The neurobiology of impulse control disorders in Parkinson’s disease: from neurotransmitters to neural networks

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Abstract
Impulse control disorders (ICD) are common neuropsychiatric disorders that can arise in Parkinson’s disease (PD) patients after commencing dopamine replacement therapy. Approximately 15% of all patients develop these disorders and many more exhibit subclinical symptoms of impulsivity. ICD is thought to develop due to an interaction between the use of dopaminergic medication and an as yet unknown neurobiological vulnerability that either pre-existed before PD onset (possibly genetic) or is associated with neural alterations due to the PD pathology. This review discusses genes, neurotransmitters and neural networks that have been implicated in the pathophysiology of ICD in PD. Although dopamine and the related reward system have been the main focus of research, recently, studies have started to look beyond those systems to find new clues to the neurobiological underpinnings of ICD and come up with possible new targets for treatment. Studies on the whole-brain connectome to investigate the global alterations due to ICD development are currently lacking. In addition, there is a dire need for longitudinal studies that are able to disentangle the contributions of individual (genetic) traits and secondary effects of the PD pathology and chronic dopamine replacement therapy to the development of ICD in PD.

Keywords Parkinson’s disease · Impulse control disorder · Neurobiology · Neuroimaging · Dopamine

Introduction
It is nowadays generally appreciated that Parkinson’s disease (PD) should not be regarded as merely a movement disorder. PD patients also commonly suffer from a broad range of non-motor symptoms. Of these, neuropsychiatric disorders are the most salient. Examples include anxiety, depression, apathy, psychosis and impulse control disorders (ICD) (Cooney and Stacy 2016). Studies in the last two decades have increasingly implicated the PD pathology, including degeneration of neurotransmitters (e.g., dopamine, serotonin or acetylcholine) in the pathophysiology of PD-related neuropsychiatric symptoms (Ceravolo et al. 2013; Frisina et al. 2009; Lim et al. 2009; Politis et al. 2010; Remy et al. 2005; Thobois et al. 2010; Voon et al. 2014; Vriend et al. 2014a, c). Strategies to manage these symptoms are therefore focused on optimising the dosage of dopaminergic medication and prescribing adjuvant pharmacotherapeutics (e.g., selective serotonin inhibitors or acetylcholinesterase inhibitors) (Connolly and Lang 2014; Seppi et al. 2011). Unlike apathy, depression and certain forms of anxiety, ICD does not improve with dopaminergic medication. In fact, development of ICD in PD has been consistently linked to the use of dopaminergic replacement therapy, most notably dopamine (D3) agonists (Joutsa et al. 2012a; Vela et al. 2016; Weintraub et al. 2010, 2013). Prevalence rates of ICD in unmedicated PD patients are similar to those of the general population (Weintraub et al. 2013). Approximately 15% of all medicated PD patients suffer from one or more clinically-significant ICD (Weintraub et al. 2010) but more patients screen positive for subclinical symptoms of ICD (Joutsa et al. 2012b; Vela et al. 2016; Vriend et al. 2014a). Examples of ICD include hypersexuality, pathological gambling, binge eating disorder and compulsive shopping (Weintraub et al. 2015). The prevalence rates of these ICDs seem to depend, among others, on cultural factors and gender (Maloney et al. 2017; Weintraub et al. 2015). Problematic
internet use has also recently been suggested as a type of PD-related ICD (Wu et al. 2014). Phenomena related to ICD are hobbyism, punding, hoarding and dopamine dysregulation syndrome (DDS) but these are thought to have a distinct pathophysiology and risk profile (Weintraub et al. 2015). Besides the use of dopamine replacement therapy, other risk factors for ICD development include male gender, early disease onset, personal or family history of (behavioral) addiction, depression and point-mutations in certain dopamine or glutamate receptor genes (Bastiaens et al. 2013; Joutsa et al. 2012b; Lee et al. 2009; Weintraub et al. 2010). Management of ICD mainly consists of reducing the dosage of dopamine replacement therapy but this may give rise to dopamine withdrawal syndrome and exacerbate motor and psychiatric symptoms (Ramirez-Zamora et al. 2016). A systematic review concluded that there is currently insufficient evidence for an effective treatment (Tanwani et al. 2015; but see Ramirez-Zamora et al. 2016). For more details about the clinical aspects of ICD, see Weintraub et al. (2015).

Despite the relatively high prevalence rates of ICD in medicated PD patients, a large proportion do not develop ICD. This reflects the high heterogeneity of PD (van Balkom et al. 2011) and also indicates that ICD develops due to an interaction between dopamine replacement therapy and an as yet unknown neurobiological vulnerability. This review focuses on the neurobiological underpinnings of ICD and its development on multiple spatial scales, from genes and neurotransmitters, to brain regions and networks.

**Dopamine**

Given the well-documented link between dopamine replacement therapy and ICD development in PD, it seems natural to suspect a direct involvement of (alterations in) the dopamine system. Before we delve into studies that implicate the dopamine system in the pathophysiology of ICD, it must be noted that dopaminergic medication—specifically dopamine D2-family receptor agonists—may also increase impulsivity by preventing pauses in D2-signaling through phasic endogenous dopamine release in the reward-related ventral striatum (Frank et al. 2004; Gerlach et al. 2003). In healthy conditions, these pauses in phasic dopamine release signal negative outcome after a particular behavioral response and tells the individual to avoid this behavior in the future (e.g. money loss after gambling) (van Eimeren et al. 2009). By preventing punishment learning but leaving positive reinforcement intact (which activates dopamine D1 receptors), dopaminergic medication impairs the encoding of harmful behavior and increases the probability of impulsive behavior and behavioral addiction. Studies in both medicated PD patients (e.g., Cools et al. 2006; Muhammed et al. 2016; Van Wouwe et al. 2017) and animal models (Cocker et al. 2017; Johnson et al. 2011; Rokosik and Napier 2012; Tremblay et al. 2017) have shown the impulsivity inducing effects of dopaminergic therapy. Nevertheless, the effects seem to depend on certain clinical and neural characteristics (e.g., baseline dopamine levels) (Claassen et al. 2011; Cools and D’Esposito 2011) and on the type of task (Voon et al. 2017). For a more thorough review on the effects of dopamine replacement therapy on impulsive behavior in PD see Voon et al. (2017). Nevertheless, although these studies show that dopaminergic medication precipitates impulsive behavior in PD patients, their use does not seem sufficient to cause clinically significant ICD.

**Dopaminergic vulnerability to ICD development**

PD patients with ICD (PD+ICD) exhibit several alterations in the dopamine system that may make them more vulnerable to the impulsivity inducing effects of dopamine replacement therapy. On the genetic level, multiple studies have associated gene polymorphisms of components of the dopamine signaling cascade with ICD but results have been mixed and generally based on small samples (Krishnamoorthy et al. 2016; Lee et al. 2009; Vallecilunga et al. 2012; Zainal Abidin et al. 2015). Multiple cross-sectional molecular imaging studies with various radiotracers for the dopamine system have compared PD+ICD with PD patients without ICD (PD−ICD) and have provided some important insights into this system’s role in ICD. Nevertheless, some caution is advised when interpreting findings from molecular imaging studies. The resolution of molecular imaging scans is relatively coarse and makes interpretation about fine-grained structures (e.g., in the midbrain) difficult, e.g., due to spillover effects. Furthermore, binding of a radiotracer to a receptor always has to compete with the endogenous neurotransmitter and therefore between-group differences may be explained by alterations in the endogenous release of dopamine, altered availability of the receptor or a combination of the two. PD+ICD have been reported to exhibit higher endogenous dopamine release in the ventral striatum during performance of a gambling task (Steeves et al. 2009) or while viewing reward-related visual cues (O’Sullivan et al. 2011; Wu et al. 2015) compared with PD−ICD. PD+ICD also show lower ‘resting-state’ binding of [11C]Raclopride (a selective tracer for the D2 receptor) (Steeves et al. 2009) and lower binding of [11C]-(+)-PHNO (a D3 receptor selective tracer) in the ventral striatum (Payer et al. 2015). In addition, lower [11C] FLB-457 binding in the midbrain to D2/3 autoreceptors was observed during a gambling task (Ray et al. 2012). Lower D2/3 receptor availability is also
found in studies on ICD or addiction in non-PD samples (Boileau et al. 2013; Volkow et al. 2002, 2008) and animal models (Dalley et al. 2007; Nader et al. 2006). Cross-sectional single photon emission computed tomography and positron emission tomography studies on the dopamine transporter (DAT) - that clears dopamine from the synaptic cleft after its release - have consistently shown reduced striatal DAT availability in PD+ICD compared with PD−ICD (Cilia et al. 2010; Lee et al. 2014; Voon et al. 2014). The problem with all studies that cross-sectionally compare PD+ICD with PD-ICD is that it is unclear if the neurobiological differences are due to already pre-existing neural characteristics (before PD or ICD onset), effects of prolonged dopaminergic therapy or alterations associated with ICD development. In that light, a retrospective follow-up study was performed that showed that lower DAT availability in the ventral striatum of medication naïve PD patients predated the development of ICD after commencing dopamine replacement therapy (Vriend et al. 2014a). Later, this finding was partly corroborated by a large prospective cohort study of PD patients that were medication-naïve at inclusion. A larger decrease in striatal DAT availability within the first year after inclusion increased the risk of ICD development after commencing dopamine replacement therapy (Smith et al. 2016). The reduced DAT availability may be interpreted as a (genetically) lower presence of DAT in the presynaptic dopamine neuron or more pronounced dopamine degeneration (Scherfler et al. 2007). In a previous review, the author postulated a tentative neurobiological model for the development of ICD, with a prominent role for degeneration of dopamine projections to the reward-related ventral striatum (Vriend et al. 2014b). This view, however, is at odds with the prevailing ‘overdose theory’ for ICD development, which states that the dosage of dopamine agonists used to supplement the loss of dopamine in the putamen to treat the motor symptoms overdose the relatively preserved ventral striatum with dopamine (Voon et al. 2011b). As a result, postsynaptic dopamine D2-like receptors are overstimulated, leading to an imbalance between the ‘on’ and ‘off’ pathways of the reward-related cortico-striatal-thalamocortical circuit, thereby promoting impulsivity. For more information about the normal physiology of the cortico-striatal-thalamocortical circuits and the neuromodulatory role of dopamine see Gerfen and Surmeier (2011) and Haber and Knutson (2010). For more details on the overdose theory, see Voon et al. (2011b). The overdose theory is based on the observation that striatal dopamine denervates along a ‘caudo-rostral’ gradient with the posterior putamen being affected first and the ventral striatum only becoming affected in the later stages of the disease (Damier et al. 1999; Hsiao et al. 2014a; Kish et al. 1988). Due to the compensatory mechanisms of the brain, motor symptoms do not develop until approximately 50–60% of the nigrostriatal dopamine projections are degenerated (Cheng et al. 2010; Fearnley and Lees 1991). The threshold for the development of ICD is, however, unknown. It is therefore possible that the risk of ICD development is already increased at a lower percentage (e.g., 30%) of degeneration of dopaminergic projections to the ventral striatum. Whether or not ventral striatal dopamine degeneration plays a role in ICD development could be investigated with radiotracers selective for the presynaptic vesicular monoamine transporter 2 (VMAT2). VMAT2 is responsible for the uptake and storage of monoamines in vesicles prior to release at the presynaptic terminal (Bohnen et al. 2006) and may be less influenced by compensatory changes that can occur after dopamine degeneration compared with DAT (Bohnen et al. 2006; Hsiao et al. 2014b; Okamura et al. 2010). No study has yet investigated VMAT2 availability in relation to ICD in PD.

In summary, there is ample and still increasing evidence that heightened reward-related ventral striatal dopamine signaling, particularly through D3 receptors, is involved in the pathophysiology of ICD in PD. What is, however, less evident is whether or not this hyperdopaminergic state is due to pre-existing variants in components of the dopamine signaling cascade, associated with alterations due to the PD pathology or secondary effects of chronic dopaminergic treatment, or ICD development.

**Beyond dopamine**

The ascending PD pathology also affects and eventually destroys, among others, serotonin- and noradrenaline-producing neurons (Braak et al. 2003). These neurotransmitter systems may also play a role in impulsive behavior and the pathophysiology of ICD. Most evidence for a role of serotonin in impulsive behavior comes from animal studies. It must be noted, however, that impulsivity is an umbrella term and encompasses multiple different subdivisions of impulsive behavior that are differently affected by serotonin signaling (Pattij and Schoffelmeer 2014; Winstanley et al. 2004). Enhancement of serotonin signaling, e.g., with selective serotonin reuptake inhibitors (SSRIs), reduces impulsive action in the five-choice serial reaction time task (Baarendse and Vanderschuren 2012; Homberg et al. 2007) but has no effect on impulsive choice in the delayed reward task (Baarendse and Vanderschuren 2012) and action cancelation in the stop-signal task (Bari et al. 2009). Similarly, lesioning serotonin-producing neurons in the raphe nucleus decreases inhibitory control in the five-choice serial reaction time task (Winstanley et al. 2004) and Go/No-Go task (Harrison et al. 1999) but has no effect on impulsive choice (Winstanley et al. 2004) or action...
cancelation (Eagle et al. 2009). In healthy humans, the SSRI citalopram enhanced activity of inhibition-related brain areas during a Go/No-Go task but had no effect on behavioral performance (Del-Ben et al. 2005; Macoveanu et al. 2012). Modulating serotonin levels during action cancelation also does not affect inhibitory control in humans (Chamberlain et al. 2006; Nandam et al. 2011), although these results may also partly reflect individual differences in the (integrity of the) serotonin system (Macoveanu et al. 2012; Ye et al. 2014). In PD - ICD patients, citalopram decreased action cancelation during the stop-signal task and enhanced task-related brain activation of the inferior frontal gyrus (Ye et al. 2014). Nevertheless, this effect was only observed in advanced stage PD patients. Only one single small study has investigated the role of serotonin in ICD in PD patients and found an association between polymorphisms in the 5-HT2a receptor gene and ICD (Lee et al. 2009).

The noradrenergic system has not been studied in relation to ICD development in PD. In PD patients without psychiatric disorders, however, atomoxetine, a selective noradrenalin re-uptake inhibitor (SNRI), was able to increase inhibition-related activity in the inferior frontal gyrus (Ye et al. 2015). In correspondence with a study in healthy controls (Nandam et al. 2011), atomoxetine had no overall effect on behavioral performance but was associated with behavioral improvement in those subjects that showed a more pronounced increase in inferior frontal gyrus activation (Ye et al. 2015). In a double-blind placebo-controlled study in PD patients, atomoxetine was able to improve action cancelation accuracy and reduce reflection impulsivity and risk taking (Kehagia et al. 2014). The link between the noradrenergic system and impulsive behavior has been studied more extensively in animal models. Overall, it can be stated that increases in noradrenergic signaling improve impulse control (Baarendse et al. 2013; Chamberlain et al. 2007; Robinson et al. 2008) but the mechanism is still unknown and is partly dependent on the subtype of impulsive behavior (see Bari and Robbins 2013 for a review).

Another neurotransmitter system that has recently been linked to ICD in PD is the opioid system. Opioid receptor antagonists, e.g., naltrexone, have been found to reduce symptoms in non-PD patients with alcohol addiction (Rosner et al. 2016; Nandam et al. 2011), pathological gambling (Grant et al. 2008) and in other disorders within the impulsive-compulsive spectrum (see Piquet-Pessoa and Fontenelle, 2016 for a review). In PD + ICD patients, naltrexone had no effect on a clinician-rated global change score in ICD severity (primary outcome measure) but only a small and not clinically relevant effect on self-reported ICD symptom severity relative to placebo (Papay et al. 2014). The neurobiological mechanism of action of naltrexone is currently unknown but for alcohol addiction it has been suggested that it reduces reward-related mesolimbic dopamine release (Middaugh et al. 2003).

In conclusion, other neurotransmitters besides dopamine may be implicated in the pathophysiology of ICD in PD, although studies on this subject are scarce. Furthermore, there are complex interactions between the dopamine, serotonin and noradrenaline system (e.g., dopamine and noradrenaline rely on the same biosynthetic pathway) (Benarroch 2009; Boureau and Dayan 2010; Rommelfanger and Weinshenker 2007) and (pharmacologically) influencing one system will also have consequences for another. This hampers clear-cut interpretation of study results.

Nevertheless, given the results from animal studies and preliminary evidence that suggest that serotonergic, noradrenergic or opioid drugs can ameliorate inhibitory control in PD, more studies into these systems are warranted.

**Imaging studies on brain structure and function during task and rest**

Although few, a number of studies have used functional neuroimaging techniques to examine brain alterations associated with ICD at the local and network level. Given the nature of ICD, neural activation studies have mainly focused on reward-based tasks. Presentation of reward-related visual cues during fMRI increased activation of the ventral striatum of PD patients with pathological gambling (Frosini et al. 2010) or hypersexuality (Politis et al. 2013) compared with those without. Conversely, during risk taking neural activity in the ventral striatum is decreased in PD + ICD compared with PD - ICD (Rao et al. 2010; Voon et al. 2011a). On the other hand, the only resting state fMRI study published to date showed no alterations between PD + ICD and PD – ICD in the connectivity of the ventral striatum with other reward-related brain areas (Carriere et al. 2015). They did, however, observe between-group differences in the connectivity of the associative striatum (anterior putamen, dorsal caudate) and to a lesser extent the motor striatum (posterior putamen). The anterior putamen showed less connectivity with, among others, the inferior temporal and frontal gyrus and anterior cingulate gyrus, while the dorsal caudate showed less connectivity with the orbitofrontal cortex, middle frontal and inferior temporal gyrus. The lower connectivity of the associative striatum in PD + ICD patients versus PD – ICD patients is consistent with the theoretical framework from Mary Phillips and colleagues on the neural basis of affective disorders, stating that an imbalance between an underactive dorsal—associative—control system and overactive ventral—limbic—emotion system can give rise to neuropsychiatric symptoms (Phillips et al. 2003, 2008). The associative striatum and connected areas are also highly involved in cognitive functions, especially executive functions (Monchi et al. 2007; O’Callaghan et al. 2014) and the reduced connectivity of the associative striatum might therefore also underlie some of the reports on executive...
effects on motor and psychiatric symptoms (Ramirez-Zamora et al. 2016). New treatments for ICD by modulating the dopaminergic and noradrenergic systems, or possibly the opioid system, are being explored.

Lastly, neuroimaging can be a powerful tool to investigate neurobiological mechanisms and risk factors for ICD. Although the relatively few studies that have investigated structural and function of brain areas and networks involved in ICD have provided important insights, they are somewhat hampered by small sample sizes and heterogeneity in study designs, making cross-study comparisons (in a meta-analysis) challenging. Furthermore, except for two (Smith et al. 2016; Vriend et al. 2014a), all the reported studies were performed cross-sectionally, making it difficult to discern whether results are explained by pre-existing (genetic) traits or associated with pathological alterations due to the PD pathology, alterations due to chronic dopamine replacement therapy or their dependence on medications for ICD.

**Conclusions and future prospects**

Based on an abundance of research, it seems clear that ICD in PD is linked to a hyperdopaminergic state. Whether this is due to overexpression of dopamine to a relatively spared ventral striatum, i.e., ‘overdose theory’ (Cools 2006; Voon et al. 2011b) or dopamine denervation-induced receptor supersensitivity of D3 receptors in the ventral striatum (Prieto et al. 2011; Vriend et al. 2014b) is still unknown (Fig. 1). It has also been argued that the PD pathology is not or only a minor contributor to the development of ICD because there are also reported cases of ICD in non-PD patients treated with dopaminergic drugs (e.g., restless legs syndrome) (Tippmann-Peikert et al. 2007). Although it is true that PD patients without medication are at higher risk of developing ICD compared with the general population (Weintraub et al. 2013), un medicated PD-ICD patients do exhibit subclinical inhibitory deficits (Obeso et al. 2011; Vriend et al. 2015) or altered reward sensitivity (Aarts et al. 2012) and medicated PD + ICD and matched PD − ICD are equally impaired in learning from punishment compared with healthy controls (Leplow et al. 2017). This suggests that the effects of the PD pathology on the dopamine system play a role in ICD development. ICD subtypes and different aspects of impulse control might be differentially affected by dopamine degeneration and dopamine suppletion (see Voon et al. 2017 for a review).

It is also important to consider the role of the serotonergic and noradrenergic systems in ICD. Serotonergic approaches to treat ICD often fail because adjusting the dopaminergic medication dosage can prompt withdrawal symptoms or exacerbate motor and psychiatric symptoms (Ramirez-Zamora et al. 2016). New treatments for ICD by modulating the serotonergic and noradrenergic, or possibly the opioid system, may circumvent this.

In conclusion, various functional and structural imaging studies have investigated ICD in PD. These studies generally implicate the reward-related prefrontal and striatal areas, although there are inconsistencies in the direction of the effect and null findings have also been reported. This is partly due to the small sample sizes of individual studies.
Dopamine denervation induced receptor supersensitivity

Dopamine Overdosing

dopamine transporter
G-protein coupled dopamine receptor
supersensitive G-protein coupled dopamine receptor
endogenous dopamine
dopamine agonist (exogenous)
dopamine projections to striatal subregions
increased connectivity
decreased connectivity
interaction. Answering this question warrants longitudinal neuroimaging studies that follow patients from the early unmedicated stages (or preferably even before PD onset). Because the development of ICD after commencing dopaminergic therapy is highly variable (Bastiaens et al. 2013), this would require following a large group of patients for multiple years.

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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