Chronic dopaminergic stimulation in Parkinson’s disease: from dyskinesias to impulse control disorders

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Dopamine is an essential neurotransmitter for many brain functions, and its dysfunction has been implicated in both neurological and psychiatric disorders. Parkinson’s disease is an archetypal disorder of dopamine dysfunction characterised by motor, cognitive, behavioural, and autonomic symptoms. While effective for motor symptoms, dopamine replacement therapy is associated not only with motor side-effects, such as levodopa-induced dyskinesia, but also behavioural side-effects such as impulse control disorders (eg, pathological gambling and shopping, binge eating, and hypersexuality), punding (ie, abnormal repetitive non-goal oriented behaviours), and compulsive medication use. We review clinical features, overlapping molecular mechanisms, and a specific cognitive mechanism of habit learning that might underlie these behaviours. We integrate these mechanisms with the emerging view of the basal ganglia as a distributive system involved in the selection and facilitation of movements, acts, and emotions.

Introduction

Dopamine neurotransmodulation is intrinsic to processes of movement and motor learning, cognition, reward processing, food intake, nociception, and endocrine and autonomic regulation. Dopaminergic dysfunction is implicated in neurological and neuropsychiatric disorders such as Parkinson’s disease (PD), schizophrenia, and drug addiction. PD is associated with both dopamine-related motor and behavioural side-effects and provides a useful model to understand the similarities and differences underlying the effects of dopamine on motor and behavioural disorders.

PD is characterised by the loss of dopaminergic nigrostriatal A9 neurons (and, to a lesser extent, retrorubral A8 and mesolimbic A10 neurons); with disease progression, non-dopaminergic nuclei, such as the locus coeruleus, the nucleus basalis of Meynert, and the dorsal raphe, are affected, and Lewy body pathology becomes widespread. The dopamine replacement therapies, which include the dopamine precursor levodopa and dopamine agonists, are very effective in treating motor symptoms, but can cause substantial motor and behavioural adverse events. These side-effects include motor fluctuations and levodopa-induced dyskinesia (LIDs), and non-motor symptoms such as mood and anxiety fluctuations, psychosis, and impulse control disorders (ICDs). LIDs are defined as involuntary, purposeless, irregular but sometimes repetitive movements, which are mainly choreic, and generally coincide with the peak anti-parkinsonian effect of levodopa. LIDs affect at least 90% of patients with PD after 10 years of levodopa treatment and are a major cause of disability. ICDs (ie, pathological gambling, compulsive shopping, hypersexuality, and binge eating), punding (ie, abnormal repetitive non-goal oriented behaviours) or hobbyism, and compulsive medication use are associated with dopaminergic therapy and are increasingly recognised in PD. Overall, the ICDs in the general population have similarities to disorders of substance addiction, hence ICDs have been viewed as behavioural addictions. The pathology of PD and the mechanisms underlying LIDs, a dopamine-associated motor side-effect, are better defined than are the mechanisms underlying ICDs, for which much less is understood. In this Review, we provide insights into potential mechanisms underlying ICDs and discuss potential similarities and differences between LIDs and ICDs.

Dyskinesias and behavioural abnormalities: clinical presentation

Levodopa-induced dyskinesias

The clinical features and major presentation types of LIDs have been described and discussed extensively in the literature (panel 1). LIDs commonly occur in patients with motor fluctuations and are related to levodopa intake. The main risk factors associated with LIDs are disease severity, disease duration, daily dose of levodopa, and age at onset (ie, 50% of patients aged 45 years or less develop LIDs within the first 2 years of treatment). Monotherapy with dopamine agonists such as ropinirole or rotigotine can also induce dyskinesias in monkeys treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and in patients with PD, but these side-effects are less common and less severe than those commonly seen with levodopa. Treatment of LIDs can be difficult, particularly in patients with severe “on-off” fluctuations as any minor reduction in levodopa or dopamine agonist dose to reduce dyskinesia leads to unbearable “off” episodes. Continuous delivery of subcutaneous apomorphine, intraduodenal levodopa, and oral delivery of the non-specific glutamate blocker amantadine, are the preferred pharmacological options for managing severe LIDs. Surgical treatment (ie, pallidotomy or bilateral deep brain stimulation [DBS] of the globus pallidus pars interna or subthalamic nucleus [STN]) is an efficient therapy to treat LIDs.

Dopamine-induced behavioural disorders

PD is associated with several non-motor symptoms, which include changes in cognition, mood, psychosis, anxiety, fatigue, and autonomic systems. We focus on the behavioural symptoms associated with dopaminergic medications, particularly in ICD, punding, and
compulsive medication use. We consider the ICDs separately given their proven association with dopamine agonists in multiple case control studies, as compared with compulsive medication use, which seems more closely associated with levodopa, and punding, in which the association between levodopa and dopamine agonists is not as clear.

**Impulse control disorders**
The ICDs reported in patients with PD include pathological gambling, hypersexuality, compulsive shopping, and binge eating. Their definitions have been extensively reviewed elsewhere and are summarised in panel 2. These ICDs are characterised by the maladaptive nature of the preoccupations in the patient, the inability to control the urges or impulses, and other pathological behaviours (such as lying or stealing) that arise to act on these urges. Although these behaviours have different levels of severity, pathology is defined by the consequences of clear distress or interference with social, financial, or occupational functioning. The behaviours should not occur exclusively within a manic episode.

Gambling behaviours can include excessive gambling or preoccupation with various lotteries, betting, casinos, bingo, and, most recently reported, internet gambling. One study reported that, of 297 patients screened, all ten patients who were identified to have problems related to pathological gambling (3·4%) preferred slot machines and scratch lottery cards, suggesting a behaviour related to immediate gratification, lower cognitive resources, and repetitive motor acts. The consequences can be drastic: one study reported a mean amount of US$10 000 lost among ten patients with PD owing to pathological gambling along with a pronounced detrimental effect on the patients’ relationships. Common behaviours reported in hypersexuality include inappropriate or excessive requests of sex from a spouse or a partner, preoccupation with pornography, telephone sex lines, masturbation, or compulsive promiscuity.

In a study that compared patients with PD with general medical patients, the frequency of gambling was 6·1% in patients with PD compared with 0·25% in controls. In a recent multicentre study of 3090 patients with PD in the USA, 13·6% of patients had ICDs. There were 6·0% of patients whose ICDs included compulsive buying, 5·2% with problem or pathological gambling, 4·3% with a binge eating disorder, and 3·5% with compulsive sexual behaviour. ICDs were more common in patients treated with dopamine agonists (17·1%) compared with those who received other treatments (6·9%). There were no differences in frequency of ICDs between those treated with pramipexole (17·7%) or ropinirole (15·5%). This frequency and association of ICDs with dopamine agonists as a class are similar to those reported in previous publications. This multicentre study reported that the risk factors associated with ICDs were younger age (60·3 years vs 64·4 years), treatment with dopamine agonists, high levodopa dose, being unmarried, and a family history of gambling problems. The study did not find an association with higher dopamine agonist dose but did find a link with higher levodopa dose, thus suggesting an intrinsic role for levodopa. Other associated factors reported include higher novelty seeking, a personal or family history of alcohol use disorders, impulsivity, younger onset PD, and depressed mood. These factors overlap with those associated with substance use disorders and gambling disorders, thus suggesting similar underlying mechanisms. The prevalence of pathological gambling in PD reported in North America is similar to that reported in other countries, including Scotland (4·4%), Italy, (6·1%), and Spain (4·8%).

Pathological gambling, compulsive shopping, and hypersexuality behaviours also occur in patients with restless legs syndrome who are treated with dopamine replacement therapy, although the prevalence is less well established. In the general population in North America, the lifetime prevalence of pathological gambling is 1·5% and that for problems related to pathological gambling is 3–5%, and the estimated point prevalence (ie, cross-sectional) is 5·8% for compulsive buying and 2–6% for binge eating disorder. Whether the rates of these behaviours in PD are increased beyond that of the general population is not clear but their significance lies in their de novo onset after the initiation of dopamine replacement.
therapy. PD itself might be “protective” (ie, associated with less risky behaviour) with lower rates of novelty seeking, smoking, and alcohol use compared with the general population, before appearance of motor symptoms. ICD behaviours might be less likely before initiation of dopaminergic medications; however, the premorbid rates of these behavioural disorders in patients with PD before dopamine replacement therapy are not known.

**Punding or hobbyism**

Punding was first described in the 1970s and is associated with psychostimulant abuse in the general population. Punding is defined as an intense fascination with excessive, repeated, non-goal-oriented, unproductive repetitive behaviours that can be simple (ie, manipulating objects or instruments or sorting of common objects) or complex hobbyism (ie, hoarding, gardening, cleaning, singing, writing, or computer use). The behaviours might be due to the disinhibition of previously learned behaviours as the phenomenology seems associated with individual factors. For example, an accountant was reported to be more likely to shuffle papers, whereas housewives were more likely to clean or clean handbags. The behaviours are disruptive, excessive, and can interfere with social and occupational function. Interruption of the behaviours leads to irritability and dysphoria.

The reported prevalence of punding in patients with PD ranges between 1.4% and 14%, with prevalence associated with differences in case ascertainment, medication practices, and clinic population. Factors associated with punding include younger disease onset, impulsivity, and higher dopamine agonist dose.

**Compulsive medication use**

Compulsive medication use is also known as dopamine dysregulation syndrome and has also been described as hedonistic homeostatic dysregulation. This behaviour is defined as excessive dopaminergic medication use associated with motor side-effects of LIDs and behavioural side-effects of ICDs, hypomania, and psychosis. The reported prevalence of compulsive medication use ranges between 3.4% and 4%, and is associated with younger age, younger age of disease onset, higher impulsivity, higher sensation seeking, smoking, experimental drug use, and depressed mood. The actual extent of abuse in this younger subpopulation is probably underestimated as patients typically minimise reporting their levodopa intake. The associated factors suggest underlying mechanistic similarities with substance use disorders.

**Psychotic symptoms**

Psychotic symptoms such as hallucinations, illusions, and delusions are also commonly associated with dopaminergic medications in patients with PD and occur in up to 40% of patients. ICDs are associated with dopamine agonists and data from a recent study also suggested an association of psychotic symptoms with dopamine agonists rather than with levodopa therapy. ICDs do not correlate with psychotic symptoms, suggesting differences in underlying pathophysiology. Psychotic symptoms are associated with older age,

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**Panel 2: Dopaminergic medication-related compulsive behaviours**

**Gambling**

Pathological gambling (DSM IV definition)

A Persistent and recurrent maladaptive gambling behaviour as indicated by five or more of the following:

1. Preoccupied about gambling
2. Increasing amount of money spent
3. Repeated unsuccessful attempt to control gambling
4. Restless or irritable when reducing time spent on gambling
5. Means of escape from problems or to relieve dysphoric mood
6. Chasing losses
7. Lies to others about gambling
8. Illegal acts to finance gambling
9. Jeopardised relationship, work, or education
10. Relies on others for money

B Does not occur exclusively during periods of hypomania or mania

C The behaviours do not occur exclusively during periods of hypomania or mania

D The behaviour must have persisted for at least 1 month

E If all criteria except C are fulfilled, the disorder is subsyndromal

**Problem gambling**

Similar to pathological gambling but is indicated by only three to four of the ten criteria

**Hypersexuality**

Proposed operational diagnostic criteria

A The sexual thoughts or behaviours are excessive or an atypical change from baseline indicated by one or more of the following:

1. Maladaptive preoccupation with sexual thoughts
2. Inappropriately or excessively requesting sex from spouse or partner
3. Habitual promiscuity
4. Compulsive masturbation
5. Use of telephone sex lines or pornography
6. Paraphilias

B The behaviour must have persisted for at least 1 month

C The behaviour causes at least one or more of the following:

1. Visible distress
2. Attempts to control thoughts or behaviour unsuccessful or result in marked anxiety or distress
3. Behaviours are time-consuming
4. Interferes substantially with social or occupational functioning

D The behaviour does not occur exclusively during periods of hypomania or mania

E If all criteria except C are fulfilled, the disorder is subsyndromal

**Compulsive shopping**

McElroy’s criteria

A Maladaptive preoccupation with buying or shopping, whether impulses or behaviour, that:

1. Are experienced as irresistible, intrusive, and/or senseless
2. Result in frequent buying of more than can be afforded, items that are not needed, or for longer periods of time than intended.

B Causes visible distress, is time-consuming, substantially interferes with social or occupational functioning, or results in financial problems

C The behaviours do not occur exclusively during periods of hypomania or mania

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disease duration and severity, cognitive impairment, dementia, and sleep disorders, indicating an association with PD pathology (reviewed elsewhere\textsuperscript{36}). Data from pathological studies have also shown an association between psychosis, atrophy, and Lewy body deposition in the parahippocampus, amygdala, and frontal, temporal, and parietal cortices.\textsuperscript{37} Pronounced cholinergic deficits have been reported and both a serotonergic-dopaminergic or a monoaminergic-cholinergic imbalance have been implicated in the pathophysiology of psychotic symptoms.\textsuperscript{38} Psychosis in PD probably implicates an interaction between dopaminergic medications (including their serotonergic effects) and the pathology of PD (particularly the balance of neurotransmitter degeneration and the extent and distribution of Lewy body deposition), as well as possible age-related atrophic or microvascular changes affecting the visual processing system. By contrast, the available evidence of ICDs in PD to date implicates a greater interaction between dopaminergic medications and an underlying susceptibility of an individual, affecting systems that are implicated in motivation and reward. The pathology of PD, including the role of different neurotransmitters, likely has a facilitative role in developing ICDs but the exact mechanisms remain to be established.

**Dopaminergic mechanisms and abnormal behaviours**

The main dopaminergic projections are part of the retrorubral field (A8), nigrostriatal (A9), mesocorticolimbic (A10), diencephalospinal (A11), and hypothalamic (A12, A13, A14) systems.\textsuperscript{37} Although dopamine cell group projections are topographically organised, the segregation is not absolute; the motor dorsal striatum and limbic ventral striatum receive innervation from all three mesencephalic dopamine cell groups.\textsuperscript{38} Furthermore, the midbrain dopaminergic neurons are reciprocally connected in a series of ascending spiralling loops from the ventral to the dorsal striatum.\textsuperscript{39} Thus, the anatomical organisation of the dopamine projections can affect motor and behavioural systems.

Extracellular dopamine homoeostasis is maintained by opposing regulatory mechanisms of dopamine release and uptake. Dopamine can be released from synaptic vesicles via exocytosis or directly from the cytoplasm across the cell membrane to the synaptic cleft.\textsuperscript{40-43} By contrast, the uptake mechanisms replenish dopamine vesicular storage via the dopamine transporter across the neuronal membrane and the vesicular monoamine transporter across the vesicular membrane; in PD, the vesicular monoamine transporter route is altered.\textsuperscript{44} These processes can be directly regulated\textsuperscript{45} and also indirectly modulated by the volume fraction or the spatial configuration of the extracellular space.\textsuperscript{46} Differing microstriatal zones can also favour dopamine release or uptake within the dorsal striatum, an organisational process known as a fountain-drain matrix.\textsuperscript{47}

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**Compulsive eating**

**Binge eating (DSM IV research diagnostic criteria\textsuperscript{22})**

A Recurrent binge eating characterised by eating large amounts in a discrete period along with a loss of control

B Three of more of the following:

1. Rapid eating
2. Feeling uncomfortably full
3. Eating large amounts when not hungry
4. Eating alone because of embarrassment of amounts
5. Feeling disgusted or guilty after overeating

C Visible distress

D Occurs 2 days per week for 6 months

E Does not occur with compensatory behaviours or during anorexia or bulimia nervosa

**Punding\textsuperscript{48}**

- An intense fascination with complex, excessive, repetitive, non-goal-oriented behaviours
- The behaviours include less complex acts such as shuffling papers, reordering bricks, or sorting handbags, or more complex acts such as hobbyism (gardening, painting), writing, or excessive computer use

**Compulsive medication use**

Giovannoni’s criteria\textsuperscript{10}

A Clinical diagnosis of levodopa-responsive Parkinson’s disease

B Need for increasing dopamine replacement therapy in excess of that required for motor signs and symptoms

C Pathological use despite severe behavioural disturbances and drug-induced dyskinesias

D Social or occupational impairment

E Development of a dopaminergic withdrawal state with dose reduction

This capacity for both rapid focal regulation and diffusion over long distances allows dopamine to act both as a fast, focal (nm), and short-acting (<10 ms) transmitter (ie, a neurotransmitter) and as a slow, diffuse (μm to mm), and long-acting (>10 ms to s) transmitter (ie, a volume transmitter).\textsuperscript{49} Theoretically, levodopa should be able to restore the neurotransmitter action of dopamine, and both levodopa and dopamine agonists should restore its action as a volume transmitter. However, in the context of severe nigrostriatal denervation, the extrasynaptic conversion of levodopa into dopamine and the persistent actions of dopamine agonists, dopaminergic replacement therapy probably cannot restore both types of physiological functions. Thus, the non-physiological stimulation of postsynaptic receptors probably has a fundamental role in the motor and behavioural disorders induced by chronic dopaminergic medication in PD.

**Abnormal dopaminergic stimulation leading to ICDs**

The molecular mechanisms of LIDs have been extensively discussed elsewhere.\textsuperscript{4-11} Here, we outline these mechanisms to provide further insights into potential links between LIDs and ICDs. LIDs are associated with the pulsatile stimulation of dopamine receptors leading...
to downstream changes in gene and protein expression. These changes, and their interaction with abnormalities in non-dopaminergic transmitter systems, can lead to altered neuronal signal firing patterns between the basal ganglia and the cortex. These molecular changes, also known as neuronal adaptation or sensitisation, are thought to underlie the motor sensitisation in LIDs.

Presynaptic mechanisms
The neuronal adaptations underlying LIDs can occur on either a presynaptic or a postsynaptic level. Presynaptic alterations of dopamine transmission after chronic levodopa treatment have been implicated in the development of LID and compulsive medication use. For example, in ¹¹C-raclopride PET studies, patients with PD and LID have greater dopamine release in the caudate and putamen with levodopa compared with patients with PD but without ICDs or LIDs, and, similarly, patients with PD with compulsive medication use have greater dopamine release in the ventral striatum with levodopa than those without ICDs or LIDs. In the latter study, the findings suggested a link between ventral striatal dopamine activity and the desire or incentive for levodopa and thus support the theory of incentive sensitisation for models of addiction. However, this remains to be confirmed through use of other neurophysiological measures. Finally, patients with PD with punding behaviour are more likely to have comorbid LIDs, suggesting similar underlying mechanisms. A link between LIDs and the behaviours of compulsive medication use and punding might be more obvious given their common association with levodopa rather than dopamine agonists. However, although ICDs are associated with dopamine agonists, the ICD behaviours in patients with PD are also related to high doses of levodopa, suggesting a potential sensitising or synergistic effect of levodopa. Thus, presynaptic alterations of dopamine transmission after chronic levodopa treatment seem to occur in both LIDs and ICDs.

Postsynaptic mechanisms
Postsynaptic adaptations in neurotransmitter and receptor interactions, as well as in signalling cascades, have been detected in animal models of LIDs. Several lines of evidence indicate that LIDs are associated with excessive expression of D1 receptors in striatonigral neurons in rodent and primate models. Levodopa (via D1 receptor stimulation) is associated with aberrant and excessive expression of the D3 receptor in the denervated dorsal striatum, thus providing a potential priming role on subsequent exposure to dopamine agonists stimulating the D3 receptor. In turn, D3 receptor stimulation maintains aberrant membrane D1 receptor localisation, thus indicating a direct effect of dopamine agonists in modulating D1 receptor activity. The role of the D2 receptor should not be dismissed, as behavioural pharmacology studies have shown that D2 receptor stimulation can have a role in behavioural sensitisation to levodopa in rats and non-human primates. Thus, stimulation of different dopamine receptors via dopamine agonists will have specific effects on neuroadaptation.

Other neurotransmitters have also been implicated in sensitisation other than dopamine. For example, adenosine 2A receptor expression is increased in D2-expressing striatopallidal neurons in patients with PD and with LID and in experimental animal models of LID. The adenosine 2A receptor has a regulatory role in the downstream signalling of D2 and glutamate receptors and might result in an imbalance of intracellular signalling. Increased expression of adenosine 2A receptor expression can also occur during cocaine self-administration in rats. Glutamate dysfunction, such as impaired synaptic plasticity and alterations in striatal receptors, has also been implicated in LID pathophysiology, and might underlie the observation that amantadine can be efficacious in treating LIDs.

Signalling cascades
Abnormalities in signalling cascades have been detected in rodent and primate models of LID and occur particularly in D1-expressing neurons. The cAMP signalling cascade and the extracellular signal-regulated kinase (ERK) signalling pathway are activated both in animal models of LIDs and after cocaine administration. Specifically, increased phosphorylation of DARPP-32 (also known as PPP1R1B) at threonine 34 occurs both in LID and after cocaine treatment in D1 neurons. Both signalling pathways are implicated in the pathophysiology underlying substance use disorders and learning processes, suggesting potential links between LIDs and ICDs.

Physiologically, LIDs are further characterised by reduced firing frequency, changes in firing patterns, and synchronisation of the STN and globus pallidus pars externalis. STN DBS is effective for both LID and for compulsive medication use and pathological gambling in patients with PD. Whether this effect is due to a decrease in medication dose, to changes in neural firing pattern, or possibly to the shift from a pulsatile to steady state stimulation with a concomitant decrease in sensitisation is not known. Whether neuronal adaptation occurs in the full range of ICD behaviours, and how the adaptations could be similar to or different from LIDs on a molecular, anatomical (ie, ventral versus dorsal), or firing pattern level, remain to be investigated.

Role of dopamine and the striatum in automatisms or habit formation
The phenomenology of LID, and also of punding, involves sequences of actions from the simplest pattern (a repetitive stereotyped movement of the lower limb as in diphasic dyskinesias) to the most complex movements (a repetitive stereotyped movement of the lower limb as in diphasic dyskinesias) to the most complex movements (a repetitive stereotyped movement of the lower limb as in diphasic dyskinesias)
behaviour such as ceaseless manipulation of an object). ICDs and compulsive medication use have similarities to substance use disorders, which are characterised by a shift from goal-oriented behaviours towards habitual or stimulus-response behaviours. Although several cognitive mechanisms could be implicated in the dopamine-associated behavioural disorders and need to be investigated,7 we restrict this discussion to mechanisms that might overlap with IIDs. Whereas the study of dopamine and the striatum has historically focused on movement control, associated behavioural and cognitive disorders also indicate that the striatum is involved in fundamental information processing. Next, we discuss the role of the striatum and dopamine in sequential actions and in habit or stimulus-response learning.

Sequential action

Several independent lines of evidence implicate the neostriatum in triggering sequences of actions. Sequential movements are disrupted in patients with PD, as evidenced by movement slowing when undertaken as part of a sequence.7,78 In primates, putaminal single unit recordings detect neuronal activation before action onset done as part of a sequence, but not when the same actions are outside of the sequence.79 In birds, basal ganglia lesions impair the capacity to learn new songs, with little effect on previously learned behaviour.80,81 While problems in switching behaviour are often reported in patients with PD,82 suggesting the coexistence of learning-dependent and learning-independent functions, most studies indicate sequence learning impairment in PD and other movement disorders.83 Thus, basal ganglia involvement in sequential activity might be specifically associated with an important role in action learning.

Habit learning or stimulus-response associative learning

Rodent, primate, and human studies have provided evidence that the basal ganglia, and particularly the dorsolateral striatum, have a key role in habit learning. Habit learning is defined as learning from repeated positive reinforcement of a particular behaviour, and is a form of stimulus-response associative learning.84-86 An important distinction has been made between habit learning and goal-oriented learning, which depends on different striatal regions. Goal-oriented learning is defined as a behaviour that is sensitive to the value of the reward, also known as action-outcome learning. This learning process can be measured by observing how the changing reward value produces an immediate behavioural effect. For example, the reward value of a particular food can be reduced by satiation, resulting in cessation of goal-oriented behaviour rewarded by that particular food. By contrast, a habit is not immediately sensitive to such a change (eg, satiation), and habits persist after the outcome has become unrewarding. However, the reduced reward value would gradually lead to extinction. Repeated training normally leads to progression from goal-oriented action to habit.87,88 This aspect of habit learning is particularly relevant to ICDs, in which behaviour that might once have led to reward continues despite negative consequences.

The neural circuits underlying habit and action-outcome learning are beginning to be elucidated. Early studies that used large striatal lesions established the importance of the striatum in learning.89-91 In rats, dorsal striatal lesions impair acquisition of tasks requiring the development of a habitual response92 and lesions of the ventral striatum impair approach to rewarding stimuli.93,94 Smaller lesions, together with modern behavioural techniques, have identified regional specialisation of learning functions within the striatum. Progression from goal-oriented to habitual responding is disrupted by dorsolateral striatal lesions.95,96 Rather than progressing to habits, animals with lesions in the striatum remained sensitive to reward devaluation throughout their training. By contrast, progression to habitual responding occurs normally with dorsomedial striatal lesions. Such evidence suggests that the dorsolateral striatum, but not the dorsomedial striatum, is implicated in the stimulus-response associations thought to underlie habitual responding. Furthermore, dopamine innervation of the dorsolateral striatum is absolutely required for habit formation in instrumental conditioning.97

Behavioural measures in human beings with neurodegenerative diseases of the basal ganglia also show that these diseases are associated with deficits in such learning processes.98,99 Electrophysiological recording studies in primates and rats are consistent with a role of the striatum and other basal ganglia structures such as the STN in these processes, by indicating reward-related activity at the cellular level100-104 and changes in single unit responses during acquisition of habits.105 The cellular mechanism underlying habit formation probably involves dopamine-dependent plasticity of corticostriatal synapses106 brought about by phasic release of dopamine.107

Habit formation is also frequently referred to in the context of addiction, typically considered a dopamine-mediated dysregulated behaviour. There is indeed a development of habits in drug-seeking behaviour. Although the dopamine system has a crucial role in this behaviour via the ventral striatum, the dorsal striatum plays a key role at the stage of habit formation.108 This dopamine-mediated behaviour is also modulated by the control of the STN, as experimental subthalamotomy can reduce motivation for drugs of abuse such as cocaine, while increasing motivation for food,109 and STN DBS can reduce compulsive medication use and pathological gambling in patients with PD.75,76 However, this STN DBS effect might not necessarily be a direct effect, as patients receive substantially less medication after surgery. Interpretations regarding the mechanism of the effects of STN DBS on ICDs are difficult because of concomitant changes in medications, the fact that STN DBS can also be associated with greater impulsivity under high conflict
Conclusions: are behavioural and motor disorders in PD part of the same continuum?
The basal ganglia forms a complex network that is involved in the selection and facilitation or the inhibition of movements, acts, and emotions. This integrated view leads to the natural speculation that the pathological consequences of dopamine dysfunction might involve unwanted movements, acts, and emotions. We suggest that the involuntary movements of LIDs and behavioural disorders of ICDs, punding, and compulsive medication use are part of a continuum and are the motor, cognitive, and emotional pathological expressions mediated by intrinsically similar physiological mechanism acting through different basal ganglia channels or subregions. For example, LID, while clearly a motor manifestation, can involve limbic domains of the basal ganglia. Characteristically, LIDs are often described as being triggered or enhanced in patients with PD by emotional factors such as stress, talking in public, or when eating. Thus, LID, rather than a simple medication-related motor manifestation, might also involve a cognitive and limbic pathophysiology.

Several unanswered questions remain. For example, what differentiates the patients that develop ICDs from those patients that do not develop ICDs even if they receive the same medication? Although we are starting to understand the clinical features associated with ICDs, this question remains unanswered at the level of neuronal function. Furthermore, why do different patients develop differing behaviours? Is this associated with individual susceptibilities (ie, either differences in environmental, cultural, or learned factors or genetic or biological factors) or with the disease process? Pre-set or learned neural representations of behavioural patterns might be disinhibited in the context of dopaminergic medications. ICDs seem more likely to be associated with various premorbid or external factors that are less relevant to LIDs. However, on neuroanatomical grounds, we suggest that the different behavioural expressions and the individual susceptibilities might also indicate differences in striatal denervation patterns of dopamine neuronal cell loss, which might differentially affect movement, behaviours, and personality traits. The preferred motor or behavioural outcome might thus be predicted by the PD-related denervation pattern of the fountain-matrix organisation of the striatum or by differences in premorbid striatal functioning. Thus, what may seem as an individual susceptibility to ICDs (eg, the association with smoking or a family history of gambling) could also reflect underlying differences in basal ganglia functioning.

Several questions also remain regarding the association between LIDs and ICDs. The association with young age, high levodopa dose, and the improvement seen with STN DBS suggests potential similarities between the disorders. Punding seems to be associated with LIDs, but an association between LIDs and ICDs remains to be established. Similarly, greater ventral striatal dopamine release of levodopa in compulsive medication use has been suggested to potentially reflect the effects of neuroadaptation. However, whether neuroadaptation does indeed occur for the range of ICD behaviours, and if this is similar to or different from LIDs on a neuroanatomical (eg, ventral versus dorsal) or molecular basis remains to be established.

As discussed above, why do only some patients exposed to the same medication present with ICDs and why do they have different behavioural presentations? What is the association with ICDs, LIDs, and substance use disorders in the general population? What are the clinical, cognitive, and neurophysiological correlates? Which of these correlates are state-related (ie, medication effect or related to the presence of the ICD), sensitisation-related (chronic medication exposure), or trait-related (premorbid diathesis). What is the role of the neurodegeneration and compensation associated with PD given that these symptoms also present in patients treated with dopaminergic agents in disorders such as restless legs syndrome? As exogenous medications affect several brain regions beyond that of the striatum, what is the role of other neural regions such as the prefrontal or orbitofrontal cortex, amygdala, or insula and of other neurotransmitters? What are the clinical risk factors that might allow screening of patients at high risk for the development of these disorders?

Currently, selection of movements, actions, and behaviours is seen as a fundamental and primary function of the basal ganglia. We have emphasised here that both involuntary movements and abnormal behaviour in patients with PD might represent part of a pathological continuum secondary to abnormal dopaminergic stimulation. We believe that understanding the common factors in addition to the differences between LIDs and ICDs on a molecular, cognitive, and neurophysiologic level might provide insights into basic mechanisms underlying not only these disorders but also motor and behavioural functioning. These apparently disparate motor and behavioural symptoms might be the resulting features of dopamine interacting with individual premorbid susceptibilities (which might be genetic or biological factors or environmental or learned factors) and individual or PD-related differences in striatal functioning.
Contributors
All authors contributed equally to this Review.

Conflicts of interest
EB is a shareholder of Motac Holdings and Chief Scientific Officer of Motac Neuroscience. Motac is a contract research organisation that tests therapeutic strategies for cognitive (eg, mild cognitive impairment and Alzheimer’s disease) and movement (eg, Parkinson’s disease and levodopa-induced dyskinesia) disorders. All other authors have no conflicts of interest.

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