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

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Abstract

Dopaminergic medications commonly used to treat Parkinson's disease can be associated with motor and non-motor behavioural side effects such as dyskinesias and impulse control disorders. These behaviours include gambling disorder, binge eating disorder, compulsive sexual behavior and compulsive shopping. Here, we review the epidemiology, demographic and genetic risk factors, as well as translational research on cognitive, cellular and molecular dysfunctions. These disorders illustrate the interaction between an individual vulnerability and exposure to dopaminergic medications, and the possible impact of Parkinson's disease. Understanding the common and distinct mechanisms underlying these behaviours, including differences between behavioural subtypes, will provide important mechanistic and therapeutic insights.

Introduction

Chronic dopaminergic medications used in the treatment of Parkinson's disease (PD) are commonly associated with motor and behavioural side effects such as dyskinesias[1] and impulse control disorders (ICDs) or behavioural addictions[2]. Involuntary movements (i.e. chorea, dystonia, etc) associated with chronic Levodopa, termed Levodopa-induced dyskinesias (LID), occur in up to 80% of treated patients. ICDs, including gambling disorder (GD), compulsive shopping or sexual behaviours, and binge eating were reported in a multicenter study to be 17.1% of those on dopaminergic medications[2]. The ICDs are hypothesized to reflect interactions between dopaminergic medications and an underlying vulnerability or susceptibility to addiction possibly interacting with the neurobiology of PD[3] (Figure 1). That the ICDs also occur in subjects requiring dopaminergic medications such as Restless Legs Syndrome suggests that while PD may play a role it may not a necessity for ICD expression[4].

Here we update new evidence published since our 2009 review[5]. The new psychiatric definitions of behavioural addictions and ICDs are reviewed in Panel 1. This update compares and contrasts the motor (e.g., LID) and non-motor (ICDs) side effects associated with DA. We review the epidemiology, demographic and genetic risk factors, as well as cognitive, cellular and molecular dysfunctions associated with these prevalent and disabling side effects of dopamine replacement therapy. We also review new preclinical and clinical treatment studies against ICDs.

Epidemiology and associated factors

In the largest multicenter study (the DOMINION study) involving 3090 PD patients[2], ICDs were identified in 13.6% (gambling in 5%, compulsive sexual behavior in 3.5%, compulsive buying in 5.7%, binge eating disorder in 4.3%) and were more common in those being treated with dopamine agonists (DA) (17.1% versus 6.9%; odds ratio 2.72 (95% CI 2.08 -3.54)) but sub-clinical manifestations can also occur. There were no differences in ICD frequencies between two commonly prescribed DA, pramipexole and ropinorole (17.7% versus 15.5%). Long-acting DA and transdermal rotigotine has been recently shown to be less likely to be associated with ICDs relative to short-acting DA suggesting a possible relevance for pulsatile administration, potentially in enhancing sensitization effects[6]. Both DA and Levodopa use were independently associated with ICDs in the DOMINION study, with an association with higher Levodopa dose but not DA dose[2]. However, the DOMINION study is cross-sectional which may be less likely to capture clinical changes in dosing. Indeed, in a small prospective study following 46 PD patients, a higher peak DA dose was observed in the ICD group,[7]. Furthermore, follow up studies show DA discontinuation or dose decrease can improve ICDs[8] supporting a relationship between DA dose and ICDs.

On multivariable analysis in the DOMINION study, the factors associated with a current ICD included DA treatment, Levodopa treatment, younger age, being unmarried, living in the United States, a family history of gambling problems and current cigarette smoking. Other associated factors identified in the cross-sectional study included greater functional impairment, and higher depression, anxiety, obsessive compulsive, impulsivity and novelty seeking scores[9]. A small prospective study showed that greater caffeine use, cigarette smoking and a trend towards higher

alcohol use were associated with ICDs[7]. That the ICDs occur only in a subset of PD subjects exposed to DA[2] suggests an underlying vulnerability or individual risk towards ICDs with similar predilection for excessive substance use. The identified factors have some similarities to those associated with reported for substance use disorders (SUD) or GD arguing for shared underlying neurobiology.

With respect to LID, following the so-called honeymoon when patients experience the full therapeutic benefit of Levodopa without major side-effects, LID progressively develop with up to 80% developing involuntary movements after 4-6 years of treatment and 80 to 90% after 10 years of treatment[10]. Risk factors include treatment duration, initial dose of Levodopa, younger age at disease onset, low body weight, female gender and more severe UPDRS II scores[11]. LID are also associated with higher anxiety, however without apparent relationship with a specific "on" or "off" motor state[12].

Two studies have identified a greater likelihood of co-occurrence of ICDs and LIDs. Punding or excessive non-goal-oriented repetitive behaviours[13] which falls within the spectrum of ICD behaviours and individuals with more than one ICD have higher dyskinesia scores[9], suggesting that motor and non-motor side effects of dopamine replacement therapy may in part be linked to a common underlying vulnerability.

The role of Parkinson's disease

In PD, neurodegeneration of more than 50% of the substantia nigra pars compacta (SNpc) dopaminergic cells projecting to motor and cognitive subregions of the dorsal striatum are thought to occur prior to onset of motor symptoms. Albeit less affected

than the SNc, ventral tegmental area (VTA) dopaminergic projections to the ventral striatum also undergo significant neurodegeneration. The VTA is much less affected by PD pathology initially. Such differential pathology results in an imbalance between dorsal and ventral striatal function. Greater preservation of dopaminergic projections to ventral limbic regions may result in an 'overdose' or reduced dynamic range of otherwise intact limbic regions during DA therapy[14]. Dopaminergic regulation of cognitive function follows a U-shaped curve, with optimal functioning occurring at an optimal dopaminergic levels and either higher or lower levels resulting in impairments in cognition[3,14]. Thus, a dopaminergic imbalance between ventral and dorsal striatal systems either at baseline or as a function of medications may be implicated.

Evidence from preclinical studies indicates that both DA and Levodopa demonstrate reinforcing effects that are enhanced in PD models. Non-contingently administered D3 receptor (D3R)-preferring DA and Levodopa promoted greater conditioned place preference in several different rat models of PD than that seen in unlesioned controls[15,16],[17]. (Figure 1) This outcome was hypothesized to reflect post-synaptic dopamine receptor super-sensitivity[17]. However, the lack of place preference in lesioned or unlesioned rats is also reported with very high doses of levodopa[16]. The reinforcing strength of *self-administered* pramipexole was not altered by 6OHDA-induced dopaminergic lesions in rats[18]. In the alpha-synuclein overexpressing rat PD model, Levodopa decreased palatability of sweetened water consumption, similar to the effect of psychostimulants on non-drug rewards[17]. These latter results are consistent with observations of compulsive medication use in 3 to 4% of PD patients on Levodopa or apomorphine[19] and help explain the observations that some forms of

ICDs are associated with adjunct Levodopa treatment[2]. More research is needed to clarify the role of dopaminergic projections in the non-motor behavioural effects of PD therapy.

Differential severity of the parkinsonian lesion and associated receptor hypersensitivity within more fine-grained striatal subregions (e.g. medial, central versus lateral ventral striatum in primate studies) may also be associated with differences in behavioural expression or the severity and latency of ICDs or LID (Box 1 and Figure 3). Other aspects of PD pathology that may influence the non-motor effects of DA include neurodegeneration affecting serotonergic and noradrenergic systems relevant to cognitive mechanisms, and also whether specific subtypes of PD might contribute to these symptoms. Notably ICDs are also associated with dopaminergic medications used in the management of Restless Legs Syndrome although its frequency may be lower (possibly related to lower and less frequent dosing)[4] suggesting that while PD may play a role, it may not be a necessity for the expression of ICDs. Several differing mechanisms may lead to a final common pathway.

Regulation of dopamine function and receptors

The exogenous administration of dopaminergic medication may alter the function of endogenous dopamine. Endogenous dopamine signaling can act either on a phasic or tonic basis[20,21]. Chronic DA or Levodopa treatment may thus interfere with physiological changes in dopamine levels related to the firing activity of dopaminergic neurons. Converging evidence show that phasic dopamine acts as

prediction errors or a reinforcement signal to guide motivated behaviours[21]. Phasic dopamine increases with novel and unexpected rewards (positive prediction error) which facilitates learning to associate earlier stimuli and actions with reward. Unexpected losses or lack of a reward are associated with a pause or cessation of dopamine neurons firing (negative prediction error) which facilitates learning to avoid associated actions that cause them, acting as a negative reinforcement signal. These reinforcing effects of phasic dopamine are complemented by direct effects of tonic dopamine on action and choice. Tonic dopamine has been postulated to represent an average reward signal over time relevant to opportunity cost and motivation[22] and elevations of tonic dopamine can increase risky decision making by altering the relative emphasis of costs vs. benefits of alternative decision[23]. Tonic dopamine can also disengage cortical regulation of subcortical systems via a presynaptic action[24]. Chronic dopaminergic treatment may also promote the tonic upregulation or downregulation of dopaminergic receptors.

In the dorsal striatum, D1 and D2 receptors (D1R, D2R) are largely segregated into the direct and indirect pathway involved in facilitating and inhibiting actions respectively. However, whether such segregated organization applies to nucleus accumbens neurons is less clear. Phasic dopamine promotes learning from positive outcomes via D1 receptors of the 'Go' pathway and promote learning from negative outcomes via D2 receptors of the 'NoGo' pathway[23,25], Exogenous dopamine is hypothesized to enhance learning from reward feedback and impair learning from negative feedback, the relative imbalance representing a candidate endophenotype of a form of impulsivity[23]. More recently, activity of nucleus accumbens D2R-expressing neurons in rodents was associated with negative prediction error and

predicted risk aversion. Timed phasic optogenetic stimulation of D2R-expressing neurons during choice (and not learning) also prevented risky choices[26]. Thus, stimulation of D2R may interfere with the detection of negative prediction errors or the representation of unfavourable outcomes, which could decrease sensitivity to negative outcomes. These features could also contribute to individual variability towards risk-seeking. The effects of dopaminergic medications are also dependent on task-demands such that dopaminergic medications enhance learning from positive but impair learning from negative feedback and increase updating of working memory. However, this also enhances working memory updating of distractors thus potentially impairing performance when present[27]. High affinity D2R may be more sensitive to low tonic activity and transient pauses associated with negative prediction errors whereas both low affinity D1R and D2R may be sensitive to large phasic dopaminergic bursts associated with positive prediction errors[28]. Evidence suggests that striatal D2R levels may not differ between PD subjects with ICDs and controls. Although one [11C]raclopride PET study suggested lower striatal D2/3R levels during a motor control task, no evidence of lower striatal D2/3R levels at baseline have been observed in subsequent studies[29,30].

The role of the D3R was initially raised given the observation of ICDs associated with pramipexole, a D2/3R preferring DA and has been highlighted in the recent FDA FAERS reports emphasizing the role of pramipexole and ropinorole and also the D3 partial agonist, aripiprazole in ICDs[31]. The proportion of reported ICD behaviours in PD tends to be associated to the relative D3R selectivity of DA[32]. Under physiological conditions, the D3R is predominantly found in the ventral striatum; however, in parkinsonian models, Levodopa exposure results in *de novo* expression of

D3R in the denervated dorsal striatum and D3R expression levels correlate with LID severity in experimental models[33]. The D3R is co-expressed with D1R in ventral striatal medium spiny neurons and these receptors interact via an intramembrane cross-talk[34]. D3R antagonism allows the restoration of normal levels of D1R at the plasma membrane in dyskinetic rats[35], further highlighting the importance of D1R-D3R interaction in LID. The role of D3R of gambling disorder in the general population has been recently emphasized using [11C]-PHNO PET imaging: although there were no group differences in striatal or nigral D2R or D3R levels in gambling disorder, D3R levels correlated with gambling severity symptoms[36] and nigral D3R levels predicted enhanced amphetamine-induced dorsal striatal dopamine release[37]. However, the role of D3R in PD subjects with ICDs is less clear as a recent study showed lower [11C]-PHNO ventral striatal binding in Levodopa-treated PD patients with ICDs, possibly related to enhanced dopamine release[38].

The chronicity of dopaminergic medication exposure may also play a role suggesting neuroadaptation effects. Whereas acute pramipexole decreases the dopaminergic mean firing rate in rodents by acting on D2 autoreceptors and inhibiting presynaptic dopamine release, subchronic pramipexole normalizes activity close to baseline presumably via adaptation of D2 autoreceptors[39]. How variability in dopamine signaling might influence these findings in ICDs remain to be investigated. Chronic Levodopa in 6-OHDA depleted rodents influences the gain associated with dopamine activity by enhancing the proportion of spontaneously active dopamine neurons or those capable of phasic activity in response to a salient stimulus (Figure 2). This outcome may be related to D2 autoreceptor downregulation[40]. Thus, with lesions, there is a preservation of the dynamic range of dopaminergic neuron activity to enable

responses to stimuli[41]. However, with chronic Levodopa or DA treatment, there is an activation of dopaminergic neuron firing such that the system is hyper-responsive to stimuli, resulting in an imbalance in stimuli driving behaviors, a mechanism that is likely relevant to ICDs.

These findings suggest either a general enhancement of dopaminergic transmission, which may be related to increases in synthesis or release, or a reduction in synaptic clearance. Dopamine reuptake via the striatal dopamine transporter (DAT) is the primary mechanism by which dopamine is removed from the synapse to terminate its action. Reduced DAT levels are reported for PD patients with ICDs[42,43] and this may predate and thus predict vulnerability to develop ICD[44,45] (Figure 2). As there currently is no clear evidence for a reduction in dopaminergic terminal density with dopaminergic therapy, lower DAT levels may result in enhanced synaptic accumulation, diffusional distance and duration of action for synaptically released dopamine. Preliminary evidence in a small PD+ICD sample using [11C]FLB-457 PET showed decreased midbrain D2/D3 auto-receptor sensitivity in subjects playing a gambling task, which would promote dopaminergic cell activity to enhance striatal dopamine release[46] (Figure 2). Lower putaminal DAT activity[47] and higher putaminal dopamine turnover[48] are also risk factors for LID, suggesting that functional and/or structural features of remaining putaminal dopaminergic terminals at treatment initiation contribute to the subsequent development of LID.

Together, these effects of enhancing physiological dopaminergic activity (enhancing gain, decreasing D2 autoreceptor sensitivity and regulation, decreasing DAT density) may have an effect on excessive ventral striatal dopamine transmission occurring in

PD patients with ICDs in specific contexts. Using (^{11}C)-raclopride PET imaging, PD patients with mixed ICDs withdrawn from their own medications overnight had heightened ventral striatal dopamine release to heterogenous reward-related visual cues relative to neutral cues (Figure 3). This was observed both off medications[30], and with Levodopa challenge with no effect of Levodopa itself[49]. PD patients with PG tested off medication also showed heightened ventral striatal dopamine release during a card gambling task and a simple motor task[50] (Figure 3). However, with an ecologically valid gambling task, PD patients tested off medications did not differ from PG although the enhanced striatal dopamine release correlated with gambling symptom severity[51]. In PD subjects with LID or with compulsive Levodopa use, enhanced dorsal or ventral striatal dopamine release is observed to Levodopa challenge suggesting that sensitization occurred during repeated Levodopa treatments[52,53] consistent with animal studies[40]. In contrast, sensitized responding to a Levodopa challenge did not occur in those with ICDs[29] suggesting that the adaptive processes for ICDs may be distinct from that associated with Levodopa-induced sensitization. Using fMRI, PD patients with hypersexuality had greater activity in a saliency network (ventral striatum, amygdala, anterior cingulate, orbitofrontal cortex) to sexual cues both on and off Levodopa. Subjective sexual desire was enhanced on Levodopa with enhanced desire correlating with activity in this saliency network[54]. Greater ventral striatal activity to gambling-related cues was also demonstrated in a small fMRI study in PD patients with ICDs off dopaminergic medications[55]. The neural activity to the conditioned cues persist off medications and are consistent with enhanced striatal dopamine release to drug cues in drug dependence studies[56]. That the effect persists off medication does not rule out an interaction between dopaminergic medication and the non-drug reward.

A role for novelty, which is similarly coded by phasic dopaminergic activity, has also been observed with enhanced novelty seeking in PD patients on dopamine replacement therapy particularly with compulsive shopping with a trend with gambling disorder but not compulsive sexual or binge eating[9]. Similarly, PD+ICDs subjects were shown to prefer novel stimuli on a probabilistic learning task irrespective of whether they were on or off medications[57].

Beyond a focus on dopamine and striatal function, studies further implicate a dopaminergic network including the orbitofrontal cortex implicated in outcome representation to flexibly guide responding and the anterior cingulate implicated in conflict, novelty and representation of reward and punishment expectation and prediction error. PD+ICDs subjects show enhanced resting state [18F]fluorodopa uptake in the medial OFC suggesting enhanced monoaminergic activity at baseline (Figure 3)[58] (Figure 3). Using a card gambling task and 15H2O-PET, PD+GD subjects showed inhibition of activity in the lateral OFC, rostral cingulate, amygdala and external pallidum following an apomorphine challenge[59] (Figure 3)[59] (Figure 3). This abnormal orbitofrontal cortex activity both at baseline and with DA challenge might impair the capacity to utilize outcomes to flexibly guide responding. Impaired connectivity at rest between the anterior cingulate and striatum (particularly the anterior putamen) in PD+ICD subjects has also been observed in converging studies[60,61].

Molecular mechanisms of LID

The molecular mechanisms underlying LID are more well-established. LID is clearly associated with multiple cellular signalling alterations, including enhanced D1R expression and signalling. Following enhanced D1 stimulation, LID is associated with widespread molecular adaptations notably in striatal medium spiny neurons. Transcriptome analysis of rodent models of LID demonstrate altered expression of numerous genes involved in several cellular functions including transcription, signal transduction, calcium homeostasis, synaptic transmission/plasticity and structure (for review, [1]). Levodopa administration leads to the rapid expression of several immediate early genes (IEG) such as FosB, ΔFosB, ARC and zif268, encoding for transcription factors that can promote sustained transcriptional activation associated with LID. A causative role for this mechanism was demonstrated via the downregulation of the negative elongation factor (NELF) protein complex, which reduced expression of ΔFosB, ARC and zif268, and abnormal involuntary movements[62]. Notably, these transcriptional regulators are implicated in synaptic plasticity and are involved in SUD.

Genetics and epigenetics of ICDs and LID:

Genetic variability at several loci can influence the patient's response to dopamine replacement therapy and the development of motor or non-motor side effects. Several studies have investigated genetic susceptibility to LID in PD with a particular emphasis on genes related to dopamine transmission, while very few studies have been performed so far for ICDs (for review,[63]). In LID, the TaqIA polymorphism in the *D2R* gene increases the risk of developing motor fluctuations, while a single nucleotide polymorphisms in the *SL6A3* gene coding for the dopamine transporter increases the latency to LID onset[64]. The Val158Met polymorphism in the *COMT*

gene and the Val66Met polymorphism in the *BDNF* gene are linked to an increased risk or earlier occurrence of LID[65,66]. Even though none of these sequence variants were found to be associated with ICDs in PD patients[67,68], some of these polymorphisms are linked to drug abuse or behavioural traits relevant to ICDs (impulsivity, risk-taking) in the general population (for review, see[69]). Interestingly, the D3R p.S9G variant is the only polymorphism that has so far been linked to both LID and ICDs in PD patients, carriers of the AA genotype having a shorter latency to develop diphasic and peak-dose LID[70] and an increased risk of ICDs[67]. It should be noted that some of the results of these genetic studies were not replicated. In a recent study using a combination of clinical assessments and a genetic multivariable panel, ICD heritability was estimated to be 57%. Genotypes from 13 candidate variants allowed improving ICD predictability compared with predictions based on clinical endpoints. Combining 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[71]. Although LID and ICDs share a number of clinical and demographic risk factors, the limited number of studies on the topic do not provide conclusive evidence to support either a distinct or shared genetic vulnerability. Nevertheless, available data indicate that genetic susceptibility can influence motor and non-motor behavioural side-effects of dopamine replacement therapy. The p.S9G variant in the D3R gene associated both with LID and ICDs suggest that a common genetic vulnerability might exist and warrant further investigations in large independent populations.

Common epigenetic mechanisms have also been implicated in LID and ICD. Examples include the transcriptional regulator, ΔFosB, long-lasting truncated splice

variant of FosB. Striatal expression of ΔFosB and FosB are most relevant to LID. Both are highly expressed in the striatum of dyskinetic experimental models[72,73]. Enhanced striatal ΔFosB is associated the development of LID, as selective silencing of striatal FosB/ΔFosB neurons reduces LID while maintaining the antiparkinsonian effect of Levodopa[74] as well as with LID severity[62,73]. ΔFosB-associated LID likely reflects dopamine receptor-linked extracellular signal-regulated kinases (ERK) and mitogen- and stress-activated kinase 1 (MSK1)[75,76].

The involvement ΔFosB in the nucleus accumbens (Nacc) is relevant to ICDs. Pramipexole triggers ΔFosB expression in the Nacc (and striatum) of both normal and dopamine lesioned rats and accumbal ΔFosB expression correlates with the motivation to self-administer pramipexole in a progressive ratio task[77]. Natural rewards such as food or sex enhance ΔFosB expression in the Nacc, striatum, prefrontal cortex and ventral tegmental area[78 79]. Sexual activity-induced ΔFosB expression can be detected after prolonged abstinence, indicating a long-lasting effect[80]. Overexpression of ΔFosB increases sucrose intake and promotes aspects of sexual behaviour[78]. Furthermore, overexpression of ΔFosB in the Nacc core increases food reinforcement and motivation[81]. Sexual activity-induced ΔFosB expression in the Nacc is dependent upon NMDA receptor activation[82], a mechanism reminiscent of Levodopa-induced FosB expression in the striatum. Together, these data suggest that enhanced ΔFosB expression following chronic dopamine replacement therapy may contribute to ICD by increasing an individual's motivational drive for rewards like food or sex potentially leading towards compulsive engagement in behaviours such as binge eating or hypersexuality. In addition to its induction by natural rewards, ΔFosB

is also linked to the trait of impulsivity, with high impulsive animals displaying higher levels of ΔFosB in the Nacc shell[83].

Learning from feedback

Recent studies highlight a role for an imbalance between learning from reward and loss outcomes in ICD behaviours. Two studies suggest that in PD+ICD patients on Levodopa or their usual medications, dopaminergic medications are associated with better learning from negative feedback relative to reward, while PD patients without ICD still showed the same pattern seen typically (i.e. better learning from reward than punishment while on medication). These studies used a difficult (P=0.60 to 0.75) 2-choice probabilistic discrimination task with learning close to chance levels with both reward and loss feedback tested within the same condition [84]. Other studies in which feedback valence was separately tested in different conditions suggest different conclusions. Using a 2-choice probabilistic discrimination task (P=0.80) PD+ICDs subjects tested on DA showed better learning from a reward feedback condition whereas PD controls on DA were slower to learn from a loss feedback condition[85]. Using a Q-learning reinforcement learning algorithm, PD+ICD subjects on versus Off DA showed greater ventral striatal activity to positive prediction error and expected reward with the opposite in PD controls (Figure 3). Similar findings were reported in the reward domain in another study[86], wherein impairments were also documented in the loss domain. Using a probabilistic classification task, PD+ICD subjects tested on dopamine replacement therapy were better at reward learning and worse at punishment learning relative to healthy controls[86]. The authors further assessed model fits of reinforcement learning algorithms. The actor-critic model suggests that the ventral striatal critic uses prediction error to learn stimulus value to update expected

future rewards, whereas the dorsal striatal actor uses the prediction error signal to encode action valuation and selection leading to rewards. The authors show that the actor-critic strategy had a better model fit than the Q-learning strategy. Using the actor-critic algorithm, PD+ICD subjects on medications showed greater reliance on a ventral striatal critic model based on stimulus value with particular impairments in learning from negative prediction errors. In contrast, PD controls (e.g; without ICD) on medication were more reliant on a dorsal striatal actor model based on action values with higher learning rates for positive prediction error. Together these studies suggest impairments in the relative balance of learning from rewards and losses.

Risk and uncertainty

Pathological behavioural choices are associated with decisions between anticipating a positive reward and negative financial, social and occupational consequences with either known (risk) or unknown probabilities (ambiguity). The evaluation of risk involves the representation of anticipated reward and loss value and their integration, representation of probability and possibly, learning from feedback. Rodent and human studies converge to suggest that DA enhance risk-taking. In rodents, the manipulation of precisely timed D2 receptor activity, associated with integration of recent unfavorable outcomes, influences risk taking choices[26]. Similarly, D1 or D2 stimulation during choice acts to increase/decrease the effective action value for alternative actions, supporting the notion that risky choice depends on integrating prospective gains and losses in the same striatal network involved in learning[23].

In rodent studies using intracranial self-stimulation (ICSS) of the medial forebrain bundle, pramipexole enhanced risk-taking[87,88]. The effects were dose-related, such that higher chronically administered doses enhanced risk-taking in all rats, with no effect of the 6-OHDA lesion[88], whereas, lower chronic doses, produced risk-taking only in a portion of 6-OHDA lesioned rats[87]. In humans, DA also increases risk-taking in both PD+ICD subjects and PD controls relative to controls with the gambling disorder subgroup showing greater risk taking[89]. Using a task selecting between sure and risky choices, PD+ICD subjects on DA showed increased risk-taking particularly to gain but not loss anticipation[90]. Similarly PD+ICD subjects on medications show greater risk taking under ambiguity in the Balloon Analogue Risk Task (BART), in which subjects pump up a balloon accumulating reward with an increasing likelihood of the balloon bursting[91].

The ventral striatum encodes both risk probability and in a bi-directional manner represents the anticipation of gain and loss values. PD subjects on DA exhibit lower ventral striatal activity to the risk prospect (i.e. the difference between possible gain and loss outcomes)[89] and to the BART[92] (Figure 3). PD+ICD subjects also had lower orbitofrontal cortex and anterior insular activity to risk representation[90]. These findings suggest possible impairments in the representation of risk or the differentiation between possible gain and loss outcomes.

Impulsivity

Emerging evidence suggests that PD+ICDs subjects have impairments in decisional but not motor impulsivity. Impulsivity is the tendency towards rapid ill-considered disinhibited choices and is a heterogeneous construct with subtypes associated with

distinct but overlapping neural substrates. 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 including response inhibition (inhibition of a prepotent response).

Converging studies show that PD+ICD subjects have enhanced delay discounting relative to PD controls while on relative to off medications[93] and while on medications compared to PD controls on medications[94]. Both PD itself and DA appear to have independent effects in enhancing delay discounting. Using an ICSS model, 6-OHDA lesioned rodents showed greater delay discounting[95]. These findings concur with never-medicated human PD subjects showing elevated delay discounting relative to controls which normalized with dopaminergic medications[96].

In a large multicenter case-control study, PD patients with compulsive shopping and GD had elevated delay discounting but neither those with compulsive shopping or sexual behaviours demonstrated such differences[97]. Impulsive choice normally demonstrates a magnitude effect, whereby lower impulsive choices accompany increasing reward magnitude. This magnitude effect in delay discounting was more pronounced in PD patients with ICDs[97]. Whereas healthy controls normally experience diminishing marginal sensitivity or a decrease in subjective value with increasing objective value, PD patients with ICDs may show more of an effect. These observations suggest that DA in those with ICDs may be associated with enhanced diminishing marginal sensitivity or greater subjective devaluation of the delayed,

higher, reward magnitude[97]. In PD+ICD subjects, greater delay discounting is associated with enhanced baseline dopaminergic terminal function in the anterior putamen as measured using [18F]fluorodopa[98]. This contrasts with dopaminergic lesions of the dorsolateral striatum enhancing delay discounting in rodents[95] and in PD in humans[96,99]. Thus, either dissociable influences from different striatal regions or dopamine tone may influence delay discounting in a U-shaped manner as has been shown for prefrontal cortex dopamine[100].

Greater reflection impulsivity or lower amount of evidence accumulated prior to a decision has also been shown to be impaired in medicated PD+ICDs subjects. In PD subjects, DA, but not Levodopa or deep brain stimulation, increased reflection impulsivity.[101]

Although one study did not detect differences in response conflict (Stroop interference task) in PD+ICD subjects compared to controls[102], comparison of ICD subtypes have shown greater Stroop impairment in compulsive sexual and eating behaviours relative to gambling disorder[103]. PD patients with gambling disorder also show greater low frequency activity in the subthalamic nucleus (STN) during risky or conflictual choices, which were not observed in those without gambling disorder.[104]

PD rodent models show an impact of the parkinsonian lesion and premorbid impulsivity on motor impulsivity. In rats, alpha-synuclein induced nigrostriatal neurodegeneration increased waiting impulsivity and impulsive action. Pramipexole increased waiting impulsivity and impulsive action both in sham and lesioned rats but its effect on waiting impulsivity in lesioned rats was enhanced in animals with pre-

existing impulsivity traits[105]. However, in contrast to impairments in decisional impulsivity in humans, studies either did not detect impairments[93] or showed improvement[106] in motor response inhibition in PD+ICD subjects tested using the stop signal task. Contrasting with ICDs, PD patients with LID display altered motor inhibition, as shown with decreased reaction time during erroneous stop trials [107].

Put together, ICDs are associated with higher decisional impulsivity (delay discounting, risk taking, reflection impulsivity) whereas LID is associated with impaired motor inhibition.

Treatment

Follow-up studies show that ICD symptoms improve in PD patients in whom DA can be decreased or discontinued[8]. However, the replacement of DA with Levodopa for motor symptoms is not always tolerable for all subjects. PD+ICD subjects are also at enhanced risk for dopamine agonist withdrawal syndrome, a stereotyped syndrome characterized by craving, autonomic and psychiatric symptoms[108]. Several randomized controlled studies have been conducted in humans. Amantadine, a dopaminergic and glutamatergic modulator, was effective in PD with GD but has also been shown in a multicenter study to be associated with an increased risk for ICDs[109]. Naltrexone, an opioid antagonist, can decrease ICD symptoms but did not improve global symptom severity[110]. In 6-OHDA lesioned rats, the atypical antidepressant mirtazapine was able to decrease pramipexole-induced risk-taking without interfering with the motor improvements afforded by the DA[87]. Cognitive behavioural therapy has been shown to improve global symptom severity[111]. Thus, the combination of

pharmacotherapy and cognitive behavioural therapy may be a particularly beneficial means to treat ICDs in those that cannot tolerate a change in dose.

STN deep brain stimulation (DBS), which allows a decrease in dopaminergic medication or discontinuation of DA, has been shown in prospective studies to improve ICDs[112,113] although can induce specific forms of impulsivity such as the inability to slow down during high conflict choices[114,115]. Not all retrospective studies demonstrate an improvement and differential outcomes may be related to early identification and careful medication titration and management. ICD subjects are at enhanced risk of post-operative apathy symptoms and dopamine agonist withdrawal syndrome. Although most ICDs improve, very rarely new onset post-operative ICD behaviours, and particularly eating behaviors post-operatively appear to remain symptomatic, worsen or have *de novo* onset. Potential mechanisms underlying these observations are discussed in Box 2.

Intraoperative physiology of the STN has allowed insight into these disorders. PD patients with ICDs or LID undergoing DBS have also been shown to have enhanced low frequency oscillatory activity at different peak frequencies and locations within the STN with cortico-subthalamic coherence implicating prefrontal and motor regions respectively[116] (Figure 3).

Summary

Emerging evidence emphasizes overlapping mechanisms underlying the ICDs and LID in PD, with a dissociable role for ventral and dorsal striatal function in cortico-striatal networks. Panel 2 compares ICDs and LID. From studies in non-human

primates, more fine-grained specificity in striatal regions may be associated with specific behavioural expression (Box 1 and Figure 3C). Studies suggest a potential enhancement of physiological dopaminergic activity in ICDs (enhancing gain, decreasing D2 autoreceptor sensitivity and regulation, decreasing DAT density) which may have an effect on excessive ventral striatal dopamine transmission (summarized in Figure 2) occurring in PD patients with ICDs in specific contexts such as cues, reward anticipation and unexpected rewards and novelty preference (Figure 3). Studies implicating the neural network in ICDs including targets of dopaminergic projections such as the striatum, orbitofrontal cortex, anterior cingulate and anterior insula are summarized in Figure 3. Striatal expression of ΔFosB appears to be a common mediator for LID and ICDs induced by Levodopa and DA.

Rodent models of PD typically exhibit enhancement of the rewarding properties of DA and Levodopa suggesting a facilitatory role for PD (Figure 1). Emerging evidence highlights enhanced learning from reward feedback with a possible impairment in learning from negative feedback. Impulsivity in the decisional (delay discounting, reflection impulsivity and risk taking) rather than the motoric (response inhibition) domains appears to be impaired in PD subjects with ICDs, which may be in part related to the relative engagement of ventral *versus* dorsal striatal regions[117]. These translational cognitive, neurophysiological molecular findings along with how they might relate to the interaction between dopaminergic medications and individual vulnerability and PD is summarized in Figure 4. Several factors discriminate amongst subtypes of ICDs including ventral striatal anatomical specificity, gender, novelty seeking, delay discounting, response conflict and the effect of STN DBS (Box 2), factors that might point towards individual vulnerability predisposing towards the

expression of different behavioural subtypes. Therapeutic interventions including medication adjustment, naltrexone and cognitive behavioural therapy have demonstrated efficacy. We highlight both overlapping and divergent neural mechanisms underlying the expression of motor and behavioural effects of dopaminergic medications. This overview illustrates the recent advances in the understanding of ICD in PD, and the likelihood of developing therapeutic protocols that will effectively treat ICDs.

Legend

Panel 1. Diagnostic criteria

The latest version of the Diagnostic and Statistical Manual of mental disorders, Version 5 (DSM-5) has developed a new category of Behavioural Addictions which includes Gambling Disorder (GD) (left panel) with Internet Gaming Disorder included within Section III as a disorder requiring more study. Binge eating disorder has also been accepted as a diagnostic category within the DSM-5 (middle panel). Operational criteria for compulsive sexual behaviours was developed specifically for Parkinson's disease (Voon et al., Neurology, 2006) and commonly used in studies.

Panel 2. Comparison of Impulse control disorders (ICDs) and Levodopa-induced dyskinesias (LID)

Abbreviations: UPDRS = Unified Parkinson's Disease Rating Scale, DA=dopamine; DAT=dopamine transporter; STN=subthalamic nucleus

Figure 1. Impulse control disorders: interaction of dopaminergic medications with Parkinson's disease and individual vulnerability

Abbreviations: Dec.=decreased; ICDs=Impulse control disorders; DA=dopamine agonists; autoR=autoreceptor

	ICDs	LID
Associated factors		
	Younger age at disease onset	
	Higher UPDRS II	

| | Levodopa treatment | |
| | Living in the United States | |
	Anxiety	
	Male gender	Female gender (*)
Increased DA release	Context-induced	Drug induced
DAT availability	Decreased striatal FP-CIT binding	
STN	Oscillatory activity (theta-alpha-range)	
	Ventral STN	Dorsal STN
	6.71 Hz	8.38 Hz

Box 1. Striatal specificity of motor and behavioral disorders in non-human primate studies

Studies in non-human primates show that specificity of striatal regions can be reversibly induced with microinjections with bicuculline, a GABAa antagonist[118]. Local dysfunction within posterior or anterior parts of the putamen respectively leads to dyskinesia and myoclonus, while local dysfunction within associative and limbic striatal territories evokes behavioral disorders. More specifically, the anterior caudate nucleus is associated with hyperactivity whereas differing subregions of the primate ventral striatum (nucleus accumbens) is associated with different behavioral disorders: the medial region is associated with compulsive sexual behaviours, the central region with repetitive grooming with licking/biting fingers and the lateral regions with hypoactivity associated with a loss of food motivation (See Figure 3C). Within the ventral striatal sub-regions, three distinct topographyically organized cortico-basal ganglia circuits were observed associated with cortical (orbitofrontal cortex, anterior cingulate cortex) and subcortical (caudal levels of basal ganglia) levels[119]. Briefly, sexual behaviours was associated with a circuit involving the orbitofrontal cortex, medial prefrontal cortex and mesial ventral striatum. Compulsive behavior 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. Finally, the 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. As these disorders of motivation were induced by bicuculline in moderately dopamine-depleted monkeys, dopamine may modulate their expression rather than be causal.

Furthermore, chronic treatment with levodopa induces dyskinesia in severely dopaminergic lesioned monkeys and hyperactive and neuropsychiatric like-behaviors (agitation, hallucinatory-like responses, stereotypies and compulsive grooming) in moderately lesioned ones[120]. Thus, dopamine replacement therapies may have a differential impact depending on the pattern and severity of the dopaminergic lesion and associated receptor hypersensitivity, resulting in the expression of different behavioural symptoms. Dyskinesias and behavioral disorders were also abolished following serotonergic lesion, suggesting another crucial player in the modulation of cortico-basal ganglia circuits.

Box 2. Potential mechanisms underlying the differential response to subthalamic stimulation of impulse control disorder subtypes

Subthalamic nucleus deep brain stimulation (STN DBS) can improve impulse control disorders (ICDs) in Parkinson's disease (PD). Although not all retrospective studies demonstrate an improvement, improvement of ICDs has been shown in the long term in prospective studies[112,113]. The capacity to decrease the dose or discontinue dopamine agonists likely plays an important role in the improvement. Other potential mechanisms may include shifting stimulation towards a continuous rather than pulsatile dopaminergic stimulation or possibly normalizing abnormal low frequency oscillations that have been shown to be enhanced in gambling disorder with conflictual risky choices[104]. However, not all ICD subtypes respond equally; in particular, pathological eating behaviours may be more likely to not improve, worsen or having de novo onset[121].

Cognitive mechanisms underlying the ICDs and the effect of STN DBS may explain the differential effect of STN DBS on reward subtypes. As described, the ICDs are impaired in decisional impulsivity such as delay discounting, risk taking and reflection impulsivity. In contrast, STN DBS improves delay discounting in rodents with no clear effect in humans, with no impairment in reflection impulsivity and possible decreases in risk taking behaviours. Thus, STN DBS in PD with ICDs may either improve or not affect these cognitive functions relevant to the ICDs. The ICDs are associated with either an improvement or no difference in motor response inhibition. STN DBS also has a mixed effect on response inhibition with greater impairments as a function of prepotency of response bias, task difficulty, baseline status and early responses dissociable from a late inhibitory process (reviewed in[114]). Differential effects from stimulation of antero-mesial limbic and cognitive subregions of the STN versus motor subregions affecting affective and inhibitory tasks may also result in differential expression of behaviours. In ICDs, the Stroop conflict interference task has been reported to be either no different from controls or more impaired with compulsive sexual behaviors and binge eating relative to gambling disorder. Here, STN DBS is most consistently associated with the inability to slow down and greater errors in the face of conflict or competing responses, which may be more relevant to competing rewards[115]. The medial prefrontal cortex and STN tracks conflict on a trial-to-trial basis with increasing theta and single unit activity related to increased decision thresholds for evidence accumulation[122]. STN DBS impairs this relationship resulting in hastened error-prone decisions to conflict. Given the differential Stroop effect in ICD subtypes, such a cognitive effect may be more relevant to ICDs with binge eating or compulsive sexual behaviours. In rodents, both STN lesions and DBS are associated with a shift of reinforcing value (progressive

ratio reinforcement and conditioned place preference) from cocaine to food rewards[123]. Following STN DBS, the exposure to and decisions related to an intake of natural rewards, particularly food, is unavoidable. Both the enhanced reinforcement value of food and hastened error-prone decisions in the context of such conflictual decisions may specifically contribute to post-operative pathological eating behaviours.

Figure 1. Impact of nigrostriatal lesions on the rewarding properties of dopamine replacement therapy (left panel) and measures of impulsivity (right panel).

(A) Conditioned place preference (CPP) with pramipexole (PPX) in rats with 6-OHDA-induced nigrostriatal neurodegeneration (**, $p<0.001$) [15]. (B) CPP with Levodopa in rats with alpha-synuclein induced nigrostriatal neurodegeneration (*, $p<0.05$) [17]. (C) PPX-induced ΔFosB expression in the striatum and Nacc of sham and 6-OHDA lesioned rats (*, $p<0.05$) with a significant correlation between ΔFosB-positive neurons in the Nacc core and the final ratio achived in a progressive ratio task ($r^2=0.67$, $p<0.05$) [18]. (D) 6-OHDA-induced nigrostriatal neurodegeneration increases impulsive choice (delay discounting task. *, $p<0.05$) [95]. (E) PPX increases waiting impulsivity (differential reinforcement of low rates of responding) in sham and alpha-synuclein induced nigrostriatal neurodegeneration. Increased effect of PPX in lesioned rats with pre-morbid impulsivity (LI: low impulsive, Int: intermediate, HI: high impulsive. *, $p<0.01$ vs saline. #, $p<0.01$ HI vs LI) [105]. (F) Enhanced effect of chronic vs acute PPX ((+/-)2mg/kg/injection) on probability discounting in sham and 6-OHDA lesioned rats 30 min and 6 hr after injection. Open symbols show baseline; shaded symbols show responding after the first injection; filled symbols show

responding after the 25th of twice daily injections (*, p<0.01 vs baseline, ^, p<0.01 vs first injection). Data for 30 min after the acute treatment in shams are not included due to confounds from motor slowing [88].

Figure 2. Example of potential mechanisms underlying the enhancement of physiological dopamine activity

Beyond the direct influence of dopamine agonists on pre- and post-synaptic receptors and its cognitive sequelae, emerging evidence suggest a potential enhancement of physiological dopaminergic activity in Impulse Control Disorders (ICDs) in Parkinson's disease (PD) relevant within specific contexts. The mechanisms that might relate directly to dopamine function include the following: (A) Multiple studies show low striatal dopamine transporter (DAT) levels in ICDs relative to PD controls including prior to the onset of medications or ICD symptoms and despite a lack of difference in disease severity. Images excerpted from[42,43] show differences in striatal DAT between PD patients with and without ICDs and differentiation from punding. Decreased DAT density might enhance the duration and spread of synaptic physiological dopamine activity. (B) Chronic Levodopa in a rodent Parkinsonian model enhances the proportion of dopamine neurons capable of spontaneous activity (i.e. capable of responding to a stimulus such as novelty, salient cues, reward anticipation) hence enhancing dopaminergic gain. This mechanism is presumed to be related to downregulation of presynaptic D2 autoreceptors. Image adapted from[40]. (C) Decreased sensitivity of the midbrain D2 autoreceptor has been shown in PD patients with ICDs relative to PD controls while playing a gambling task thus decreasing D2 autoregulation of dopaminergic activity[46].

Figure 3. Examples of the neural network implicated in Impulse Control Disorders in Parkinson's disease

The neural network implicated in Impulse Control Disorders (ICDs) in Parkinson's disease (PD). (A) Relative to PD controls, the medial orbitofrontal cortex (OFC) shows baseline elevated dopamine synthesis capacity in ICD subjects off medication (left) which may impair the capacity to utilize outcomes to flexibly guide behaviours. ICD subjects show abnormal decreased activity to apomorphine and dopamine agonist challenge in lateral OFC, cingulate and ventral striatum (not shown) to risk representation (second from left) and a gambling task (right)[58,59,90]. (B) Relative to PD controls, ICD subjects show enhanced ventral striatal dopamine release to rewarding cues (left), a gambling task (second from left) and enhanced ventral striatal BOLD activity to reward anticipation and unexpected outcomes (second from right). ICD subjects show abnormal inhibition of baseline ventral striatal activity during an ambiguous risk task (right). The decrease in activity to risk representation might reflect impaired representation of the difference between anticipated gain and loss outcomes[29,50,85,124]. (C) Illustration of sub-regions of the non-human primate ventral striatum with specificity for sexual, aversive and food motivated behaviours and the effects of serotonergic (5-HT) and dopaminergic (DA) denervation (See also Box 1). Excerpted from[120,125]. (C) Local field potential recordings of PD patients with pre-operative ICDs or Levodopa-induced dyskinesia undergoing deep brain stimulation of the subthalamic nucleus (STN) show different low frequency peaks localized to ventral versus dorsal STN with greater prefrontal and motor coherence respectively[116].

Figure 4. Summary of findings in human studies of Impulse Control Disorders in Parkinson's disease

The figure illustrates a summary of the findings in Impulse Control Disorders (ICDs) in Parkinson's disease and illustrates their role in the interactions between individual vulnerability and dopaminergic medications with a possible influence of Parkinson's disease. Abbreviations: DA=dopamine agonist; autoR=autoreceptor; Dec=decrease; FHx=family history

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Panel 1

Gambling Disorder (DSM-5)	Binge eating disorder (DSM-5)	Operational criteria for compulsive sexual behavior in Parkinson's disease
Persistent and recurrent problem gambling: 4+ in 12 month – Increasing amounts to achieve desired excitement – Restless or irritable when cutting down – Repeated unsuccessful attempts to stop – Preoccupied with gambling – Gambles when distressed – Loss chasing – Lies to conceal extent – Social consequences – Relies on others for money	A. Recurrent persistent binge eating B. Binge eating episodes: 3+ – Eating more rapidly – Eating until uncomfortably full – Eating large amounts despite lack of hunger – Eating alone due to embarassment – Feeling disgusted, depressive or guilty C. Marked distress D. Absence of compensatory behaviours	A. Sexual thoughts or behaviours excessive or an atypical change: 1 or more for >1 month – Preoccupation – Inappropriate or excessively requesting sex from partner – Habitual promiscuity – Compulsive masturbation – Pornography or telephone sex lines – Paraphilias B. Consequences: 1 or more – Marked distress – Attempts to control unsuccessful – Time consuming – Interferes significantly with social or occupational functioning C. Not exclusively during hypomania or mania D. If all except C fulfilled, the disorder is subsyndromal

Figure 1

Figure 2
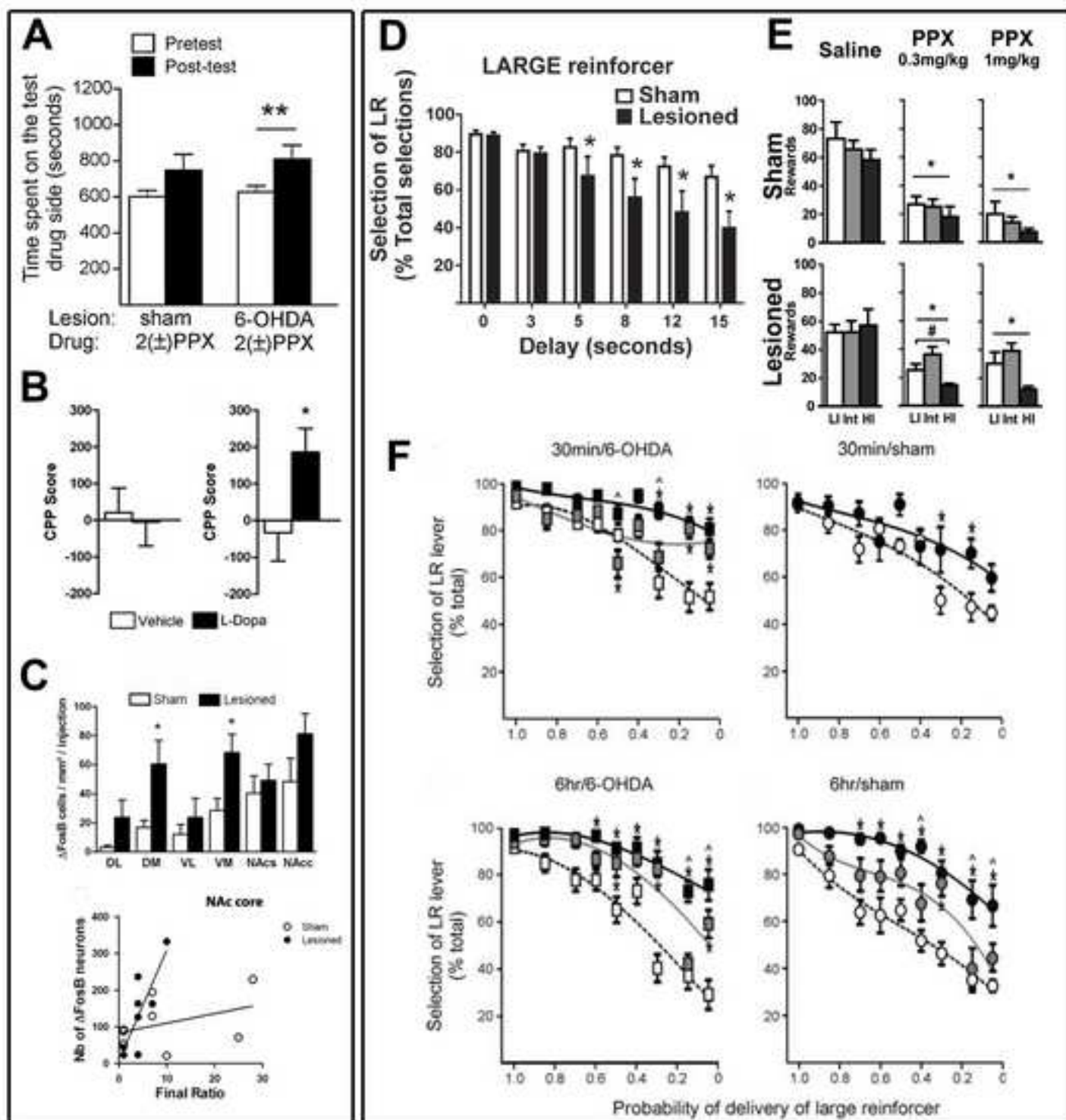**Click here to download high resolution image**

A

123I-FP-CIT BP

PD   PD+ICD Punding

Striatal dopamine transporter (DAT)

Dopamine gain

Midbrain D2 autoreceptor

B

Control

Stimulus → Variable gain → Dopamine signal

Chronic Levodopa

Stimulus → Constant maximal gain → **Dopamine signal**

C

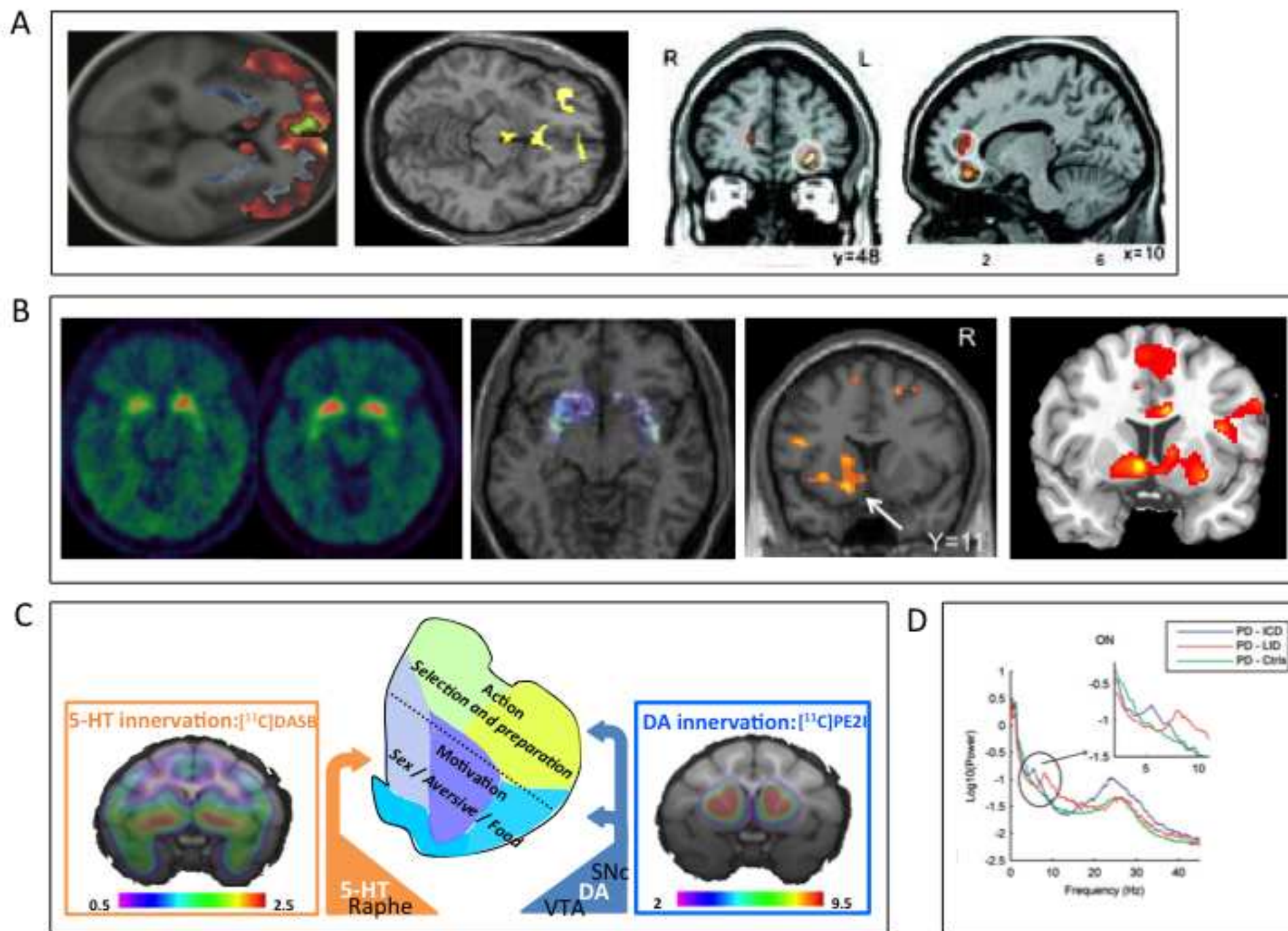Mean midbrain [11C]FLB-457 BP

Control
Gambling task

PD   PD+PG
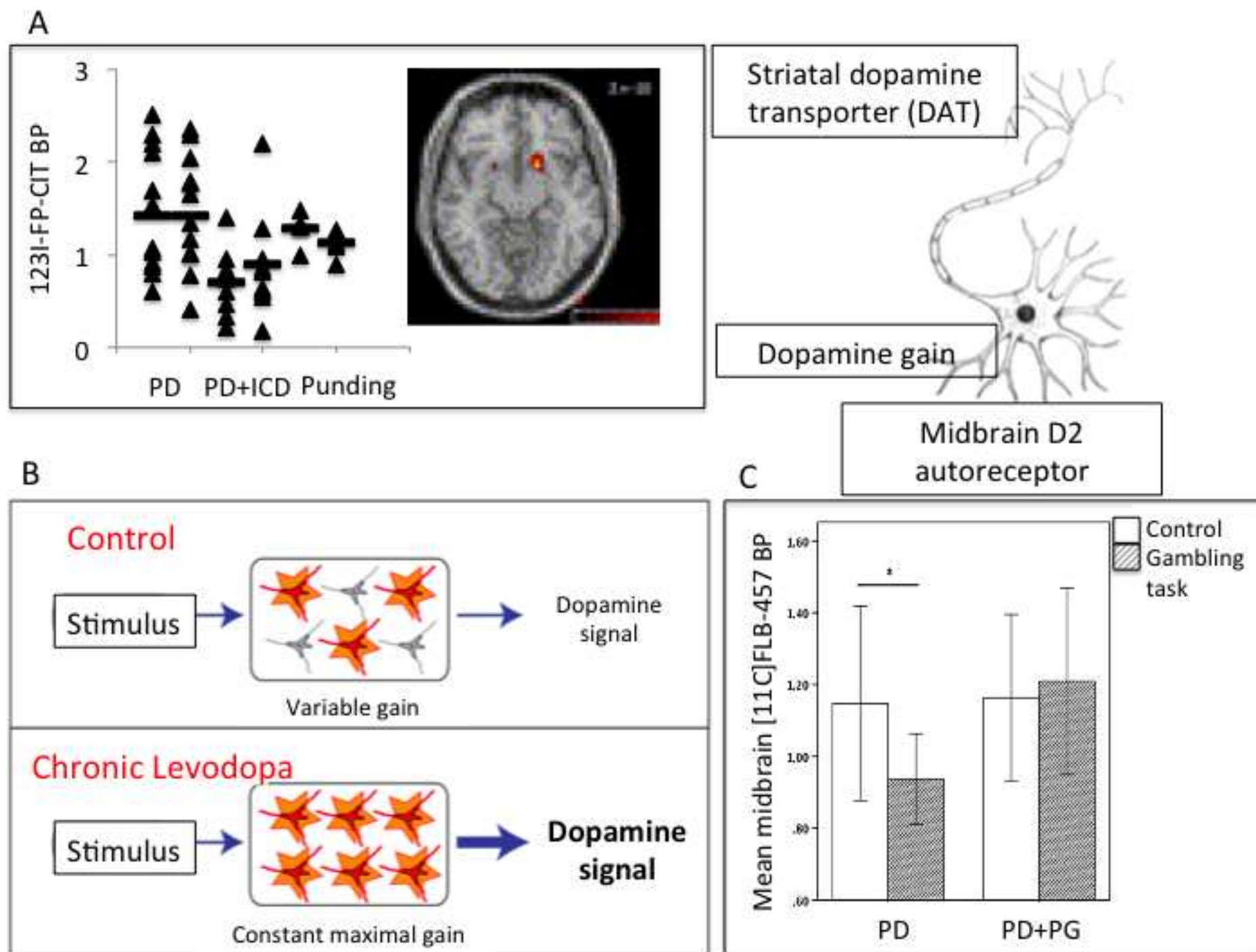
Figure 4
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