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[1] and impulse control disorders.[2] 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[2] 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 hobbyism), 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),[2] 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,[3,4] 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%).[2] A post-hoc review[5] 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.[6] Both dopamine agonist and levodopa use were independently associated with impulse control disorders in the DOMINION study;[2] 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).[7] Furthermore, longitudinal studies show that dopamine agonists discontinuation or dose reduction can improve impulse control disorders,[8] supporting a dose-dependent association.

The DOMINION study[2] 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.[9] A small study[7] 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,[2] 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 dyskinesias 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 dyskinesias 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 studies[9,11] have identified an increased probability of impulse control disorder and levodopa-induced dyskinesias 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 dyskinesia scores than those without.[9] 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 than 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 D_3 receptor (D_3R) expression in dorsal striatal regions; relative sparing or abberant neurodegeneration of dopaminergic limbic regions

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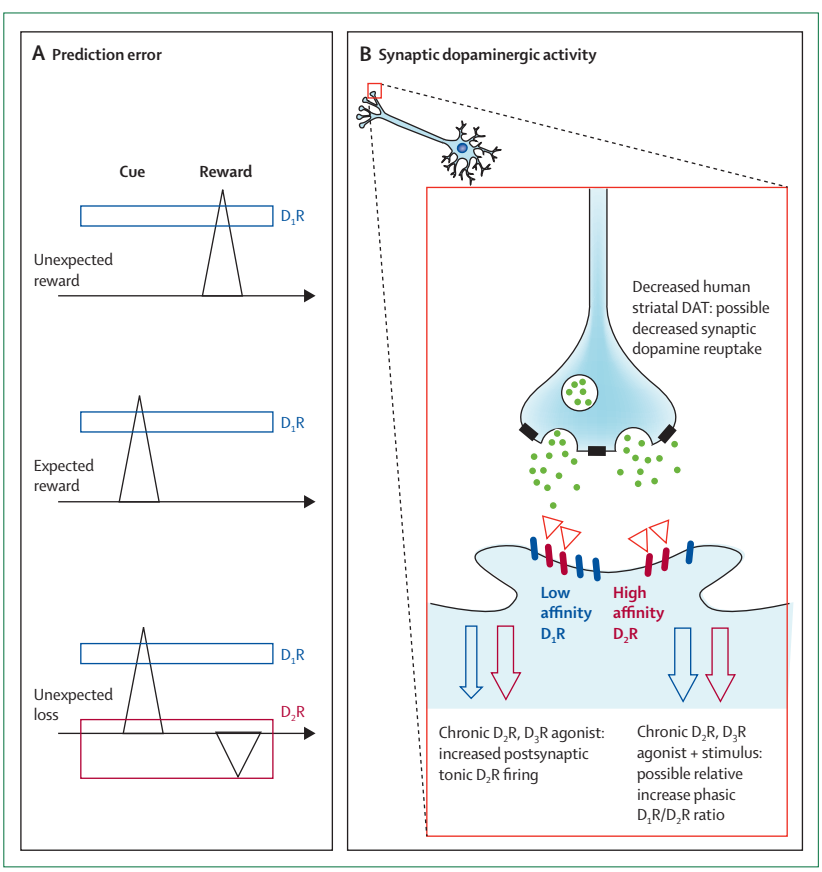

***Figure 1*: Synaptic D_1 and D_2 receptor stimulation and prediction error**
(A) Phasic dopamine increases with unexpected rewards (positive prediction error), which facilitates learning to associate stimuli and actions with reward. Unexpected losses or lack of a reward are associated with a pause or cessation of firing of dopaminergic neurons (negative prediction error), which facilitates learning to avoid associated actions. Tonic dopamine has been postulated to represent an average reward signal relevant to opportunity cost and motivation. Tonic dopamine can also disengage cortical regulation of subcortical systems via a presynaptic action. Phasic dopamine promotes learning from positive outcomes via D_1 receptors (so-called Go pathway) to facilitate movement and promotes learning from negative outcomes via D_2 receptors (so-called NoGo pathway) to inhibit movement.[13] High affinity D_2R might be sensitive to low tonic activity and transient pauses in signalling (negative prediction errors), whereas both low affinity D_1R and D_2R might be sensitive to large phasic dopaminergic bursts (positive prediction errors).[14] Tonic stimulation of D_2 receptors by dopamine agonists might impair the detection of negative prediction errors. (B) Schematic diagram of changes in patients with Parkinson's disease and impulse control disorders on dopamine agonists with decreased striatal dopamine transporter (black square) concentrations. D_2R and D_3R agonists (red triangle) tonically bind to D_2R . Stimulus-induced phasic dopaminergic activity has been hypothesised to shift stimulation of the low affinity postsynpatic D_1R relative to the tonically-stimulated D_2R, promoting so-called Go approach behaviours.[15] DAT=dopamine active transporter. D_1R=dopamine receptor D_1. D_2R=dopamine receptor D_2. D_3R=dopamine receptor D_3.

***Panel 1:* Specificity of ventral striatal subregions and behavioural disorders**

Pharmacological primate studies[16,17] show that different regions in the striatum regulate different behaviours. Local dysfunction induced by microinjections with bicuculline, a $GABA_A$ 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.[16] 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.[18] 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.

See Online for appendix

might be associated with differential motor, cognitive, and limbic effects of dopamine agonist therapy (appendix); and differential involvement of the parkinsonian lesion on striatal subregions might have an effect on the severity and latency of impulse control disorders or levodopa-induced dyskinesias (panel 1; appendix).

Preclinical studies in animal models of Parkinson's disease[19–22] indicate that both dopamine agonists and levodopa have reinforcing effects. Dopamine agonists with high affinity for D_3R receptors and levodopa promote conditioned place-preference (whereby rodents prefer places associated with a reinforcing drug to places associated with a placebo) in several rat models of Parkinson's disease, compared with control littermates (figure 2).[19–21] This outcome was hypothesised to reflect postsynaptic dopamine receptor super-sensitivity because increased sensitivity of dopamine receptors was observed after the concentration of endogenous dopamine was reduced following the degeneration of dopamine neurons.[1,21] The lack of place-preference in lesioned or unlesioned wild-type rodents has also been reported after administration of very high doses of levodopa.[20] The reinforcing property of self-administered pramipexole was not altered by 6-hydroxydopamine (6-OHDA)-induced dopaminergic lesions in rats.[22] In the α-synuclein overexpressing rat model, levodopa decreased the interest of the animals in other non-drug rewards (ie, sweetened water consumption), in a similar way to the effect of psychostimulants.[21]

Studies that focus on other psychiatric symptoms of Parkinson's disease have highlighted the role of Parkinson's disease pathology in impulse control disorders. For example, Parkinson's disease-related apathy might be relevant to their development. Deep brain stimulation (DBS) of the subthalamic nucleus in patients with Parkinson's disease allows for withdrawal of dopaminergic medications, subsequently improving impulse control disorders, but it is associated with new-onset apathy.[23] This apathy responds to the D_2 and D_3 receptor dopamine agonist, piribedil.[24] Additionally, Parkinson's disease apathy is associated with serotonergic deficits of the right anterior caudate and orbitofrontal cortex, and potentially ventral striatal dopaminergic deficits,[25] and with decreased reward sensitivity on termination of dopamine agonist therapy.[26] Therefore, features of Parkinson's disease pathology that influence other non-motor effects of dopamine agonists—eg, neurodegeneration of serotonergic and noradrenergic systems—might be relevant to the development of impulse control disorders.

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 D_2-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 D_2-autoreceptors. After chronic pramipexole treatment, the firing rate of noradrenergic locus coeruleus activity also normalised, but burst activity remained low.[28] By contrast, chronic pramipexole treatment increased the spontaneous firing rate and burst activity of serotonergic dorsal raphe neurons.[28]

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[27] (figure 3B). This enhanced proportion of spontaneously active dopaminergic neurons also appears to be related to D_2 autoreceptor downregulation.[27] Thus, with parkinsonian lesions the dynamic range of dopaminergic neuron activity is preserved to enable responses to stimuli. Chronic levodopa treatment is commonly co-administered with dopamine agonists, and thus dopaminergic neuron firing might be hyper-responsive to stimuli, resulting in an imbalance in stimuli-driving behaviours, a mechanism that is probably relevant to the development of impulse control disorders.

Findings from a small study of patients with Parkinson's disease and impulse control disorders (n=7)[29] using ^{11}C-FLB-457 PET support these preclinical findings. The study showed decreased midbrain D_2 and D_3 autoreceptor sensitivity in participants doing a gambling task, which would promote dopaminergic activity and enhance striatal dopamine release (figure 3).

Further abnormalities of the dopaminergic system in patients with Parkinson's disease and impulse control disorders have been shown at the synaptic level. Reduced concentrations of striatal dopamine transporter (DAT) are consistently reported for these patients,[30,31] and might predate and thus predict susceptibility to the development of impulse control disorders[32,33] (figure 2). Dopamine reuptake via striatal DAT is the primary mechanism by which dopamine is removed from the synapse to terminate its action. Because no clear evidence exists for a structural reduction in dopaminergic terminal density, the low DAT concentrations seen in patients with Parkinson's disease and impulse control disorders might result in increased synaptic accumulation, diffusional distance, and duration of action for dopamine. Low putaminal DAT activity[34] and high putaminal dopamine turnover[35] are also risk factors for levodopa-induced dyskinesias, suggesting that functional or structural features of remaining putaminal dopaminergic terminals at treatment initiation contribute to the subsequent development of levodopa-induced dyskinesias.

Although a ^{11}C-raclopride PET study[36] showed lower striatal D_2R or D_3R concentrations during a motor control task in patients with Parkinson's disease with impulse control disorders than those without impulse control disorders, no evidence of lower striatal D_2R or D_3R concentrations at baseline have been observed in subsequent studies.[36,37] Enhanced stimulus-related physiological dopaminergic activity might have an effect on excessive ventral striatal dopamine transmission in patients with Parkinson's disease and impulse control disorders. In a study using ^{11}C-raclopride PET imaging,[36] unmedicated patients with Parkinson's disease and impulse control disorders had heightened ventral striatal dopamine release to heterogeneous reward-related visual cues relative to neutral cues (appendix). This effect was observed both off medication and after a levodopa challenge, with no effect of levodopa itself.[36] 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[38] (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.[39] 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,[40] consistent with animal studies.[27] By contrast, sensitised responses to a levodopa challenge did not occur in patients with Parkinson's disease and impulse control disorders,[36] suggesting that the adaptive processes for these disorders might be distinct from those associated with levodopa-induced sensitisation. In a study using functional MRI,[41] 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, whereby enhanced desire correlated with functional MRI activity in this saliency network.[41]

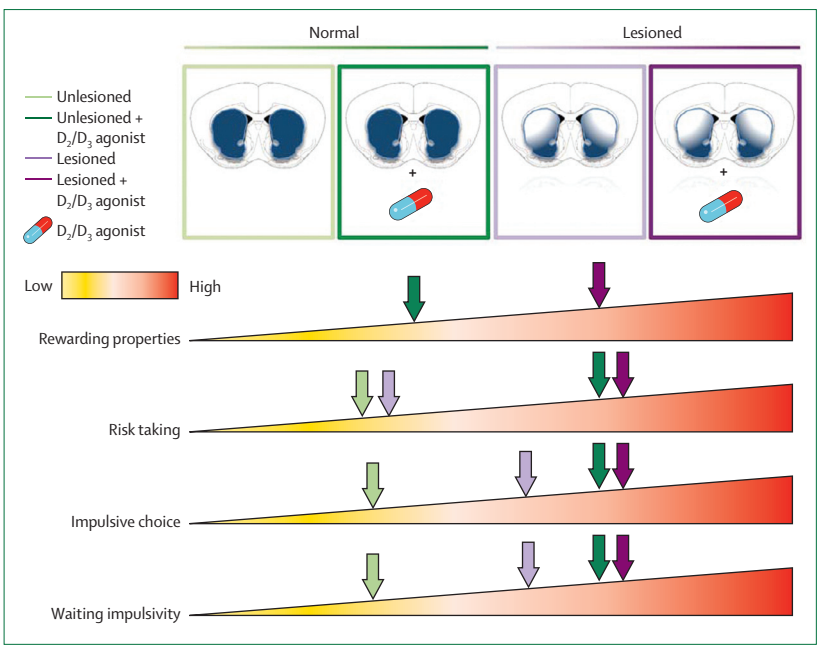

***Figure 2*: Effect of nigrostriatal lesions and D_2 or D_3 agonists on the rewarding properties of dopamine replacement therapy**

Nigrostriatal degeneration results in an increase in the rewarding properties of D_2 and D_3 agonists. The nigrostriatal lesion might also contribute to the pathophysiology of impulse control disorders by increasing impulsivity. Exposure to D_2 or D_3 agonists contributes to increased risk taking and impulsivity.

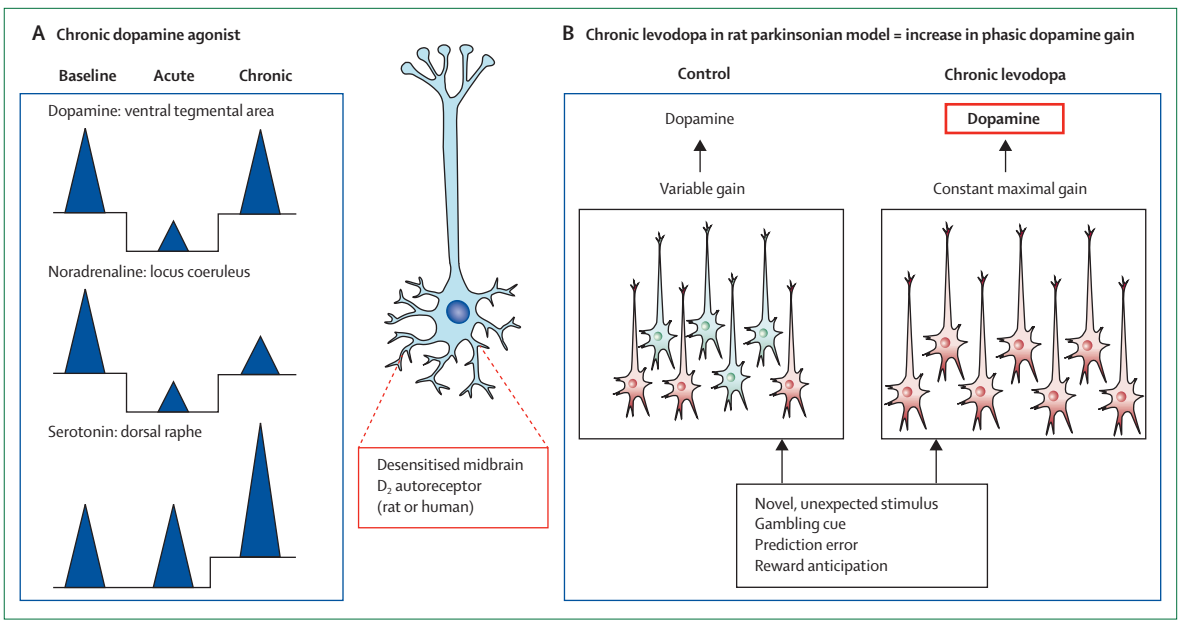

***Figure 3*: Potential effects of chronic dopaminergic medications on presynaptic neuronal function**
(A) Subchronic D_2 and D_3 receptor agonist stimulation shows a range of acute and chronic effects on the neuronal tonic (lines) and burst firing (blue triangles) activity of the dopaminergic ventral tegmental area, the noradrenergic locus coeruleus, and the serotonergic dorsal raphe. (B) Chronic levodopa administration in a parkinsonian rodent model is associated with an increase in the proportion of spontaneously firing neurons (red neurons) capable of eliciting a phasic response to a salient stimulus. This mechanism is mediated by desensitisation of D_2 autoreceptors. Red boxes indicate greater endogenous synaptic dopamine release. Image created using data from Harden and Grace.[27]

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 D_3R was initially investigated following the observation that impulse control disorders were associated with chronic pramipexole treatment, a dopamine agonist with high affinity for D_2 and D_3 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 D_3 partial agonist aripiprazole in the pathogenesis of impulse control disorders.[43] A greater association was observed between addicitive behaviours and dopamine agonists with higher D_3R selectivity (eg, pramipexole and ropinirole) than those with lower D_3R selectivity.[44] Under physiological conditions, D_3R is predominantly found in the ventral striatum; however, in parkinsonian models, levodopa exposure results in de-novo expression of D_3R in the denervated dorsal striatum, and D_3R expression levels correlate with the severity of levodopa-induced dyskinesias. The D_3R is implicated in motivation, physiological and behavioural responses to drug cues, and novelty-seeking behaviours,[45] and is co-expressed with D_1R in ventral striatal medium spiny neurons, whereby these receptors interact via intramembrane crosstalk. D_3R antagonism allows the restoration of normal D_1R numbers at the plasma membrane in dyskinetic rats, highlighting the importance of the D_1R–D_3R interaction in levodopa-induced dyskinesias. The role of D_3R in gambling disorders in the general population has been shown using ^{11}C-PHNO PET imaging.[46] However, the role of D_3R in patients with Parkinson's disease with impulse control disorders is less clear; a study of ^{11}C-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 ^{18}F-fluorodopa uptake in the medial orbitofrontal cortex, suggesting enhanced monoaminergic activity (appendix).[50] In a study using a card gambling task and $^{15}H_2O$-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[51] (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.[52,53] 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.[1] Enhanced D_1 stimulation causes widespread molecular adaptations in striatal medium spiny neurons.[1] Transcriptome analysis of rodent models of levodopa-induced dyskinesia shows altered expression of genes involved in transcription, signal transduction, calcium homoeostasis, synaptic transmission or plasticity, and synaptic structure.[1] 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.[54] 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.[13] 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 D_2Rs[71] 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,[15] 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.[15] In a study using a Q-learning reinforcement learning algorithm,[15] 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 D_1R neurons relative to the so-called NoGo D_2R neurons tonically activated by dopamine agonists[15] (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).[13] In another study,[72] 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[72] 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.[72] Not all studies on instrumental learning have been consistent;[73] 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

Panel 2: Genetics and epigenetics

Several studies have investigated genetic susceptibility to levodopa-induced dyskinesias in Parkinson's disease, typically implicating genes related to dopamine transmission, but a consensus remains elusive. Impulse control disorders remain largely uninvestigated.[55] In levodopa-induced dyskinesias, the *TaqIA* polymorphism in the *D2R* gene can increase the risk of developing motor fluctuations, whereas a single nucleotide polymorphisms in the *SL6A3* gene, coding for the dopamine transporter, increases the latency to levodopa-induced dyskinesia onset.[56] The Val158Met polymorphism in the *COMT* gene[57] and the Val66Met polymorphism in the *BDNF* gene[58] might be linked to an increased risk or earlier occurrence of levodopa-induced dyskinesias,but subsequent studies did not replicate associations between *BDNF* gene polymorphisms and levodopa-induced dyskinesias.[56,59] None of these sequence variants was found to be associated with impulse control disorders in patients with Parkinson's disease.[60,61] Notably, some of these polymorphisms might be linked to drug misuse or behavioural traits relevant to impulse control disorders (eg, impulsivity and risk taking) in the general population.[62] A polymorphism in the *D3R* p.S9G variant has been linked to both levodopa-induced dyskinesias and impulse control disorders in patients with Parkinson's disease; carriers of the AA genotype had a shorter latency to develop diphasic and peak-dose levodopa-induced dyskinesias, 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.[63] 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,[1] 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.[9,74–76] 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.[77] 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.[78]

In a large multicentre case-control study,[9] 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.[9]

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 ^{18}F-fluorodopa, than patients with Parkinson's disease without impulse control disorders,[79] 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.[80]

Reflection impulsivity—ie, 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.[81] In individuals with Parkinson's disease, dopamine agonists (but not levodopa or DBS) increased reflection impulsivity.[82] 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 task[83] and the Stroop interference task.[84] 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.[85] 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.[86]

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.[87] Pramipexole increased waiting impulsivity and impulsive action in both sham and lesioned rats, but its effect in lesioned rats was enhanced in rats with pre-lesion impulsivity traits.[87] 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.[74,88] By contrast, patients with Parkinson's disease with levodopa-induced dyskinesias display altered motor inhibition compared with those without levodopa-induced dyskinesias.[89]

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 D_2-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.[90] D_1 or D_2 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,[91,92] 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,[92] whereas lower chronic doses produced risk taking only in a proportion of 6-OHDA lesioned rats.[91] 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.[93] 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.[94] 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.[95] Opposite effects were observed in patients with Parkinson's disease without impulse control disorders,[95] 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[96] on dopamine agonists show lower ventral striatal activity to the risk prospect (ie, the difference between possible gain and loss outcomes) than do 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[94] (appendix). Patients with Parkinson's disease and impulse control disorders on dopamine agonists have lower orbitofrontal cortex and anterior insular activity to risk representation[96] than when off dopamine agonists, with high acitivity 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.[97] 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.[98] 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 a gambling disorders relative to placebo,[99] but amantadine has also been shown to be associated with an increased risk for impulse control disorders in a multicentre study.[100] Naltrexone, an opioid antagonist, decreased symptoms in patients with Parkinson's disease, relative to placebo, but did not improve global symptom severity.[101] Cognitive behavioural therapy has been shown to improve global symptom severity[102] 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.[91] 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.[103,104] Continuous delivery of apomorphine can improve pre-existing impulse control disorders but can result in the development of novel or additional addictive behaviours.[104] In case reports,[105,106] 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,[23,107] 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.[108] Retrospective studies[109,110] 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.[23,98] 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.[111] 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 contol disorders and dyskinesias, implicating prefrontal or motor regions, respectively[115] (appendix).

Conclusions and future directions

Emerging evidence highlights the overlapping mechanisms underlying impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease

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.[23,107] 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.[86] 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.[111]

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.[108] 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[112] 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.[113] 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.[114] 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 D_2 autoreceptors might enhance synaptic accumulation and diffusion of endogenous dopamine (figures 1, 3). Furthermore, enhanced postsynaptic tonic D_2R stimulation might interfere with learning from negative outcomes and might also shift towards relative activation of available D_1R in the context of important stimuli, thus facilitating so-called Go behaviours. Further studies that investigate the role of D_3 and D_4 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

Search strategy and selection criteria

We searched MEDLINE using the following terms: ("Parkinson" OR "dopamine agonist" OR "levodopa") AND ("impulse control disorder" OR "impulsivity" OR "addiction" OR "dyskinesia") limited to articles published in English between Sept 3, 2011, and Sept 3, 2016. The abstracts were reviewed for relevant manuscripts.

striatal regions.[116] 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,[13] and the role of ambiguity in mapping future outcomes.[97] 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.

Contributors

VV, P-OF, and TCN did the literature search, created the figures, and wrote the first draft. EB, MJF, AAG, JO, MR-O, and VS-F contributed to writing and editing the manuscript.

Declaration of interests

VV is a Medical Research Council Senior Fellow and has been an expert witness on court proceedings involving dopamine agonists. EB receives grants from the Michael J Fox Foundation, Agence Nationale de la Recherche, and France Parkinson, and personal fees from Motac Neuroscience, and Motac Holdings. Motac Neuroscience is a contract research organisation providing services for the pharmaceutical and biotechnology industries. TCN receives grants from the Michael J Fox Foundation, the National Center for Responsible Gaming, and the National Institutes of Health. AAG receives grants from Janssen, grants and personal fees from Lundbeck, and personal fees from Johnson & Johnson, Pfizer, Alkermes, Otsuka, Autofony, Roche, Ascubio, Lilly, and Takeda. MJF receives personal fees from F. Hoffman La Roche. JO received honorarium for lecturing from GlaxoSmithKline, Lundbeck, UCB Pharma, Teva Neuroscience, and Boehringer Ingelheim, and recieves grants from the Spanish Ministry of Education and the European Union. P-OF, V-SF, and MR-O declare no competing interests.

References

1 Bastide MF, Meissner WG, Picconi B, et al. Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease. *Prog Neurobiol* 2015; **132:** 96–168.

2 Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 2010; **67:** 589–95.

3 Voon V, Hassan K, Zurowski M, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. *Neurology* 2006; **67:** 1254–57.

4 Voon V, Hassan K, Zurowski M, et al. Prospective prevalence of pathologic gambling and medication association in Parkinson disease. *Neurology* 2006; **66:** 1750–52.

5 Antonini A, Chaudhuri KR, Boroojerdi B, et al. Impulse control disorder related behaviours during long-term rotigotine treatment: a post hoc analysis. *Eur J Neurol* 2016; **23:** 1556–65.

6 Rizos A, Sauerbier A, Antonini A, et al, for the EUROPAR and the IPMDS Non-Motor-PD-Study Group. A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists. *Eur J Neurol* 2016; **23:** 1255–61.

7 Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. *Mov Disord* 2013; **28:** 327–33.

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

9 Voon V, Sohr M, Lang AE, et al. Impulse control disorders in parkinson disease: a multicenter case–control study. *Ann Neurol* 2011; **69:** 986–96.

10 Warren Olanow C, Kieburtz K, Rascol O, et al. Factors predictive of the development of levodopa-induced dyskinesia and wearing-off in Parkinson's disease. *Mov Disord* 2013; **28:** 1064–71.

11 Evans AH, Katzenschlager R, Paviour D, et al. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. *Mov Disord* 2004; **19:** 397–405.

12 Voon V, Schoerling A, Wenzel S, et al. Frequency of impulse control behaviours associated with dopaminergic therapy in restless legs syndrome. *BMC Neurol* 2011; **11:** 117.

13 Collins AG, Frank MJ. Opponent actor learning (OpAL): modeling interactive effects of striatal dopamine on reinforcement learning and choice incentive. *Psychol Rev* 2014; **121:** 337–66.

14 Goto Y, Grace AA. Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. *Nat Neurosci* 2005; **8:** 805–12.

15 Voon V, Pessiglione M, Brezing C, et al. Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. *Neuron* 2010; **65:** 135–42.

16 Sgambato-Faure V, Worbe Y, Epinat J, Feger J, Tremblay L. Cortico-basal ganglia circuits involved in different motivation disorders in non-human primates. *Brain Struct Funct* 2016; **221:** 345–64.

17 Tremblay L, Worbe Y, Thobois S, Sgambato-Faure V, Feger J. Selective dysfunction of basal ganglia subterritories: From movement to behavioral disorders. *Mov Disord* 2015; **30:** 1155–70.

18 Beaudoin-Gobert M, Epinat J, Metereau E, et al. Behavioural impact of a double dopaminergic and serotonergic lesion in the non-human primate. *Brain* 2015; **138:** 2632–47.

19 Riddle JL, Rokosik SL, Napier TC. Pramipexole- and methamphetamine-induced reward-mediated behavior in a rodent model of Parkinson's disease and controls. *Behav Brain Res* 2012; **233:** 15–23.

20 Zengin-Toktas Y, Authier N, Denizot H, et al. Motivational properties of D2 and D3 dopamine receptors agonists and cocaine, but not with D1 dopamine receptors agonist and L-dopa, in bilateral 6-OHDA-lesioned rat. *Neuropharmacology* 2013; **70:** 74–82.

21 Engeln M, Fasano S, Ahmed SH, et al. Levodopa gains psychostimulant-like properties after nigral dopaminergic loss. *Ann Neurol* 2013; **74:** 140–44.

22 Engeln M, Ahmed SH, Vouillac C, Tison F, Bezard E, Fernagut PO. Reinforcing properties of pramipexole in normal and parkinsonian rats. *Neurobiol Dis* 2013; **49:** 79–86.

23 Lhommee E, Klinger H, Thobois S, et al. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. *Brain* 2012; **135:** 1463–77.

24 Thobois S, Lhommee E, Klinger H, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain* 2013; **136:** 1568–77.

25 Maillet A, Krack P, Lhommee E, et al. The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease. *Brain* 2016; **139:** 2486–502.

26 Muhammed K, Manohar S, Ben Yehuda M, et al. Reward sensitivity deficits modulated by dopamine are associated with apathy in Parkinson's disease. *Brain* 2016; **139:** 2706–21.

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. *J Neurosci* 1995; **15:** 6157–66.

28 Chernoloz O, El Mansari M, Blier P. Sustained administration of pramipexole modifies the spontaneous firing of dopamine, norepinephrine, and serotonin neurons in the rat brain. *Neuropsychopharmacology* 2009; **34:** 651–61.

29 Ray NJ, Miyasaki JM, Zurowski M, et al. Extrastriatal dopaminergic abnormalities of DA homeostasis in Parkinson's patients with medication-induced pathological gambling: a [11C] FLB-457 and PET study. *Neurobiol Dis* 2012; **48:** 519–25.

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. *Neurobiol Dis* 2010; **39:** 98–104.

31 Voon V, Rizos A, Chakravartty R, et al. Impulse control disorders in Parkinson's disease: decreased striatal dopamine transporter levels. *J Neurol Neurosurg Psychiatry* 2014; **85:** 148–52.

32 Smith KM, Xie SX, Weintraub D. Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. *J Neurol Neurosurg Psychiatry* 2015; **87:** 864–70.

33 Vriend C, Nordbeck AH, Booij J, et al. Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease. *Mov Disord* 2014; **29:** 904–11.

34 Hong JY, Oh JS, Lee I, et al. Presynaptic dopamine depletion predicts levodopa-induced dyskinesia in de novo Parkinson disease. *Neurology* 2014; **82:** 1597–604.

35 Lohle M, Mende J, Wolz M, et al. Putaminal dopamine turnover in de novo Parkinson disease predicts later motor complications. *Neurology* 2016; **86:** 231–40.

36 O'Sullivan SS, Wu K, Politis M, et al. Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. *Brain* 2011; **134:** 969–78.

37 Wu K, Politis M, O'Sullivan SS, et al. Single versus multiple impulse control disorders in Parkinson's disease: an (1)(1)C-raclopride positron emission tomography study of reward cue-evoked striatal dopamine release. *J Neurol* 2015; **262:** 1504–14.

38 Steeves TD, Miyasaki J, Zurowski M, et al. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. *Brain* 2009; **132:** 1376–85.

39 Joutsa J, Johansson J, Niemela S, et al. Mesolimbic dopamine release is linked to symptom severity in pathological gambling. *Neuroimage* 2012; **60:** 1992–99.

40 Evans AH, Pavese N, Lawrence AD, et al. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. *Ann Neurol* 2006; **59:** 852–58.

41 Politis M, Loane C, Wu K, et al. Neural response to visual sexual cues in dopamine treatment-linked hypersexuality in Parkinson's disease. *Brain* 2013; **136:** 400–11.

42 Djamshidian A, O'Sullivan SS, Wittmann BC, Lees AJ, Averbeck BB. Novelty seeking behaviour in Parkinson's disease. *Neuropsychologia* 2011; **49:** 2483–88.

43 Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. *JAMA Intern Med* 2014; **174:** 1930–33.

44 Seeman P. Parkinson's disease treatment may cause impulse-control disorder via dopamine D3 receptors. *Synapse* 2015; **69:** 183–89.

45 Sokoloff P, Le Foll B. The dopamine D3 receptor, a quarter century later. *Eur J Neurosci* 2016; published online Sept 7. DOI:10.1111/ejn.13390.

46 Boileau I, Payer D, Chugani B, et al. The D2/3 dopamine receptor in pathological gambling: a positron emission tomography study with [11C]-(+)-propyl-hexahydro-naphtho-oxazin and [11C]raclopride. *Addiction* 2013; **108:** 953–63.

47 Payer DE, Guttman M, Kish SJ, et al. [(1)(1)C]-(+)-PHNO PET imaging of dopamine D(2/3) receptors in Parkinson's disease with impulse control disorders. *Mov Disord* 2015; **30:** 160–66.

48 Kolling N, Behrens T, Wittmann MK, Rushworth M. Multiple signals in anterior cingulate cortex. *Curr Opin Neurobiol* 2016; **37:** 36–43.

49 Rudebeck PH, Murray EA. The orbitofrontal oracle: cortical mechanisms for the prediction and evaluation of specific behavioral outcomes. *Neuron* 2014; **84:** 1143–56.

50 Joutsa J, Martikainen K, Niemela S, et al. Increased medial orbitofrontal [18F]fluorodopa uptake in Parkinsonian impulse control disorders. *Mov Disord* 2012; **27:** 778–82.

51 van Eimeren T, Pellecchia G, Cilia R, et al. Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. *Neurology* 2010; **75:** 1711–16.

52 Carriere N, Lopes R, Defebvre L, Delmaire C, Dujardin K. Impaired corticostriatal connectivity in impulse control disorders in Parkinson disease. *Neurology* 2015; **84:** 2116–23.

53 Cilia R, Cho SS, van Eimeren T, et al. Pathological gambling in patients with Parkinson's disease is associated with fronto-striatal disconnection: a path modeling analysis. *Mov Disord* 2011; **26:** 225–33.

54 Bastide MF, Bido S, Duteil N, Bezard E. Striatal NELF-mediated RNA polymerase II stalling controls l-dopa induced dyskinesia. *Neurobiol Dis* 2016; **85:** 93–98.

55 Jimenez-Urbieta H, Gago B, de la Riva P, Delgado-Alvarado M, Marin C, Rodriguez-Oroz MC. Dyskinesias and impulse control disorders in Parkinson's disease: from pathogenesis to potential therapeutic approaches. *Neurosci Biobehav Rev* 2015; **56:** 294–314.

56 Kaplan N, Vituri A, Korczyn AD, et al. Sequence variants in SLC6A3, DRD2, and BDNF genes and time to levodopa-induced dyskinesias in Parkinson's disease. *J Mol Neurosci* 2014; **53:** 183–88.

57 de Lau LM, Verbaan D, Marinus J, Heutink P, van Hilten JJ. Catechol-O-methyltransferase Val158Met and the risk of dyskinesias in Parkinson's disease. *Mov Disord* 2012; **27:** 132–35.

58 Foltynie T, Cheeran B, Williams-Gray CH, et al. BDNF val66met influences time to onset of levodopa induced dyskinesia in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2009; **80:** 141–44.

59 Cheshire P, Bertram K, Ling H, et al. Influence of single nucleotide polymorphisms in COMT, MAO-A and BDNF genes on dyskinesias and levodopa use in Parkinson's disease. *Neurodegener Dis* 2014; **13:** 24–28.

60 Lee JY, Lee EK, Park SS, et al. Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. *Mov Disord* 2009; **24:** 1803–10.

61 Vallelunga A, Flaibani R, Formento-Dojot P, Biundo R, Facchini S, Antonini A. Role of genetic polymorphisms of the dopaminergic system in Parkinson's disease patients with impulse control disorders. *Parkinsonism Relat Disord* 2012; **18:** 397–99.

62 Cilia R, van Eimeren T. Impulse control disorders in Parkinson's disease: seeking a roadmap toward a better understanding. *Brain Struct Funct* 2011; **216:** 289–99.

63 Kraemmer J, Smith K, Weintraub D, et al. Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2016; **87:** 1106–11.

64 Bastide MF, Dovero S, Charron G, et al. Immediate-early gene expression in structures outside the basal ganglia is associated to l-DOPA-induced dyskinesia. *Neurobiol Dis* 2014; **62:** 179–92.

65 Engeln M, Bastide MF, Toulme E, et al. Selective inactivation of striatal FosB/ΔFosB-expressing neurons alleviates L-dopa-induced dyskinesia. *Biol Psychiatry* 2014; **79:** 354–61.

66 Fasano S, Bezard E, D'Antoni A, et al. Inhibition of Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1) signaling in the striatum reverts motor symptoms associated with L-dopa-induced dyskinesia. *Proc Natl Acad Sci USA* 2010; **107:** 21824–29.

67 Engeln M, Ahmed SH, Vouillac C, Tison F, Bezard E, Fernagut PO. Reinforcing properties of Pramipexole in normal and parkinsonian rats. *Neurobiol Dis* 2012; **49:** 79–86.

68 Pitchers KK, Vialou V, Nestler EJ, Laviolette SR, Lehman MN, Coolen LM. Natural and drug rewards act on common neural plasticity mechanisms with DeltaFosB as a key mediator. *J Neurosci* 2013; **33:** 3434–42.

69 Beloate LN, Weems PW, Casey GR, Webb IC, Coolen LM. Nucleus accumbens NMDA receptor activation regulates amphetamine cross-sensitization and deltaFosB expression following sexual experience in male rats. *Neuropharmacology* 2016; **101:** 154–64.

70 Velazquez-Sanchez C, Ferragud A, Moore CF, Everitt BJ, Sabino V, Cottone P. High trait impulsivity predicts food addiction-like behavior in the rat. *Neuropsychopharmacology* 2014; **39:** 2463–72.

71 Chernoloz O, El Mansari M, Blier P. Long-term administration of the dopamine D3/2 receptor agonist pramipexole increases dopamine and serotonin neurotransmission in the male rat forebrain. *J Psychiatry Neurosci* 2012; **37:** 113–21.

72 Piray P, Zeighami Y, Bahrami F, Eissa AM, Hewedi DH, Moustafa AA. Impulse control disorders in Parkinson's disease are associated with dysfunction in stimulus valuation but not action valuation. *J Neurosci* 2014; **34:** 7814–24.

73 Djamshidian A, O'Sullivan SS, Lees A, Averbeck BB. Effects of dopamine on sensitivity to social bias in Parkinson's disease. *PLoS One* 2012; **7:** e32889.

74 Leroi I, Barraclough M, McKie S, et al. Dopaminergic influences on executive function and impulsive behaviour in impulse control disorders in Parkinson's disease. *J Neuropsychol* 2013; **7:** 306–25.

75 Housden CR, O'Sullivan SS, Joyce EM, Lees AJ, Roiser JP. Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. *Neuropsychopharmacology* 2010; **35:** 2155–64.

76 Voon V, Reynolds B, Brezing C, et al. Impulsive choice and response in dopamine agonist-related impulse control behaviors. *Psychopharmacology (Berl)* 2010; **207:** 645–59.

77 Tedford SE, Persons AL, Napier TC. Dopaminergic lesions of the dorsolateral striatum in rats increase delay discounting in an impulsive choice task. *PLoS One* 2015; **10:** e0122063.

78 Al-Khaled M, Heldmann M, Bolstorff I, Hagenah J, Munte TF. Intertemporal choice in Parkinson's disease and restless legs syndrome. *Parkinsonism Relat Disord* 2015; **21:** 1330–35.

79 Joutsa J, Voon V, Johansson J, Niemela S, Bergman J, Kaasinen V. Dopaminergic function and intertemporal choice. *Transl Psychiatry* 2015; **5:** e491.

80 Kayser AS, Allen DC, Navarro-Cebrian A, Mitchell JM, Fields HL. Dopamine, corticostriatal connectivity, and intertemporal choice. *J Neurosci* 2012; **32:** 9402-9.

81 Djamshidian A, O'Sullivan SS, Sanotsky Y, et al. Decision making, impulsivity, and addictions: do Parkinson's disease patients jump to conclusions? *Mov Disord* 2012; **27:** 1137–45.

82 Djamshidian A, O'Sullivan SS, Foltynie T, et al. Dopamine agonists rather than deep brain stimulation cause reflection impulsivity in Parkinson's disease. *J Parkinsons Dis* 2013; **3:** 139–44.

83 Wylie SA, Claassen DO, Huizenga HM, et al. Dopamine agonists and the suppression of impulsive motor actions in Parkinson disease. *J Cogn Neurosci* 2012; **24:** 1709–24.

84 Djamshidian A, O'Sullivan SS, Lees A, Averbeck BB. Stroop test performance in impulsive and non impulsive patients with Parkinson's disease. *Parkinsonism Relat Disord* 2011; **17:** 212–14.

85 Vitale C, Santangelo G, Trojano L, et al. Comparative neuropsychological profile of pathological gambling, hypersexuality, and compulsive eating in Parkinson's disease. *Mov Disord* 2011; **26:** 830–36.

86 Rosa M, Fumagalli M, Giannicola G, et al. Pathological gambling in Parkinson's disease: subthalamic oscillations during economics decisions. *Mov Disord* 2013; **28:** 1644–52.

87 Engeln M, Ansquer S, Dugast E, Bezard E, Belin D, Fernagut PO. Multi-facetted impulsivity following nigral degeneration and dopamine replacement therapy. *Neuropharmacology* 2016; **109:** 60–77.

88 Claassen DO, van den Wildenberg WP, Harrison MB, et al. Proficient motor impulse control in Parkinson disease patients with impulsive and compulsive behaviors. *Pharmacol Biochem Behav* 2015; **129**: 19–25.

89 Cerasa A, Donzuso G, Morelli M, et al. The motor inhibition system in Parkinson's disease with levodopa-induced dyskinesias. *Mov Disord* 2015; **30:** 1912–20.

90 Zalocusky KA, Ramakrishnan C, Lerner TN, Davidson TJ, Knutson B, Deisseroth K. Nucleus accumbens D2R cells signal prior outcomes and control risky decision-making. *Nature* 2016; **531:** 642–46.

91 Holtz NA, Tedford SE, Persons AL, Grasso SA, Napier TC. Pharmacologically distinct pramipexole-mediated akinesia vs. risk-taking in a rat model of Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2016; **70:** 77–84.

92 Rokosik SL, Napier TC. Pramipexole-induced increased probabilistic discounting: comparison between a rodent model of Parkinson's disease and controls. *Neuropsychopharmacology* 2012; **37:** 1397–408.

93 Djamshidian A, Jha A, O'Sullivan SS, et al. Risk and learning in impulsive and nonimpulsive patients with Parkinson's disease. *Mov Disord* 2010; **25:** 2203–10.

94 Rao H, Mamikonyan E, Detre JA, et al. Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. *Mov Disord* 2010; **25:** 1660–69.

95 Claassen DO, van den Wildenberg WP, Ridderinkhof KR, et al. The risky business of dopamine agonists in Parkinson disease and impulse control disorders. *Behav Neurosci* 2011; **125:** 492–500.

96 Voon V, Gao J, Brezing C, et al. Dopamine agonists and risk: impulse control disorders in Parkinson's disease. *Brain* 2011; **134:** 1438–46.

97 Averbeck BB, Djamshidian A, O'Sullivan SS, Housden CR, Roiser JP, Lees AJ. Uncertainty about mapping future actions into rewards may underlie performance on multiple measures of impulsivity in behavioral addiction: evidence from Parkinson's disease. *Behav Neurosci* 2013; **127:** 245–55.

98 Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson disease. *Arch Neurol* 2010; **67:** 58–63.

99 Thomas A, Bonanni L, Gambi F, Di Iorio A, Onofrj M. Pathological gambling in Parkinson disease is reduced by amantadine. *Ann Neurol* 2010; **68:** 400–04.

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

101 Papay K, Xie SX, Stern M, et al. Naltrexone for impulse control disorders in Parkinson disease: a placebo-controlled study. *Neurology* 2014; **83:** 826–33.

102 Okai D, Askey-Jones S, Samuel M, et al. Trial of CBT for impulse control behaviors affecting Parkinson patients and their caregivers. *Neurology* 2013; **80:** 792–99.

103 Catalan MJ, de Pablo-Fernandez E, Villanueva C, et al. Levodopa infusion improves impulsivity and dopamine dysregulation syndrome in Parkinson's disease. *Mov Disord* 2013; **28:** 2007–10.

104 Todorova A, Samuel M, Brown RG, Chaudhuri KR. Infusion Therapies and Development of Impulse Control Disorders in Advanced Parkinson Disease: Clinical Experience After 3 Years' Follow-up. *Clin Neuropharmacol* 2015; **38:** 132–34.

105 Rotondo A, Bosco D, Plastino M, Consoli A, Bosco F. Clozapine for medication-related pathological gambling in Parkinson disease. *Mov Disord* 2010; **25:** 1994–95.

106 Bonfils NA, Benyamina A, Aubin HJ, Luquiens A. Clozapine use for refractory impulse control disorders in Parkinson's disease: a case report. *Psychopharmacology (Berl)* 2015; **232:** 3677–79.

107 Amami P, Dekker I, Piacentini S, et al. Impulse control behaviours in patients with Parkinson's disease after subthalamic deep brain stimulation: de novo cases and 3-year follow-up. *J Neurol Neurosurg Psychiatry* 2015; **86:** 562–64.

108 Jahanshahi M, Obeso I, Baunez C, Alegre M, Krack P. Parkinson's disease, the subthalamic nucleus, inhibition, and impulsivity. *Mov Disord* 2015; **30:** 128–40.

109 Moum SJ, Price CC, Limotai N, et al. Effects of STN and GPi deep brain stimulation on impulse control disorders and dopamine dysregulation syndrome. *PLoS One* 2012; **7:** e29768.

110 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* 2009; **16:** 1148–52.

111 Zahodne LB, Susatia F, Bowers D, et al. Binge eating in Parkinson's disease: prevalence, correlates and the contribution of deep brain stimulation. *J Neuropsychiatry Clin Neurosci* 2011; **23:** 56–62.

112 Voon V, Droux F, Morris L, et al. Decisional impulsivity and the associative-limbic subthalamic nucleus in obsessive-compulsive disorder: stimulation and connectivity. *Brain* 2016; published online Dec 31. DOI:10.1093/brain/aww309.

113 Cavanagh JF, Wiecki TV, Cohen MX, et al. Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold. *Nat Neurosci* 2011; **14:** 1462–67.

114 Baunez C, Dias C, Cador M, Amalric M. The subthalamic nucleus exerts opposite control on cocaine and 'natural' rewards. *Nat Neurosci* 2005; **8:** 484–89.

115 Rodriguez-Oroz MC, Lopez-Azcarate J, Garcia-Garcia D, et al. Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. *Brain* 2011; **134:** 36–49.

116 Voon V, Dalley JW. Translatable and back-translatable measurement of impulsivity and compulsvity: convergent and divergent processes. Curr Top Behav Neurosci 2016; **28:** 53–91.