivity, resulting in the expression of different behavioural symptoms. Dyskinesias and behavioural disorders were also abolished following a serotonergic lesion, suggesting another crucial component in the modulation of corticobasal ganglia circuits.

### Effects of chronic dopaminergic medications

Dopaminergic medications can influence endogenous dopamine function in the brain at a presynaptic (figure 3) or synaptic level (figure 1). Chronic dopamine agonist or levodopa treatment can interfere with the phasic and tonic activity of dopaminergic neurons, and might be associated with long-term neuroadaptation, which can include regulation of receptor and transporter density. In rodents, acute pramipexole treatment decreases the mean firing rate and burst firing activity (possibly reflecting tonic and phasic firing, respectively) of dopaminergic neurons in the ventral tegmental area by acting on D₂-autoreceptors and inhibiting presynaptic dopamine release (figure 3A). However, chronic pramipexole administration normalises tonic firing and the number of bursts per minute, but the number of neurons exhibiting burst activity following chronic pramipexole treatment is lower than after acute administration, suggesting lower phasic activity. This normalisation is related to desensitisation of D₂-autoreceptors. After chronic pramipexole treatment, the firing rate of noradrenergic locus coeruleus activity also normalised, but burst activity remained low. By contrast, chronic pramipexole treatment increased the spontaneous firing rate and burst activity of serotonergic dorsal raphe neurons.

Chronic levodopa treatment in 6-OHDA-depleted rodents influences the gain associated with dopamine activity by enhancing the proportion of spontaneously active dopaminergic neurons or those capable of phasic activity in response to a salient stimulus, such a novel or unexpected reward (relevant to prediction error), a
conditioned cue (predicted cue), or a reward anticipation in the context of risk-taking or impulsivity, with no effect of levodopa itself. Unmedicated patients with Parkinson’s disease and pathological gambling also showed heightened ventral striatal dopamine release during a card gambling task and a simple motor task (appendix). However, in a study using an actual gambling task, unmedicated patients with Parkinson’s disease and pathological gambling did not differ from those without pathological gambling, although the enhanced striatal dopamine release correlated with gambling symptom severity. In patients with Parkinson’s disease with levodopa-induced dyskinesias or with compulsive levodopa use, enhanced ventral striatal dopamine release is observed in response to a levodopa challenge. This effect was observed both off medication and after a levodopa challenge, with no effect of levodopa itself. Unmedicated patients with Parkinson’s disease and pathological gambling also showed heightened ventral striatal dopamine release during a card gambling task and a simple motor task (appendix). However, in a study using an actual gambling task, unmedicated patients with Parkinson’s disease and pathological gambling did not differ from those without pathological gambling, although the enhanced striatal dopamine release correlated with gambling symptom severity. In patients with Parkinson’s disease with levodopa-induced dyskinesias or with compulsive levodopa use, enhanced ventral striatal dopamine release is observed in response to a levodopa challenge, suggesting that sensitisation occurs during repeated levodopa treatments, consistent with animal studies. By contrast, sensitised responses to a levodopa challenge did not occur in patients with Parkinson’s disease and impulse control disorders, suggesting that the adaptive processes for these disorders might be distinct from those associated with levodopa-induced sensitisation. In a study using functional MRI, patients with Parkinson’s disease and hypersexuality had higher activity than patients with Parkinson’s disease without impulse control disorders in a saliency network (ventral striatum, amygdala, anterior cingulate, and orbitofrontal cortex) to sexual cues both with and without levodopa treatment. Subjective sexual desire was enhanced on levodopa, whereas enhanced desire correlated with functional MRI activity in this saliency network.
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A role for novelty seeking, whereby novelty is represented by phasic dopaminergic activity, has also been observed. Patients with Parkinson’s disease on dopamine replacement therapy have enhanced novelty seeking behaviours, particularly patients with compulsive shopping or gambling disorder, but not those with compulsive sexual behaviours or binge eating.9 Patients with Parkinson’s disease and impulse control disorders were shown to prefer novel stimuli on a probabilistic learning task irrespective of medication status.42

The role of the D₃R was initially investigated following the observation that impulse control disorders were associated with chronic pramipexole treatment, a dopamine agonist with high affinity for D₂ and D₃ receptors. This association has been highlighted in 2014 US Food and Drug Administration Adverse Event Reporting System reports,43 emphasising the role of pramipexole and ropinirole, and also the D₃ partial agonist aripiprazole in the pathogenesis of impulse control disorders.43 A greater association was observed between addictive behaviours and dopamine agonists with higher D₃R selectivity (eg, pramipexole and ropinirole) than those with lower D₃R selectivity.44 Under physiological conditions, D₃R is predominantly found in the ventral striatum; however, in parkinsonian models, levodopa exposure results in de-novo expression of D₃R in the denervated dorsal striatum, and D₃R expression levels correlate with the severity of levodopa-induced dyskinesias. The D₃R is implicated in motivation, physiological and behavioural responses to drug cues, and novelty-seeking behaviours, and is co-expressed with D₁R in ventral striatal medium spiny neurons, whereby these receptors interact via intramembrane crosstalk. D₃R antagonism allows the restoration of normal D₁R numbers at the plasma membrane in dyskinetic rats, highlighting the importance of the D₁R–D₃R interaction in levodopa-induced dyskinesias. The role of D₃R in gambling disorders in the general population has been shown using ¹¹C-PHNO PET imaging.46 However, the role of D₃R in patients with Parkinson’s disease with impulse control disorders is less clear; a study of ¹¹C-PHNO PET in levodopa-treated patients with Parkinson’s disease and impulse control disorders showed lower ventral striatal binding than patients with Parkinson’s disease without impulse control disorders, possibly related to enhanced dopamine release.47

Studies have implicated a dopaminergic network, including the orbitofrontal cortex, in the encoding of goals and reward, and loss outcomes that allows for flexibility in behavioural choices, and have also implicated the anterior cingulate in conflict resolution, novelty seeking, representation of reward and punishment expectation, and prediction error.48,49 Patients with Parkinson’s disease and impulse control disorders show enhanced resting state ¹⁸F-fluorodopa uptake in the medial orbitofrontal cortex, suggesting enhanced monoaminergic activity (appendix).50 In a study using a card gambling task and ¹⁵H₂O-PET, patients with
Parkinson’s disease and pathological gambling showed inhibition of activity in the lateral orbitofrontal cortex, rostral cingulate, amygdala, and external pallidum following an apomorphine challenge (appendix). Abnormal orbitofrontal cortex activity both at baseline and with a dopamine agonist challenge might impair the patient’s capacity to use goals to flexibly guide responses. Patients with Parkinson’s disease with impulse control disorders also show impaired connectivity at rest between the anterior cingulate and striatum. These studies highlight the relevance of a network that includes the orbitofrontal cortex, the anterior cingulate, the anterior insula, and the striatum.

Mechanisms of levodopa-induced dyskinesias

Levodopa-induced dyskinesias are associated with changes in cellular signalling pathways. Enhanced D₁ stimulation causes widespread molecular adaptations in striatal medium spiny neurons. Transcriptome analysis of rodent models of levodopa-induced dyskinesia shows altered expression of genes involved in transcription, signal transduction, calcium homeostasis, synaptic transmission or plasticity, and synaptic structure. Levodopa triggers rapid expression of several immediate early genes such as FosB, Arc, and Zif268, which might promote the sustained transcriptional activation associated with levodopa-induced dyskinesias. A causative role for this mechanism was shown by lentiviral downregulation of the negative elongation factor protein complex in 6-OHDA-treated rats, which reduced expression of ΔFosB, Arc, and Zif268, and decreased abnormal involuntary movements in these rodents. Notably, the transcriptional regulators implicated in synaptic plasticity have also been shown to be involved in drug misuse disorders. The genetic and epigenetic mechanisms underlying levodopa-induced dyskinesias and impulse control disorders are discussed in panel 2.

Learning from reward and loss

Dopaminergic medications can influence cognitive processes such as learning from feedback, risk-taking, and impulsivity. Dopaminergic medications are hypothesised to enhance learning from positive feedback (ie, rewards) and impair learning from negative feedback (ie, losses); this relative imbalance presents as impulsivity. Novel rewards are associated with enhanced striatal phasic dopamine release, also known as positive prediction error (or the difference between what one receives and what one expects). By contrast, losses or unexpected omissions of reward are associated with a phasic cessation of dopamine activity, also known as negative prediction error. Thus, chronic stimulation of postsynaptic D₂Rs might interfere with the detection of negative prediction errors or the representation of unfavourable outcomes, which could decrease sensitivity to negative outcomes (figure 1).

Studies in human beings highlight an imbalance between learning from reward and loss outcomes in addictive behaviours. In a study using a two-choice probabilistic discrimination task, patients with Parkinson’s disease and impulse control disorders on dopamine agonists showed enhanced learning from rewards, compared with patients without impulse control disorders only, and impaired learning off dopamine agonists relative to healthy controls. In a study using a Q-learning reinforcement learning algorithm, a formula based on the concept that prediction errors are used to update the value of subsequent choices and calculate measures of learning and choice patterns, patients with Parkinson’s disease and impulse control disorders had higher ventral striatal activity to positive prediction error and expected reward when treated with dopamine agonists, compared with no dopamine agonist treatment. The opposite occurs in patients with Parkinson’s disease only (appendix). Thus, during chronic dopamine agonist exposure, stimulus-driven phasic dopamine release might preferentially activate the low affinity so-called Go D₁R neurons relative to the so-called NoGo D₂R neurons tonically activated by dopamine agonists (figure 1). This hypothesis is consistent with findings and models of dopamine agonist effects more broadly (ie, in treated patients with Parkinson’s disease without impulse control disorders, and in other populations treated with dopamine agonists). In another study, similar findings were reported in the reward domain in patients with Parkinson’s disease and impulse control disorders, whereby impairments were also documented in the loss domain. A probabilistic classification task in which participants decided whether a stimulus was associated with pressing a right or left button showed that medicated patients with Parkinson’s disease and impulse control disorders were better at reward learning and worse at punishment learning than healthy controls. The behaviour of medicated patients with Parkinson’s disease and impulse control disorders was better characterised by a ventral striatal critic model (which describes the use of prediction error to learn stimulus values and update expected future rewards), with impairments in learning from negative prediction errors, than medicated patients without impulse control disorders. By contrast, the behaviour of medicated patients with Parkinson’s disease but without impulse control disorders was better characterised by a dorsal striatal actor model (which describes the use of prediction error to encode action valuation and selection leading to rewards), with higher learning rates for positive prediction error. Not all studies on instrumental learning have been consistent; however, these inconsistencies could be related to methodological differences.

Impulsivity in Parkinson’s disease

Emerging evidence suggests that patients with Parkinson’s disease and impulse control disorders have impairments in decisional but not motor impulsivity. Impulsivity is a
Parkinson's disease and impulse control disorders have more frequent bias to make a specific response because it is repeated or (inhibition of a prepotent response whereby individuals are responses), and motor forms such as response inhibition response conflict (slowing and errors with competing impulsivity (rapid decision making), risk taking, and reduced sensitivity to adverse outcomes during learning, refl ection delayed reward), reduced sensitivity to adverse outcomes, and an increased risk of impulse control disorders, than carriers of the CC genotype.60

In a study of 276 patients with Parkinson's disease,63 the heritability of impulse control disorders was estimated to be 57%. Genotypes from 13 candidate variants allowed improved predictability of impaired impulse control disorders, compared with predictions based on clinical endpoints. The combination of genetic and clinical variables further increased the accuracy of the model. Within the genetic panel selected, OPRK1, HTR2A, and DDC were the strongest predictive factors.64 The p.S9G variant in the D3R gene is associated both with levodopa-induced dyskinesias and impulse control disorders, indicating a common genetic susceptibility. Although these disorders share several clinical and demographic risk factors, the small number of studies on the topic do not provide conclusive evidence to support either distinct or shared genetic susceptibility. Moreover, genetic studies need to be replicated in large independent populations before definitive conclusions can be drawn.

Common epigenetic mechanisms have also been suggested, such as those leading to the accumulation of the transcriptional regulator ΔFosB.64 Selective silencing of neurons expressing ΔFosB reduces levodopa-induced dyskinesias in rodents and primates, while maintaining the antiparkinsonian effect of levodopa.65 Dyskinesias are associated with increased expression of ΔFosB. Thus, ΔFosB-associated levodopa-induced dyskinesias probably reflect activation of extracellular signal-regulated kinase and stress-activated kinase 1.66 Such dysregulation is associated with structural changes at the level of neuronal spines and synapses that can lead to aberrant synaptic plasticity, a mechanism thought to underlie drug addiction.

Pramipexole triggers ΔFosB expression in the nucleus accumbens and the striatum of both healthy and dopamine-lesioned rats, and its expression correlates with the motivation to self-administer pramipexole.67 Natural rewards such as food or sex increase ΔFosB expression in the nucleus accumbens, striatum, prefrontal cortex, and ventral tegmental area of rats. Sexual activity-induced ΔFosB expression can be detected after prolonged abstinence, indicating a long-lasting effect.68 Overexpression of ΔFosB increases sucrose intake and promotes aspects of sexual behaviour. Furthermore, viral overexpression of ΔFosB in the nucleus accumbens increases food reinforcement and motivation in rats. ΔFosB expression in the nucleus accumbens and the striatum are dependent on NMDA receptors.69 These data suggest that enhanced ΔFosB expression following chronic dopamine replacement therapy might contribute to impulse control disorders by increasing an individual’s motivational drive for rewards, such as food or sex, potentially leading to compulsive engagement in behaviours such as binge eating or hypersexuality. In addition to induction by natural rewards, ΔFosB is also linked to impulsivity, with highly impulsive animals displaying high levels of ΔFosB in the nucleus accumbens shell.70

heterogeneous construct manifested by a tendency towards rapid, ill considered, disinhibited choices. Impulsivity can be broadly divided into decisional forms, including delay discounting (preference of a small immediate over a larger delayed reward), reduced sensitivity to adverse outcomes (negative prediction errors) during learning, reflection impulsivity (rapid decision making), risk taking, and response conflict (slowing and errors with competing responses), and motor forms such as response inhibition (inhibition of a prepotent response whereby individuals are biased to make a specific response because it is repeated or more frequent).

Multiple lines of evidence show that patients with Parkinson’s disease and impulse control disorders have enhanced delay discounting, whereby individuals have a preference for a small immediate reward over a larger delayed reward. This enhancement is observed in patients with Parkinson’s disease and impulse control disorders, relative to medicated controls with Parkinson’s disease.71–73 Both Parkinson’s disease pathology and dopamine agonists appear to have independent effects in enhancing delay discounting. In a study using intracranial self-stimulation as the positive reinforcer, whereby rodents can self-administer a reward via electrical stimulation of the medial forebrain bundle, 6-OHDA lesioned rats had increased delay discounting relative to sham controls.74 These findings concur with those from never-medicated patients with Parkinson’s disease who showed elevated
delay discounting relative to healthy controls, which normalised with dopaminergic medications. In a large multicentre case-control study,7 patients with Parkinson’s disease with compulsive shopping and a gambling disorder had elevated delay discounting, but patients with Parkinson’s disease with compulsive eating or sexual behaviours did not. Impulsive choice usually has a magnitude effect whereby less impulsive choices accompany an increasing reward magnitude. This magnitude effect in delay discounting was more pronounced in patients with Parkinson’s disease and impulse control disorders than patients with Parkinson’s disease without impulse control disorders.7

Patients with Parkinson’s disease and impulse control disorders have greater delay discounting, associated with increased baseline dopaminergic function in the anterior putamen, as measured using ¹⁸F-fluorodopa, than patients with Parkinson’s disease without impulse control disorders,8 an effect that might reflect compensatory mechanisms. Thus, dissociable influences from different striatal regions or dopamine tone might influence delay discounting in a U-shaped manner.9

Reflection impulsivity—which rapid decision making or accumulation of little evidence before making a decision—was higher in medicated patients with Parkinson’s disease and impulse control disorders than those without impulse control disorders, but similar to that reported for people with drug misuse disorders.10 In individuals with Parkinson’s disease, dopamine agonists (but not levodopa or DBS) increased reflection impulsivity.10 By contrast, rapid decisions in the context of conflict were unimpaired in medicated patients with Parkinson’s disease and impulse control disorders, as assessed by the Simon task11 and the Stroop interference task.12 However, more Stroop interference test impairments in patients with Parkinson’s disease with compulsive sexual or eating behaviours were observed than in patients with Parkinson’s disease with a gambling disorder.13 Patients with Parkinson’s disease with gambling disorders also have more low frequency activity in the subthalamic nucleus during risk-taking or conflictual choices than do patients with Parkinson’s disease without impulse control disorders.14

Rodent models of Parkinson’s disease reveal an effect of both parkinsonian lesions and individual impulsivity traits on motor impulsivity. In rats, α-synuclein-induced nigrostriatal neurodegeneration increases waiting impulsivity (a tendency to respond too early) and impulsive action compared with sham controls.15 Pramipexole increased waiting impulsivity and impulsive action in both sham and lesioned rats, but its effect in lesioned rats was enhanced in rats with prelesion impulsivity traits.16 By contrast to rodent studies and to impairments in decisional impulsivity in human beings, either no impairments or improvements are observed in motor impulsivity in patients with Parkinson’s disease and impulse control disorders relative to those without impulse control disorders. Medicated patients with Parkinson’s disease and impulse control disorders either do not show impairment or show improvement in motor-response inhibition.17,18

By contrast, patients with Parkinson’s disease with levodopa-induced dyskinesias display altered motor inhibition compared with those without levodopa-induced dyskinesias.19

Thus, impulse control disorders are associated with higher decisional impulsivity (delay discounting, risk taking, and reflection impulsivity), whereas levodopa-induced dyskinesias are associated with impaired motor inhibition.

Risk and ambiguity
Pathological behavioural choices are associated with decisions anticipating a positive reward and negative financial, social, or occupational consequences with either known (risk) or unknown probabilities (ambiguity). The evaluation of risk involves the representation of anticipated reward and loss values and their integration, the representation of probability, and learning from feedback. Results of rodent and human studies suggest that dopamine agonists enhance risk taking. In rodents, striatal D₂-containing neurons are activated in response to unfavourable events that result from risky decisions, and timed amplification of this activity during the decision period decreases risk-taking choices.20 D₁ or D₂ stimulation during decision making respectively increases or decreases the value of an action for choosing between different actions, perhaps reflecting an integration of prospective gains and losses in the same striatal networks that are involved in learning.13

In rodent studies using intracranial self-stimulation of the medial forebrain bundle,11,12 pramipexole has been shown to increase risk taking. The effects were dose dependent, such that higher chronically administered doses enhanced risk taking in all rats, with no effect of the 6-OHDA lesion.21 whereas lower chronic doses produced risk taking only in a proportion of 6-OHDA lesioned rats.22 In human beings, dopamine agonists increase risk taking in both patients with Parkinson’s disease with and without impulse control disorders, and patients with a gambling disorder have the most frequent risk-taking behaviours.23 In a study using a task selecting between safe and risky choices, patients with Parkinson’s disease and impulse control disorders had increased risk taking, particularly to gain, but not loss anticipation, irrespective of medication status.9 Similarly, dopamine agonists increased risk taking under ambiguity in patients with Parkinson’s disease and impulse control disorders compared with those who were not taking dopamine agonists.9 Opposite effects were observed in patients with Parkinson’s disease without impulse control disorders,24 as determined by the Balloon Analogue Risk Task (BART), whereby patients inflate a balloon accumulating reward, but with an increasing likelihood of the balloon bursting (ie, the punishment).
The ventral striatum is involved in processing risk probability and representation of the anticipation of gain and loss values in a bidirectional manner, with increased activity for gains and decreased activity for losses. Patients with Parkinson’s disease and impulse control disorders on dopamine agonists show lower ventral striatal activity to the risk prospect (ie, the difference between possible gain and loss outcomes) than those off dopamine agonists. Similarly, patients with Parkinson’s disease and impulse control disorders show lower ventral striatal activity to the BART than patients with Parkinson’s disease without impulse control disorders (appendix). Patients with Parkinson’s disease and impulse control disorders on dopamine agonists have lower orbitofrontal cortex and anterior insular activity to risk representation than when off dopamine agonists, with high activity to risk representation in patients without impulse control disorders. These findings suggest possible impairments in the representation of risk or the dynamic capacity to track changes in risk variance (the difference between possible gain and loss outcomes).

Taken together, findings on delay discounting, reflection impulsivity, and risk taking highlight impairments across tasks that require a mapping of action outcome representations, particularly under ambiguity. Risk assessment in particular requires the capacity to represent possible rewards and losses; impairments in the representation of rewards and losses will also influence risk biases.

**Treatment of impulse control disorders**

The symptoms of impulse control disorders improve after decreasing or discontinuing dopamine agonist treatment in patients with Parkinson’s disease. However, the replacement of dopamine agonists with levodopa for the treatment of motor symptoms is not tolerable for many patients. Patients with Parkinson’s disease and impulse control disorders are at an increased risk for developing dopamine agonist withdrawal syndrome—a syndrome characterised by craving, autonomic, and psychiatric symptoms—compared with patients with Parkinson’s disease without an impulse control disorder. Several randomised controlled studies have been done with the overall aim of managing addictive behaviours in patients with Parkinson’s disease. Amantadine, a dopaminergic and glutamatergic modulator, was effective at reducing symptoms of impulse control disorders in patients with Parkinson’s disease and levodopa-induced dyskinesias relative to placebo, but amantadine has also been shown to be associated with an increased risk for impulse control disorders in a multicentre study. Naltrexone, an opioid antagonist, decreased symptoms in patients with Parkinson’s disease, relative to placebo, but did not improve global symptom severity. Cognitive behavioural therapy has been shown to improve global symptom severity in patients with Parkinson’s disease and impulse control disorders, relative to individuals on a waiting list for therapy.

In 6-OHDA-lesioned rats, the atypical antidepressant mirtazapine reduced pramipexole-induced risk-taking behaviours without interfering with the motor improvements afforded by the dopamine agonist. Two small uncontrolled studies (both n=8) in patients with Parkinson’s disease and impulse control disorders indicated that continuous delivery of levodopa might improve impulse-control symptoms and compulsive medication use. Continuous delivery of apomorphine can improve pre-existing impulse control disorders but can result in the development of novel or additional addictive behaviours. In case reports, the antipsychotic clozapine has been reported to be potentially useful in the treatment of impulse control disorders. Clearly, further studies on pharmacotherapies for impulse control disorders are warranted.

Prospective studies of DBS of the subthalamic nucleus, which allows a decrease or discontinuation of dopaminergic medication, have shown that it can improve impulse control disorders, but DBS can also induce specific forms of impulsivity, such responding more quickly during high conflict choices, whereby two choices are very similar, evoking competing responses. Retrospective studies have shown either no difference or worsening of preoperative impulse control disorders in patients who underwent subthalamic nucleus DBS. These differences between prospective and retrospective studies highlight the importance for early identification of patients with presurgical impulse control disorders and careful medication titration, follow-up, and management. Patients with Parkinson’s disease and impulse control disorders are at increased risk of postoperative apathy symptoms and dopamine agonists withdrawal syndrome, relative to those without impulse control disorders.

Although most impulse control disorders improve following DBS, rarely new-onset postoperative addictive behaviours can develop; eating behaviours in particular often seem to remain symptomatic, worsen, or have de-novo onset postoperatively. Potential mechanisms underlying these observations are discussed in panel 3.

Intraoperative physiological recordings in the subthalamic nucleus have provided insights into the mechanisms of impulse control disorders and levodopa-induced dyskinesia. Patients with Parkinson’s disease with these disorders who underwent DBS have been shown to have enhanced low frequency oscillatory activity with cortico-subthalamic coherence compared with those with impulse control disorders and dyskinesias, implicating prefrontal or motor regions, respectively (appendix).

**Conclusions and future directions**

Emerging evidence highlights the overlapping mechanisms underlying impulse control disorders and levodopa-induced dyskinesias in Parkinson’s disease.
and D₄ receptors are warranted. Studies focusing on the behaviours. Further studies that investigate the role of D₃ context of important stimuli, thus facilitating so-called Go interfere with learning from negative outcomes and might enhanced postsynaptic tonic D₂R stimulation might enhance synaptic accumulation and diffusion of striatal DAT and desensitised D₂ autoreceptors might also shift towards relative activation of available D₁R in the area to adequately contribute to reward processing (appendix). In rodent models, Parkinson’s disease enhances the rewarding properties of dopamine agonists and levodopa (figure 2). Impairments in impulsivity in the decisional rather than the motor domains and an emerging role for apathy (eg, anhedonia and motivational deficits) might be related to the relative engagement of ventral versus dorsal

**Panel 3: Differential response to subthalamic stimulation in impulse control disorder**

Deep brain stimulation (DBS) of the subthalamic nucleus can improve impulse control disorders in patients with Parkinson’s disease. Although not all retrospective studies have shown an improvement, long-term improvement of impulse control disorders has been shown in prospective studies. The capacity to decrease the dose or discontinue dopamine agonists probably plays an important role in the improvement of impulse control disorder symptoms. Other potential mechanisms include shifting stimulation towards a continuous rather than pulsatile dopaminergic stimulation, or possibly normalising abnormal low frequency oscillations that have been shown to be enhanced in gambling disorders with conflictual risky choices. However, not all impulse control disorder subtypes respond equally; in particular, pathological eating behaviours might be more likely to not improve, worsen, or have de-novo onset.

Cognitive mechanisms underlying impulse control disorders and the effect of subthalamic nucleus DBS could explain the differential effect of DBS on reward subtypes. Impulse control disorders are impaired in decisional impulsivity such as delay discounting, risk taking, and reflection impulsivity. By contrast, subthalamic nucleus DBS improves delay discounting in rodents. In studies of patients with Parkinson’s disease targeting the motor subthalamic nucleus, stimulation has no clear effect on delay discounting or reflection impulsivity and possibly decreases risk-taking behaviours. Subthalamic nucleus DBS in patients with Parkinson’s disease and impulse control disorders can either improve or not affect these cognitive functions. Impulse control disorders are associated with either an improvement or no difference in motor response inhibition. Subthalamic nucleus DBS also has a mixed effect on response inhibition. Differential effects from stimulation of anteromesial limbic and cognitive subregions of the subthalamic nucleus versus motor subregions can also result in differential expression of behaviours. A study has shown that stimulation targeting the anterior associative-limbic subthalamic nucleus in obsessive compulsive disorder increases reflection impulsivity and delay discounting, an effect that might be specific to the associative-limbic rather than the motor subthalamic nucleus. Whereas impulse control disorders are characterised by increased decisional impulsivity, subthalamic nucleus stimulation in patients with Parkinson’s disease appears not to affect or to improve decisional impulsivity, although localisation effects (limbic-associative vs motor subthalamic nucleus) could be relevant.

In impulse control disorders, the Stroop conflict interference task and Simon task have been reported to be either no different from controls or more impaired in people with compulsive sexual behaviours or binge eating, relative to those with a gambling disorder. Subthalamic nucleus DBS is most consistently associated with the inability to slow down and greater errors when facing conflict or competing responses. Subthalamic nucleus DBS results in hastened error-prone decisions to conflict. Given the differential Stroop effect in impulse control disorder subtypes, such a cognitive effect might be more relevant to binge eating or compulsive sexual behaviours. In rodents, both subthalamic nucleus lesions and DBS are associated with a shift of reinforcing value (progressive ratio reinforcement and conditioned place preference) from cocaine to food rewards. Both the enhanced reinforcement value of food and hastened error-prone decisions can contribute to postoperative pathological eating behaviours in these rodents.

(appendix). This evidence emphasises the interactions between chronic dopaminergic medications, the neurobiology of Parkinson’s disease, and underlying individual susceptibility.

Chronic dopamine agonist medication is associated with a mild decrease in phasic dopaminergic activity (figure 3), which might lead towards a decrease in goal-directed or motivational responding to less important stimuli. However, in the context of novel, unexpected rewarding stimuli, conditioned cues, or reward anticipation, several mechanisms appear to drive phasic dopaminergic activity. Levodopa enhances dopamine gain, thus increasing stimulus-driven phasic dopaminergic activity. Reduced striatal DAT and desensitised D₂ autoreceptors might enhance synaptic accumulation and diffusion of endogenous dopamine (figures 1, 3). Furthermore, enhanced postsynaptic tonic D₂R stimulation might interfere with learning from negative outcomes and might also shift towards relative activation of available D₁R in the context of important stimuli, thus facilitating so-called Go behaviours. Further studies that investigate the role of D₃ and D₄ receptors are warranted. Studies focusing on the role of augmentation, or the worsening of symptoms after starting therapy, in restless legs syndrome could provide further insights into the interaction between dopaminergic medications, susceptibility, and neuroplasticity.

Within the dorsoventral axis of the striatum, distinct dopaminergic neurons originating from the ventral tegmental area or the substantia nigra pars compacta locally modulate movement and reward with a fast time scale. Such dichotomous dopamine signalling is likely to be compromised during chronic dopaminergic therapy with dopamine agonists, restoring the processing of movement secondary to the loss of neurons in the substantia nigra, but disrupting the capacity of remaining neurons in the ventral tegmental area to adequately contribute to reward processing (appendix). In rodent models, Parkinson’s disease enhances the rewarding properties of dopamine agonists and levodopa (figure 2). Impairments in impulsivity in the decisional rather than the motor domains and an emerging role for apathy (eg, anhedonia and motivational deficits) might be related to the relative engagement of ventral versus dorsal

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The text continues with a discussion on various aspects of impulse control disorders and the role of subthalamic nucleus DBS in Parkinson’s disease, emphasizing the interactions between chronic dopaminergic medications, the neurobiology of Parkinson’s disease, and individual susceptibility. The text also highlights the interactions between chronic dopamine agonist medication and the neurobiology of Parkinson’s disease, as well as the potential implications of these interactions for the development of new therapeutic strategies.
striatal regions. Beyond the striatum, a network including the orbitofrontal cortex, anterior cingulate, and anterior insula is implicated (appendix). The role of Parkinson’s disease-related impulsivity, apathy, and Parkinson’s disease subtypes (eg, genetic or sporadic) as premorbid risk factors, and particularly the role of serotonin and noradrenaline remain to be clarified. Computational models have been applied to unify hypotheses of dopamine function and the balance of reward and loss, and the role of ambiguity in mapping future outcomes. Differences between behavioural subtypes as a function of sex, impulsivity and novelty processing, and the influence of subthalamic nucleus DBS have been demonstrated.

From a clinical perspective, studies extend beyond medication adjustment in the treatment of impulse control disorders, demonstrating potential efficacy of naltrexone, cognitive behavioural therapy, and DBS of the subthalamic nucleus. Large-scale studies are needed to identify individual risk factors and novel therapeutic targets for impulse control disorders.


cit References


44 Seeman P. Parkinson’s disease treatment may cause impulse-control disorders.

43 Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling in Parkinson disease.


38 Steeves TD, Miyasaki J, Zurowski M, et al. Increased striatal dopamine release in Parkinsonian patients with pathological gambling.


33 Smith KM, Xie SX, Weintraub D. Incident impulse control disorder via dopamine D3 receptors.

32 Smith KM, Xie SX, Weintraub D. Incident impulse control disorder via dopamine D3 receptors.

31 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.

30 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.


27 Harden DG, Grace AA. Activation of dopamine cell firing by repeated L-DOPA administration to dopamine-depleted rats: its potential role in mediating the therapeutic response to L-DOPA treatment.


24 Rudebeck PH, Murray EA. The orbitofrontal nucleus: cortical mechanisms for the prediction and evaluation of specific behavioral outcomes.


20 Seeman P. Parkinson’s disease treatment may cause impulse-control disorders.


16 Seeman P. Parkinson’s disease treatment may cause impulse-control disorders.


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