HHS Public Access

Author manuscript

Int Rev Psychiatry. Author manuscript; available in PMC 2019 March 11.

Published in final edited form as:

Int Rev Psychiatry. 2017 December ; 29(6): 618–627. doi:10.1080/09540261.2017.1398139.

Positron emission tomography in Parkinson's disease: insights into impulsivity

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Abstract

This study reviews previous studies that employ positron emission tomography (PET) imaging assessments in Parkinson's disease (PD) patients with and without Impulsive Compulsive Behaviours (ICB). This begins with a summary of the potential benefits and limitations of commonly utilized ligands, specifically $D_{2/3}$ receptor and dopamine transporter ligands. Since previous findings emphasize the role of the ventral striatum in the manifestation of ICBs, this study attempts to relate these imaging findings to changes in behaviour, especially emphasizing work performed in substance abuse and addiction. Next, it reviews how increasing disease duration in PD can influence dopamine receptor expression, with an emphasis on differential striatal and extra-striatal changes that occur along the course of PD. Finally, it focuses on how extra-striatal changes, particularly in the orbitofrontal cortex, amygdala, and anterior cingulate, may influence the proficiency of behavioural regulation in PD. The discussion emphasizes the interaction of disease and medication effects on network-wide changes that occur in PD, and how these changes may result in behavioural dysregulation.

Dopamine and impulsivity in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder most commonly associated with a variety of motor features, including rigidity, bradykinesia, and tremor (Dickson et al., 2009; Kalia & Lang, 2015). Nigrostriatal dopamine depletion has long been implicated as the most likely mechanism underlying this group of symptoms (Lindner et al., 1999), a conclusion supported by the effectiveness of dopamine replacement therapies in ameliorating PD-related motor deficits (Kish, Shannak, & Hornykiewicz, 1988). However, PD is also linked with a variety of non-motor symptoms, including depression, anxiety, apathy, autonomic dysfunction, cognitive impairment, as well as hallucinations and delusions (Chaudhuri, Healy, Schapira, & National Institute for Clinical Excellence, 2006). Moreover, there is evidence of additional changes to personality and behaviour, where PD patients exhibit reduced participation in novelty- and sensation-seeking behaviours, and a general tendency towards conservative, risk-averse choices (Evans, Lawrence, et al., 2006; Menza, Golbe, Cody, & Forman, 1993). Previous findings indicate that this psychiatric phenotype may be

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Disclosure statement

D.C. has received personal fees from AbbVie, Acadia, Huntington Study Group, Lundbeck, Neurocrine, Teva Neuroscience, outside of submitted work. A.S. has no conflicts of interest.

related to altered dopaminergic signalling, localized broadly across the mesocorticolimbic network (these regions include the ventral striatum, amygdala, anterior cingulate, and thalamus) (Remy, Doder, Lees, Turjanski, & Brooks, 2005).

Accordingly, dopamine replacement therapy can produce unintended effects on personality and behaviour, leading to heightened impulsivity, novelty seeking, and altered weighing of reward and punishment (Bodi et al., 2009). In certain individuals, these medication-induced behavioural changes are more severe, and can eventually lead to a problematic compulsion towards reward-driven activities. These are collectively defined as impulsive-compulsive behaviours (ICBs), where the most common manifestations are the pursuit of gambling, shopping, sex, and eating (Voon, Potenza, & Thomsen, 2007; Weintraub, David, Evans, Grant, & Stacy, 2015). Participation in repetitive, non-goal-directed behaviours (known as punding) and an increased interest in personal hobbies have also been included under the general umbrella of ICB symptoms (Voon et al., 2007); however, questions remain regarding potential distinctions in the neurobiology and cause of hobbyism/punding vs ‘classical’ ICBs (Evans et al., 2004; Voon et al., 2014). Combined with the fact that the two behavioural categories are often co-expressed, the use of ‘ICBs’ as a term must be considered with this potential heterogeneity in mind. As a result, the present review is focused on studies investigating the four more-strictly defined ICBs, but punding constitutes a potential confounding factor.

Due to the fact that ICBs present in a sub-set of PD patients (note that prevalence estimates vary greatly, from 15–40% treated with dopamine replacement therapies) (Garcia-Ruiz et al., 2014; Weintraub et al., 2015), a number of previous studies have sought to identify causative neurobiological factors that predict ICB vulnerability. This information is valuable in understanding the basic underpinnings of ICB, and, more generally, the factors that contribute to behavioural alterations in PD. Because the initiation of dopamine replacement therapies (especially dopamine agonist) suggests a causative role between dopamine therapy and changes to behaviour, dopamine molecular imaging strategies such as positron emission tomography (PET) have been especially useful in expanding our understanding of the neurobiologic basis of these presentations. In this review, we summarize past work, with the goal of integrating previous findings and distinguishing areas where further exploration is needed. First, we discuss evidence of altered pre- and post-synaptic dopamine receptor and dopamine transport density in the basal ganglia in the context of ICB, as well as potential differences in dopamine release properties. Next, we discuss these changes in the context of the disease-related changes that occur as part of the PD disease progression. Finally, we discuss the relatively under-studied topic of extra-striatal dopaminergic biomarkers, and the need for further examination.

Dopamine D_2 and D_3 receptor expression in ICB

While there is some indication that levodopa can play a role in the development of ICBs, a preponderance of evidence implicates dopamine receptor agonist (DAgonist) medication as a more specific causative factor, substantiated by the fact that discontinuation or reduction of DAgonist in ICB+ individuals results in symptomatic improvement (Claassen, Kanoff, & Wylie, 2013). Commonly administered DAgonists (e.g. ropinerole and pramipexole) exert

their pharmacological effect by preferentially binding D_2-like dopamine receptors ($D_3 > D_2$). This understanding has encouraged an investigation of how $D_{2/3}$ functions in the context of the mesocorticolimbic dopaminergic system, and whether abnormalities in receptor expression could be related to impulsivity in PD.

D_2 and D_3 radioligand qualities

In order to better delineate the role of dopaminergic molecular biomarkers underlying impulsivity in PD, past studies have successfully used PET imaging techniques to investigate dopamine-related changes in patients with ICB. This has been accomplished through the use of a number of radioligands with different properties, a highly influential factor in interpreting previous results. For the most part, prior investigations of $D_{2/3}$ receptor status in PD and ICB have used compounds with the ability to assay either extra-striatal or striatal binding, but not both concurrently.

[^{11}C]raclopride is a $D_{2/3}$ radioligand with a relatively low receptor affinity, rendering it most appropriate for measuring $D_{2/3}$ in the receptor-rich striatum (Hall, Ogren, Kohler, & Magnusson, 1989; Hirvonen et al., 2003). It has been occasionally used in certain extra-striatal areas with comparatively high $D_{2/3}$ levels, such as the thalamus (Hirvonen et al., 2003), but it cannot effectively quantify binding potential in the cortex. On the other hand, high-affinity radioligands such as [^{11}C]FLB-457 can assess binding in extra-striatal regions with limited $D_{2/3}$ expression (such as the cortex), but cannot accurately estimate binding in the striatum (Farde et al., 1997; Hall et al., 1989). Other radioligands have been used in PD populations, but have similar limitations: [^{11}C]-(+)-PHNO is a D_2-like radioligand that has relatively high preferential affinity for the dopamine D_3 vs the D_2 receptor, with the ability to measure binding in striatal and limited extra-striatal regions (such as the midbrain) (Boileau et al., 2009), but cannot fully describe extended limbic and cortical areas (Egerton et al., 2010). As a result, prior work has largely focused upon striatal $D_{2/3}$ binding, with a smaller selection focusing extrastriatally instead. A second important consideration when interpreting results is whether the study measures $D_{2/3}$ binding with or without concurrent stimulus. When a pharmacological challenge or behavioural task is administered to study subjects during scanning, binding values are more likely to reflect stimulus-evoked dopamine release. Because endogenous synaptic dopamine competes with radioligand binding, decreased values likely reflect increased dopamine release, rather than lower $D_{2/3}$ expression. When scanning is conducted without stimulus, binding is more likely to be related to baseline receptor status.

PET measures of $D_{2/3}$ in ICB

Prior PET experiments of ICB+ subjects have applied all aforementioned radioligands to populations that differ based on ICB status, testing pharmacologic/behavioural effects on receptor binding, and resting-state binding. Using [^{11}C]raclopride (Steeves et al., 2009) and [^{11}C]-(+)-PHNO (Payer et al., 2015), two studies have reported decreased $D_{2/3}$ binding in the ventral striatum at baseline in ICB+ patients, which could either indicate reduced receptor expression or an increased baseline dopamine tone. Payer et al. (2015) also indicated a relationship between ICB severity and ventral striatal $D_{2/3}$ binding, where lower

$D_{2/3}$ correlated with more severe symptoms. However, other [^{11}C]raclopride studies have not replicated this effect, observing no difference between groups (Evans, Pavese, et al., 2006; O'Sullivan et al., 2011). Using [^{11}C]FLB-457, $D_{2/3}$ binding outside the striatum has been examined, indicating that ICB+ patients are distinguished by increased binding in the anterior cingulate cortex, where state impulsivity positively correlated with midbrain and anterior cingulate binding at baseline (Ray et al., 2012).

These reports have also investigated the effects of various acute stimuli on dopamine release. Evans, Pavese, et al. (2006) administered doses of levodopa as a pharmacological challenge, reporting decreased binding (indicating increased dopamine release) in the ventral striatum of ICB+ patients, which correlated positively with symptom severity. O'Sullivan et al. (2011) similarly used levodopa, but observed increased ventral striatal dopamine release only during visual presentation of reward-related cues (but not neutral cues). Concurrent participation in a gambling task also resulted in greater release of dopamine in the ventral striatum (Steeves et al., 2009) and diminished dopamine release in the midbrain (Ray et al., 2012). Previous PET investigations of D $_{2/3}$ binding in ICB+ are summarized in Table 1.

Combined, these reports indicate the presence of altered dopaminergic function in the ventral striatum. In the context of the broader literature on maladaptive reward-based behaviours and addiction in otherwise healthy humans, there is a variety of evidence that heavily supports the involvement of dopamine, and, more specifically, $D_{2/3}$ receptors. In pre-clinical models, decreased ventral striatal $D_{2/3}$ receptor expression is associated with greater trait impulsivity (as indexed by the ability to withhold premature motor responses) as well as drug-taking behaviour in rodents and non-human primates (Dalley et al., 2007; Nader et al., 2006). Previous studies also consistently reveal ventral striatal $D_{2/3}$ reductions in human drug addiction (Trifilieff & Martinez, 2014).

In contrast, when ventral striatal $D_{2/3}$ is artificially over-expressed, motivation for long-term effortful outcomes over short-term reward is increased (Trifilieff et al., 2013) and intake of cocaine and alcohol is decreased (Thanos, Michaelides, Umegaki, & Volkow, 2008; Thanos et al., 2001). Over the long-term, these changes may become more extensive, where reductions in dorsal $D_{2/3}$ receptor distribution emerge after the behaviour has become chronic (Dalley et al., 2007; Nader et al., 2006). While involvement of this phenomenon in ICB is inconclusive, as baseline striatal binding reductions were observed in some studies (Payer et al., 2015; Steeves et al., 2009) but not replicated in others (Evans, Pavese, et al., 2006; O'Sullivan et al., 2011), pre-existing ventral striatal $D_{2/3}$ reductions could be a potential mechanism conferring vulnerability to impulsive behaviour and ICB. The lack of uniform results may be influenced by the relatively small sample sizes included in previous work, necessitating the need for future studies. Additional studies are also needed to better understand extra-striatal $D_{2/3}$ in the context of ICB. Ray et al. (2012) indicated increased binding in the anterior cingulate, which aligns well with the known association between the structure and reward processes (Haber & Behrens, 2014). However, the behavioural relevance of $D_{2/3}$ localized to the anterior cingulate is unclear.

The finding of ICB-related increases in striatal dopamine release in response to levodopa and reward- or gambling-related stimuli appears consistent throughout prior work (Evans,

Pavese, et al., 2006; O'Sullivan et al., 2011; Steeves et al., 2009). In this way, it is also possible that ICB+ individuals are characterized by an acute or functional hyperdopaminergic state, either instead of, or in addition to, long-term patterns of receptor expression. Past studies that address biologic causes of addiction define a clear role for striatal dopamine release. Overall, the ventral striatum mediates the reward prediction and evaluation components of instrumental conditioning, functioning as a key intermediary in the reinforcing effects characteristic of addiction's initial stages (Everitt & Robbins, 2005; O'Doherty et al., 2004). Moreover, ventral striatal dopamine transmission is an essential component in maintaining both the reinforcement and psychostimulant properties of drugs of abuse (Caine & Koob, 1994; Pettit, Ettenberg, Bloom, & Koob, 1984). Downstream from the ventral striatum, dopamine release is also crucial in more dorsal areas of the structure, where it is essential to functional mechanisms of habit-based learning in addiction paradigms (Vanderschuren, Di Ciano, & Everitt, 2005; Yin, Knowlton, & Balleine, 2004). A net increase of striatal dopamine release in ICB+ individuals could, therefore, lead to differences in both vulnerability to addiction and the tendency to maintain subsequent compulsive patterns of maladaptive behaviour. It is also possible that ICB+ is characterized by heightened dopamine release in the midbrain (Ray et al., 2012). The interface between ventral and dorsal striatal areas is conducted via the feed-forward striato-nigro-striatal loop (Haber & Knutson, 2010); therefore, dysfunctional dopamine release may be a network-wide phenomenon.

PET measures of the dopamine transporter in ICB

Another dopaminergic biomarker that expresses differences in ICB is the dopamine transporter (DAT). A number of studies have emphasized reductions in ventral striatal dopamine transporter (DAT) levels, as quantified by single-photon emission computed tomography (SPECT) using [^{123}I]FP-CIT (Cilia et al., 2010; Voon et al., 2014; Vriend et al., 2014). Similarly, a large longitudinal investigation using data acquired from the Parkinson's Progression Markers Initiative (PPMI) found that lower binding in the putamen and total striatum at any point after baseline was linked to the development of ICBs, where a decrease in caudate and total striatum DAT binding over the first year on dopamine replacement therapy was also a risk factor (Smith, Xie, & Weintraub, 2016). This change could result either from a loss of dopaminergic nigrostriatal terminals (Scherfler et al., 2007), a compensatory down-regulation of DAT (Troiano et al., 2009), or a pre-existing natural variation in DAT density (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009). Regardless of cause, it appears likely that this change is related to co-localized increases in ventral striatal dopamine release observed in studies of $D_{2/3}$ density, as decreased DAT availability could be linked with reduced pre-synaptic monoamine re-uptake. Resulting increases in ventral striatal synaptic dopamine have been associated with the manifestation of impulsive behaviours in pre-clinical models (Baarendse & Vanderschuren, 2012; Pattij, Janssen, Vanderschuren, Schoffelmeer, & van Gaalen, 2007), which may proceed through impairment of negative feedback processes during episodes of reward learning (Frank, Seeberger, & O'Reilly, 2004). Previous SPECT investigations of DAT binding in ICB are summarized in Table 2.

Longitudinal changes to $D_{2/3}$ in PD patients

A key question is whether dopaminergic biomarkers that appear to be abnormal in ICB (such as altered $D_{2/3}$ expression or altered patterns of circuit-wide dopamine release) were pre-existing, or were generated by long-term experiences. Chronic treatment with $D_{2/3}$ receptor agonists likely affects $D_{2/3}$ levels through mechanisms of receptor internalization (Itokawa et al., 1996; Kim et al., 2001), and is known to induce desensitization of D_2 autoreceptors in rodents (Chernoloz, El Mansari, & Blier, 2009) meaning that group differences in these cellular responses to medication could also be involved. Another crucial concern is the effect of PD-related neurodegeneration, which is especially important in attempting to understand the status of the extra-striatal areas that are not well-captured by previous ICB-related work.

A number of previous PET studies have examined this issue, using a variety of radioligands to investigate determinants of both motor and non-motor PD symptoms. The presence of altered $D_{2/3}$ levels within the basal ganglia of PD patients is well-substantiated by previous work. Using [^{11}C]raclopride, one previous report indicated that early PD is characterized by increased BP_{ND} in the putamen and no difference in the caudate relative to healthy controls. However, progression into moderate PD resulted in net decreases to striatal BP_{ND}, where putamen levels were now comparable to control subjects, and the caudate expressed significant reductions (Antonini, Schwarz, Oertel, Pogarell, & Leenders, 1997). Other [^{11}C]raclopride studies have parallelled this result through the finding that upregulation of striatal $D_{2/3}$ is preserved throughout the early phase of PD (Rinne et al., 1993), and that this upregulation is apparent in the putamen rather than the caudate (Rinne et al., 1995).

In the striatum, $D_{2/3}$ receptor upregulation is the initial post-synaptic compensatory mechanism in response to the dopamine degeneration, which is then followed by more long-term post-synaptic adaptations (Falardeau, Bedard, & Di Paolo, 1988). As midbrain cell-death occurs in the ventrolateral portion, where cell bodies largely project to the posterior striatum (especially the posterior putamen), it is likely that the largest DA reduction and subsequent receptor upregulation more heavily affect the putamen vs the caudate (Gibb & Lees, 1991; Rinne et al., 1993, 1995). Due to the relative restriction of this pattern to the putamen, long-term post-synaptic reductions in $D_{2/3}$ expression affect both structures (Antonini et al., 1994). $D_{2/3}$ distinctions in the globus pallidus have been previously observed in a [^{11}C]-(+)-PHNO study of PD, reporting significantly reduced binding in comparison to control subjects (Boileau et al., 2009).

Overall, it is clear that PD produces long-term effects on $D_{2/3}$ binding in the basal ganglia, affecting interpretation of studies completed in ICB+ populations. Because of the dorsal-ventral gradient of $D_{2/3}$ loss in the striatum due to PD (where portions of the posterior putamen are affected before the anterior caudate), the ventral striatum could be relatively spared from the dopaminergic denervation present in the dorsal portions of the structure. Subsequent use of DAgonist therapy could appropriately rescue the hypodopaminergic state in the dorsal striatum and thereby produce therapeutic motor effects, but ‘overdose’ more well-preserved ventral striatal tracts, inducing ICBs (Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). This understanding would align with past evidence linking heightened dopamine with impulsive behaviours (Baarendse & Vanderschuren, 2012; Frank

et al., 2004; Pattij et al., 2007) and increased dopamine release with ICB (Evans, Pavese, et al., 2006; O'Sullivan et al., 2011; Steeves et al., 2009). However, evidence of decreased baseline ventral striatal $D_{2/3}$ binding in ICB could complicate this interpretation (Payer et al., 2015; Steeves et al., 2009), as this pattern would not correspond with the expected outcome in the context of greater nigrostriatal terminal preservation. While these reports could be a result of increased baseline synaptic dopamine or receptor internalization in response, PET studies in ICB have not been able to disentangle long-term pre-synaptic and post-synaptic receptor expression from acute dopamine release, and it is likely that ICB is produced by the inter-play of a number of factors.

Previous PET studies have assayed extra-striatal $D_{2/3}$ BP_{ND} using the radioligand [^{11}C]FLB-457, reporting decreased BP_{ND} in the thalamus, anterior cingulate cortex, dorsolateral and ventromedial pre-frontal cortex, orbitofrontal cortex, temporal cortex, precuneus, and fusiform gyrus (Kaasinen et al., 2000; Ko et al., 2013). These changes were evident in advanced rather than early PD, and a longitudinal [^{11}C]FLB-457 investigation found that extra-striatal $D_{2/3}$ loss parallelled disease progression and occurred at a faster rate than in the striatum (Kaasinen, Aalto, NAgren, Hietala, Sonninen, & Rinne, 2003). As a result, loss of autoreceptors secondary to degeneration of mesotelencephalic dopamine neurons, as well as loss of post-synaptic $D_{2/3}$ is likely involved. Broadly, dopaminergic signalling in many components of extra-striatal limbic networks appear to be affected by PD. Abnormalities in these areas could also play a role in the manifestation of ICBs, and future studies should further investigate $D_{2/3}$ expression and dopamine release in these regions. Previous PET investigations of $D_{2/3}$ binding in PD are summarized in Table 3.

Medication effects on imaging results

In the context of previously reported DAT differences in ICB, similar questions of chronic agonist treatment and the effects of PD are also relevant. Pramipexole is known to exert specific effects on DAT expression in PD patients, which can be distinguished from other dopamine replacement therapies (Guttman et al., 2001; Parkinson Study Group, 2002). Moreover, striatal DAT reductions following initiation of therapy have been linked to development of ICBs (Smith et al., 2016). Additionally, reduced DAT binding is a well-known feature of the nigrostriatal denervation that proceeds as part of the PD course, to the point that reduced striatal DAT levels observed through SPECT are sometimes used as a diagnostic tool for PD (Lindner et al., 1999; Perlmutter & Norris, 2014; Scherfler et al., 2007). Therefore, it is likely that interpretation of this biomarker in the context of ICB and impulsivity could also be complex.

Future directions: extra-striatal dopaminergic biomarkers and impulsivity

In investigating both $D_{2/3}$ and DAT as biomarkers of impulsivity, past work has largely focused on distinctions that localize to the striatum. Given the extensive dopaminergic innervation in this area relative to extra-striatal locations, this specificity is unsurprising. In combination, these data clearly emphasize a difference in the structural and functional aspects of the ventral striatum, which is in alignment with the area's importance in the reward circuit (Haber & Behrens, 2014). However, previous studies using [^{11}C]FLB-457 to

capture extra-striatal $D_{2/3}$ in PD have also shown considerable differences outside of the striatum, highlighting that changes in these areas could also serve as important determinants of ICB and impulsivity in general (Kaasinen et al., 2000, 2003; Ko et al., 2013). Furthermore, other regions interact with the ventral striatum to subserve crucial components of reward learning, impulsivity, and decision-making. The importance of the midbrain is unmistakable, as the major source of dopaminergic input throughout the brain (Haber & Behrens, 2014), while the orbitofrontal cortex, amygdala, and anterior cingulate are associated with abstract evaluation and encoding of stimuli, maintenance of expected reward information, and selection of appropriate responses, respectively (Gleichgerrcht, Ibanez, Roca, Torralva, & Manes, 2010). Only Ray et al. (2012) has previously approached this topic in the context of ICB, through the use of [^{11}C]FLB-457 to observe changes in midbrain and the anterior cingulate $D_{2/3}$ that correlated with state impulsivity. However, additional studies are needed to replicate and extend this finding, which was observed in a relatively small number of patients. In addition, although [^{11}C]FLB-457 provides highly accurate estimates of cortical $D_{2/3}$, analysis of more receptor-rich limbic regions such as the amygdala or hippocampus could benefit from the use of other radioligands with more rapid washout, such as [^{18}F]fallypride (Mukherjee et al., 1999; Narendran et al., 2009; Olsson, Halldin, Swahn, & Farde, 1999). Similarly, radioligands such as [^{18}F]fallypride that can estimate both striatal and extrastriatal $D_{2/3}$ could provide a comprehensive depiction of dopaminergic changes across the network relevant to impulsivity in PD, either through assessment of receptor expression or dopamine release.

Conclusion

Through the use of a variety of techniques and molecular dopaminergic biomarkers, it is clear that ICB, impulsivity in PD, as well as other non-motor symptoms, are likely to result from a complex system of neurochemical changes. Future experiments should assess the development of ICBs in a de novo PD population through a longitudinal method, with specific attention towards pre-existing and subsequent changes in D_2-like receptor expression in the striatum and extra-striatal areas. If decreased ventral striatal binding potential predicts subsequent development of ICB, it would provide a powerful clinical tool, permitting screening and individualization of medication routines to avoid negative behavioural outcomes. Overall, these findings emphasize a distinct association between medication-induced-reward-driven-behaviours and altered expression of D_2-like receptors in key striatal and extra-striatal components of reward networks in PD.

Acknowledgments

Funding

D.C. has received grant support from the National Institutes of Health [NINDS; R01NS097783, K23NS080988], Michael J. Fox Foundation, as well as AbbVie, Bristol-Myers Squibb, C2N, CHDI, Eli Lilly, Teva, Vaccinex, and Wave Pharmaceuticals.

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Table 1.

Summary of D_2-like receptor PET findings in ICB

First Author	Last Author	Publication Year	Radioligand	ICB Type	Method	Significant ROIs
Evans	Piccini	2006	[^{11}C]raclopride	Dopamine Dysregulation Syndrome	Acute (levodeopa challenge)	Ventral striatum ($^{+}$)
					Baseline	None
					Behavioral correlation (disease severity[a])	Ventral striatum (pos.)
Steeves	Strafella	2009	[^{11}C]raclopride	Pathological gambling	Acute (gambling task)	Ventral striatum ($^{+}$)
					Baseline (control task)	Ventral striatum ($ICB+<ICB-$)
O'Sullivan	Piccini	2011	[^{11}C]raclopride	General ICB	Acute (levodopa + neutral cues)	None
					Acute (levodopa + reward-related cues)	Ventral striatum ($^{+}$)
					Baseline	None
Ray	Strafella	2012	[^{11}C]FLB-457	Pathological gambling	Acute (gambling task)	Midbrain ($^{-}$)
					Baseline (control task)	ACC ($ICB+>ICB-$)
					Behavioral correlation (state impulsivity[b])	Midbrain (pos.) ACC (pos.)
Payer	Boileau	2015	[^{11}C]-($^{+}$)-PHNO	General ICB	Baseline	Ventral striatum ($ICB+<ICB-$) Dorsal striatum ($ICB+>ICB-$)
					Behavioral correlation (ICB severity[a,b])	Ventral striatum (neg.)

(ICB+>ICB-): indicates baseline D2/3 BPnd increase in ICB+ compared to ICB- subjects

(ICB+<ICB-): indicates baseline D2/3 BPnd decrease in ICB+ compared to ICB- subjects

(+): indicates increased dopamine release in ICB+ subjects

(−): indicates decreased dopamine release in ICB+ subjects

(pos.): indicates positive correlation

(neg.): indicates negative correlation

ACC: anterior cingulate cortex

a: "wanting" drug (Drug Effects Questionnaire)

b: Barratt Impulsivity Scale-11

Table 2.

Summary of DAT SPECT findings in ICB

Authors	Publication Year	Radioligand	ICB Type	Method	Significant ROIs
Cilia et al.	2010	[^{123}I]FP-CIT	Pathological gambling	Baseline	Ventral striatum (ICB+<ICB-)
Voon et al.	2014	[^{123}I]FP-CIT	General ICB	Baseline	Ventral striatum (ICB+<ICB-)
Vriend et al.	2014	[^{123}I]FP-CIT	General ICB	Baseline (longitudinal)	Ventral striatum (ICB+<ICB-) Ventral striatum (ICB+<ICB-)
Smith et al.	2016	DaTSCAN™ [^{123}I]β-CIT	General ICB	Baseline (longitudinal)	Right caudate[a] (ICB+<ICB-) Right putamen[b] (ICB+<ICB-) Total striatum[a,b] (ICB+<ICB-)

(ICB+>ICB-): indicates baseline DAT binding increase in ICB+ compared to ICB- subjects

(ICB+<ICB-): indicates baseline DAT binding decrease in ICB+ compared to ICB- subjects

a: over the first first year

b at any post-baseline visit

Table 3.

Summary of D_2-like receptor PET findings in PD

Authors	Publication Year	Radioligand	PD Severity	Significant ROIs
Rinne et al.	1993	[^{11}C]raclopride	Early PD	striatum (^*)
			Moderate PD (+6 months)	striatum (^*)
Rinne et al.	1995	[^{11}C]raclopride	Early PD	putamen (PD>HC)
Antonini et al.	1997	[^{11}C]raclopride	Early PD	putamen (PD>HC)
			Moderate PD (+3 to 5 yrs.)	Caudate (PD<HC) Caudate (−) Putamen (−)
Kassinen et al.	2000	[^{11}C]FLB-457	Early PD Advanced PD	-- dlPFC (PD<HC) ACC (PD<HC) ACC (−) temporal cortex (PD<HC) thalamus (PD<HC)
Kassinen et al.	2003	[^{11}C]FLB-457	Early PD	--
			Moderate PD (+3 to 5 yrs.)	dlPFC (−) temporal cortex (−) thalamus (−)
Boileau et al.	2009	[^{11}C]-(+)-PHNO	Moderate PD	ventral striatum (PD<HC) globus pallidus (PD<HC) putamen (>HC)
Ko et al.	2013	[^{11}C]FLB-457	Moderate PD	dlPFC (PD<HC) vlPFC (PD<HC) ACC (PD<HC) OFC (PD<HC) middle temporal (PD<HC) inferior temporal (PD<HC) fusiform (PD<HC) precuneus (PD<HC) thalamus (PD<HC)

(PD>HC): indicates baseline D2/3 BPnd increase in PD compared to HC subjects

(PD<HC): indicates baseline D2/3 BPnd decrease in PD compared to HC subjects

(+): indicates D2/3 increase longitudinally

(−): indicates D2/3 reductions longitudinally

(^*): indicates D2/3 increase in hemisphere contralateral to first symptom, relative to ipsilateral hemisphere

ACC: anterior cingulate cortex

dlPFC: dorsolateral prefrontal cortex

vlPFC: ventrolateral prefrontal cortex

OFC: orbitofrontal cortex