REVIEW

Linking Neuroscience With Modern Concepts of Impulse Control Disorders in Parkinson's Disease

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ABSTRACT: Patients with Parkinson's disease (PD) may experience impulse control disorders (ICDs) when on dopamine agonist therapy for their motor symptoms. In the last few years, a rapid growth of interest for the recognition of these aberrant behaviors and their neurobiological correlates has occurred. Recent advances in neuroimaging are helping to identify the neuroanatomical networks responsible for these ICDs, and together with psychopharmacological assessments are providing new insights into the brain status of impulsive behavior. The genetic associations that may be unique to ICDs in PD are also being identified. Complementing human studies, electrophysiological and biochemical studies in animal models are providing insights into neuropathological mechanisms associated with these disorders. New animal models of ICDs in PD patients are being implemented that should provide critical means to identify efficacious therapies for PD-related motor deficits while avoiding ICD side effects. Here, we provide an overview of these recent advances, with a particular emphasis on the neurobiological correlates reported in animal models and patients along with their genetic underpinnings. © 2014 International Parkinson and Movement Disorder Society

Key Words: dopamine agonists; pramipexole; L-dopa; 6-OHDA; imaging; PET; fMRI; basal ganglia; prefrontal cortex

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Impulse control disorders (ICDs) are diagnosed in otherwise healthy people, and untreated patients with de novo Parkinson's disease (PD) show a similar prevalence of ICDs to that of healthy controls.[1] However, ICD prevalence is significantly higher in PD patients who are on dopamine agonist therapy.[2] Impulse control disorders are diverse, including pathological gambling, hypersexuality, paraphilias, binge eating, and excessive shopping. Although milder impulsivity is observed even in the absence of ICDs in PD, the emergence of these disorders can have an exceedingly grave impact on the quality of life for the affected PD patient, as well as their families and caretakers. Some PD patients undergoing levodopa (L-dopa) therapy show a related disorder, referred to as dopamine dysregulation syndrome (DDS). With a different profile from ICDs, DDS includes compulsive drug-related seeking and procurement (akin to drug addiction) and stereotypic behaviors. The focus of this discussion is on ICDs and their particular association with dopamine agonists. Currently, the main therapeutic approaches for reducing ICDs in PD is dose reduction, discontinuation of the offending agent, or switching to a different dopamine replacement protocol, all of which can undermine the motor benefits afforded by the agonist. Identifying means to avoid or manage agonist-associated ICDs is essential. Advances in clinical research are detailing the ICD profile in PD, and these descriptions provide the basis for studies on the neurobiology of the disorders, and for discovery of viable new targets for therapeutic interventions. Here, we overview recent advances in ICD identification and assessments, neurobiological and genetic underpinnings defined by both clinical and preclinical experimentation, and potential means to thwart ICDs during pharmacotherapy for PD motor symptoms.

Risk, Uncertainty, and Impulsivity in Parkinson's Disease and Rodent Models

Impulsivity, often defined by the lack of behavioral inhibition, reflects abnormalities in decision making (choice) and motor control (response inhibition). Impulsive choice is characterized by a preference for immediately available rewards (even if smaller), instead of delayed rewards (even if larger), which can be quantified in *delay discounting tasks*. Impulsive choice can be described in PD patients with ICDs using delay discounting tasks with either hypothetical long delayed monetary rewards[3,4] or real-time short delay monetary rewards.[3] PD patients with ICDs consistently demonstrate a strong preference for the small immediate rewards. Disrupted delay discounting with intact reward incentive performance in PD patients

presenting ICDs likely reflects impairment in waiting for the delayed reward, rather than an enhanced incentive toward the small immediate reward.[4] Although impulsive choice normally demonstrates a magnitude effect, whereby lower impulsive choices accompany increasing reward magnitude, this effect is less pronounced in PD patients with ICDs, suggesting that dopamine agonists may be associated with greater subjective devaluation of the delayed, higher reward magnitude.[3] The result is greater impulsivity toward the smaller, immediate choice. Pathological behavioral choices can be associated with either positive or negative outcomes, consistent with definitions of choice related to risk (with known or unknown probabilities).[5] These can be measured in *probability discounting tasks*. Studies focusing on risk anticipation without outcome show that dopamine agonists increase risk-taking in PD patients with ICDs.[5,6] This risk-taking bias appears to be unrelated to loss aversion.[6] Greater reflection impulsivity (or decisions under uncertainty without adequate information sampling),[5] delay discounting,[2,5] and novelty seeking in the context of uncertainty[7] may reflect underlying uncertainty about mapping future actions into rewards.[8] Motor response inhibition is also impaired by PD, with, for example, increased stop-signal reaction times and more frequent NoGo commission errors,[9,10] although a limited role exists for dopamine in modulating these motor inhibition tasks. Finally, although impulsive PD patients do not perform differently from nonimpulsive PD patients on the Stroop color word test (which probes inhibition of prepotent responses), dopamine agonists in PD patients with ICDs do enhance the rapidity of decision making (also known as reflection impulsivity), suggesting that the long-term negative consequences may not be as carefully considered as they otherwise would be.[11]

Many aspects of human ICDs and the identifying tasks can be recapitulated in (or deconstructed for) testing in laboratory animals. This is a critical step toward providing relief for those who suffer from ICDs, because animal models expand our capacity to identify neurobiological constructs that contribute to these disorders and, thus, therapeutic targets. Unfortunately, the wealth of species-related tasks on ICDs have not been widely applied to animal models of PD. One study in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–treated *Macaca mulatta* monkeys using a motor readiness (impulse control) task reported increases in reaction time at delays of 1, 2, and 3 seconds, suggesting a possible increase in impulsivity in these animals.[12] In rats with 6-hydroxydopamine–induced lesions of the dorsolateral striatum, delayed discounting tasks using delays of 3 to 15 seconds and intracranial self-stimulation as the reward, reveal a greater intolerance to the longer

delay than that seen in controls.[13] However, these outcomes do not parallel reports for the "normal" incidence of ICDs in de novo PD patients.[1] Because the delays tested in animal studies were very short, disrupted discounting may have reflected, at least in part, temporal processing errors, for interval timing within the seconds to minutes range is dysregulated in striatal neuropathologies.[14] Probability discounting has also been tested in rats with 6-hydroxydopamine–induced lesions of the striatum using intracranial self-stimulation[15] and with this task, discounting is *not* altered by striatal lesions,[15] in keeping with normal incidence of ICDs reported for de novo PD patients.[1] Probability discounting with self-stimulation rewards also emulate the association of dopamine agonist treatment and ICDs in PD, for long-term treatments. Pramipexole increases the preference for the risky choice in the lesioned rats (as well as in unlesioned controls), and this effect is reversed on terminating the pramipexole, and reinstated when the agonist treatment is reintroduced.[15] These studies are helping to clarify the relationship between the parkinsonian brain state and the presence of a dopamine agonist on ICD-like profiles.

Neuroanatomical Substrates Associated With Impulse Control Disorders in Parkinson's Disease

Imaging studies have been used to identify the neural networks and receptor abnormalities underlying impulsivity and ICDs in PD. In the general population, impulsive subjects show larger amphetamine-induced release of dopamine in the striatum.[16] Similar abnormalities also have been reported in PD patients with pathological gambling. For example, after presentation of a reward, PET studies show increased dopamine release and reduction in dopamine transporter in the ventral striatum of PD patients with pathological gambling.[17,18] Recently, radiotracers with high affinity for extrastriatal D2/D3 receptors (e.g., [18F] Fallypride, [11C] FLB-457) have provided evidence of the role of extrastriatal regions in the pathogenesis of ICDs in PD patients.[16,19] A [11C] FLB-457 PET study revealed differences in midbrain and medial prefrontal dopaminergic activity between PD patients with and without pathological gambling.[19] Thus, dopamine receptor abnormalities,[17,19] including reduction in transporter proteins,[18,20] support the hypothesis that PD itself may predispose patients to impulsivity. The contribution of the effects of chronic dopamine agonist therapy requires careful consideration,[21-23] this implies that dopamine agonists in general may predispose PD patients to risky behavior that is responsible for the aberrant decision-making process.

Recently, in patients with PD, different aspects of inhibition control/impulsivity were shown to rely on different neural networks.[24] These positron emission tomography (PET) activation studies showed that impulsive choices acted mainly on the decision-making neural network with reduced activation of the medial prefrontal cortex and posterior cingulate. These changes appeared quite different from what has been reported with impulsive actions associated with stimulation of the subthalamic nucleus, which largely affect the activation of the cortical areas underlying reactive and proactive response inhibition of motor response inhibition.[25]

Studies focusing on risk anticipation without outcome show that dopamine agonists increase risk taking in PD patients with ICDs[6,26] that is accompanied by lower ventral striatal, orbitofrontal, and anterior cingulate activity.[6] Reductions in ventral striatal activity are consistent with a functional magnetic resonance imaging (fMRI) study of PD patients with ICDs using the balloon analogue risk task (BART) that examines uncertainty with feedback.[27] Impairments in 'executive' function and working memory also have been demonstrated, and are linked to changes in the dorsolateral prefrontal cortex. For example, visuospatial working memory 'on' medication is impaired in medicated PD patients with ICD compared with those without.[11] Similarly, PD patients with ICD when 'on' or 'off' medications have a significantly reduced digit span compared with PD and control groups.[26] These results suggest that dorsolateral cortex and ventral striatal circuitry in PD with ICD might be adversely affected by an imbalance in dopaminergic systems. This could arise from a relative 'overdose' from exogenous dopaminergic agonists when 'on' medication, and possibly even from endogenous dopamine (as compared with levels in the motor cortex to dorsal striatum) when 'off' medication.

The incidence of ICDs in untreated PD patients is not much greater than that seen in the normal population.[1] However, impulsivity can present in PD even in the absence of ICDs, and this occurs across a wide range of behavioral, symptomatic, and neuropsychological measures.[9,10,28] It is a multifaceted construct, with choice impulsivity (as above), reductions in the analysis of available evidence for decision making ('reflection impulsivity'[29]), and impairments of motor inhibition (eg, Stop-signal tasks or NoGo paradigms). These dimensions of impulsivity may be synergistic and multifactorial in PD. For example, in addition to the well-known deficits of dopamine, PD also depletes noradrenaline[30] and serotonin[31] and changes white matter tracts that connect prefrontal regions for inhibitory control to the striatum.[32]

Considerable evidence shows that serotonin regulates action restraint in terms of both behavior and activation of the critical right inferior frontal gyrus.[33-39]

Noradrenaline reuptake inhibition also improves inhibition and activation of the right inferior frontal gyrus.[40-43] Accordingly, Ye et al.[44,45] investigated the potential for serotonergic reuptake inhibition by citalopram and noradrenergic reuptake inhibition by atomoxetine to improve response inhibition in patients with PD. They studied both changes in behavior (for clinical relevance) and fMRI (for translation between PD and systems neuroscience studies of inhibition). Atomoxetine enhanced activation of the right inferior frontal gyrus during a Stop-Signal task, in proportion to disease severity (Unified Parkinson's Disease Rating Scale [UPDRS]).[45] Behavioral improvements were associated with increased activation of the right inferior frontal gyrus; higher structural frontostriatal connectivity; and functional connectivity between cortex and striatum. Citalopram similarly improved response inhibition performance, and enhanced inferior frontal activation in patients with more severe disease (UPDRS).[44] A simple machine learning approach to predict a meaningful behavioral response to atomoxetine and citalopram (eg, 30% reductions in the effect of PD on performance)[46] reveals that common demographic and clinical metrics (age, UPDRS, L-dopa dose) and baseline structural imaging (diffusion-weighted imaging of the frontrostriatal tract) enable prediction accuracy of 80%, which could support stratification into clinical trials. Together, these reports illustrate the insights gained from combining multimodal brain imaging with psychopharmacological studies. These potential therapies for impulsivity in PD are adjunctive to continuing dopaminergic medication.

Complementing human imaging studies are electrophysiological and biochemical assessments in awake-behaving laboratory rodents. Such studies have revealed that the prefrontal cortex, ventral striatum, and their dopaminergic innervation play critical roles in directing behavior toward rewards and reinforcement learning.[47-50] These neural elements are implicated in PD, and as overviewed previously, their role in impulsive behavior in humans is beginning to be resolved.[27,51,52] The association with dopamine agonist treatment and ICDs in PD[53] suggests an involvement of dopamine signaling in these behaviors.

The ventral striatum (including the nucleus accumbens) interfaces cortical and limbic inputs, and its outputs to downstream structures that regulate motor and reward-related behaviors. Striatal neuronal ensembles are critical for approach behaviors, providing an energizing signal for behavior,[54] although the exact role remains unclear. Some studies suggest that the striatum is more active during behavioral inhibition than approach,[55] whereas others support separate neural circuits within the nucleus accumbens that govern 'Go' and 'NoGo' processes.[56] To measure how the nucleus accumbens encodes reward expectation,

approach ('Go'), and inhibition of behavior ('NoGo'), Roitman and colleagues recorded the pattern of firing of individual nucleus accumbens neurons in rodents performing an impulsivity task.[57] In this task, rats were trained to press a lever that is presented unexpectedly at random intervals for a palatable, sucrose pellet reward. Rats quickly learn to engage in this reward-directed behavior. On a minority of trials (25%), lever presentation is accompanied by a 'NoGo' cue that instructs the rat to withhold the lever press, and successful inhibition is reinforced with reward as in Go trials. The magnitude of the neural response to the onset of each trial depended on whether the animal initiated or inhibited behavior. Higher levels of nucleus accumbens activity at the time of lever presentation preceded behavioral inhibition of the lever press, whether correctly for NoGo trials, or in error on Go failures.[57] Two populations emerged to contribute to the overall elevation in activity that preceded behavioral restraint. One population responded with increases in firing rate at the onset of each trial, with larger increases preceding the inhibition of lever presses. The second population responded with a reduction in firing rate at trial onset, with smaller reductions preceding the inhibition of the prepotent behavioral response. These two populations of neurons might constitute different pathways of dopaminergic communication through the nucleus accumbens (D1/substance P/dynorphin-direct pathway vs. D2/enkephalin-indirect pathway). Possibly the two types of responses are intermixed in both pathways, and that both contribute to the precise regulation of behavior.[58] Reductions in activity attributable to larger decreases and smaller increases would respectively bias the output toward a release of inhibition over motor initiation in such downstream structures as the ventral pallidum.[59] These single-neuron recordings from rats are complementary to, and enhance the resolution of, human imaging studies showing that this circuitry may contribute to the risky decision making reported for PD patients who exhibit ICDs[6,24] (Fig. 1).

The assessment of the maladaptive processes associated with PD pathology is aiding the translation from single-neuron studies to the clinic. That severe dopaminergic lesions are associated with PD motor pathology and these are associated with compensatory mechanisms within the dopamine system, including increased tyrosine hydroxylase activity, decreased reuptake, and increased D2 receptor number that occurs during the course of dopaminergic deafferentation,[60,61] is well documented. However, one factor that does not change with these large lesions is the activity state of the dopamine neurons, that is, the proportion of dopamine neurons active, their average firing rate, and pattern are unchanged. This is thought
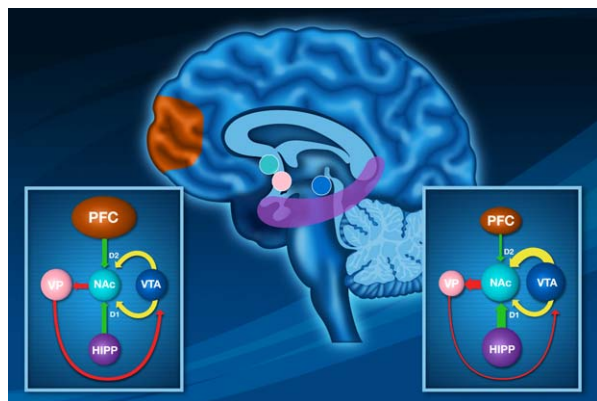
FIG. 1. A diagram showing the primary excitatory drives of the ventral striatum and its modulation by dopamine. The ventral hippocampal input arising from the hippocampal subiculum (HIPP) is believed to be involved in context dependency. As such, this drive should function to maintain focus on the context of the current task to the exclusion of competing stimuli. In contrast, evidence indicates that one function of the prefrontal cortex (PFC) is to facilitate behavioral flexibility, or the propensity to deviate from a task that is no longer rewarding. The dopamine system exerts differential inputs on these pathways, with increased dopamine input facilitating the hippocampal input via a D1-dependent process, whereas D2 stimulation attenuates prefrontal cortical drive. A model of functioning of this system[74] suggests that when a task is rewarding, there is an increase in dopamine input, facilitating the hippocampal drive to maintain focus on the currently rewarded task while preventing the prefrontal cortex from deviating from this task. *Lower Left:* A diagram showing that the hippocampal drive maintains this dopamine input via disinhibition of the ventral tegmental area (VTA) via nucleus accumbens (NAc)-ventral pallidal (VP) circuits. However, if a behavior fails to produce a reward, there would be an attenuation of dopamine neuron activity (negative reward prediction error, decreasing hippocampal drive, and disinhibiting the prefrontal cortex. This would enable the prefrontal cortex to shift focus to a different response. When a response is encountered that produces reward, the resultant increase in dopamine drive would lock the system into the new state by facilitating focus on the new task by the hippocampus while disabling prefrontal behavioral flexibility. *Lower Right:* A diagram showing disruption of normal NAc function in the event of overactive dopaminergic drive mediated by dopamine agonists, as is proposed to occur during ICDs. These agonists have a high affinity for the D2 family of dopamine receptors, which reduce excitatory influences from the prefrontal cortex. Thus, an abnormally high and persistent activation of D2 receptors is proposed to circumvent the normal efficient functioning of this gated system, and the balance of influences by inputs from the prefrontal cortex and hippocampus is disrupted. In such conditions, there would be a continued potentiation of hippocampal focus independent of the rewarding nature of the stimuli, causing the organism to perseverate an impulsive task. Because of the high levels of D2 receptor activation, the prefrontal cortex would not be capable of shifting behaviors toward a more goal-oriented condition, thereby locking the system in this behaviorally ineffective state.

to preserve the dynamic range of the response, that is, the changes at the terminal enable the dopamine neuron electrophysiological activity to exhibit the same magnitude of increase to a stimulus.[62] One process that undermines the preservation of dynamic range is repeated treatment with dopaminergic drugs. Moreover, the type of dopaminergic drug administered can have very different consequences with regard to its impact on the dopamine system. Thus, after repeated L-dopa, an increase occurs in the proportion of dopamine neurons firing.[63] This maybe a double-edged

sword, for although L-dopa increases dopamine neuron activity and hence dopamine release, it also limits the ability of the system to respond with increases to a stimulus. Indeed, this is proposed to underlie the "on-off" effects observed with L-dopa treatment. Although this process reflects the compensatory changes that take place in response to a lesion and dopamine replacement therapy in the motor system, a similar condition can exist in the limbic system as well. Thus, repeated administration of an indirect dopamine agonist, such as amphetamine, followed by withdrawal, increases the proportion of dopamine neurons firing in the ventral tegmental area[64] in a manner analogous to what occurs in the substantia nigra with repeated L-dopa administration. The consequence is that, with increased proportion of dopamine neurons firing, the system would be rendered hyperresponsive to stimuli.

Dopamine neurons fire in two states: at baseline, they fire in a single-spiking, irregular pattern.[65] When exposed to a salient stimulus, dopamine neurons fire in bursts.[66,67] To burst fire, however, a dopamine neuron has to already be firing. Thus, although burst firing may represent the dopamine "signal," the number of neurons firing represents the amplification factor, with more neurons firing enabling a larger dopamine signal.[68,69] The number of firing neurons is thought to be controlled by environmental contingencies, and repeated dopaminergic drug administration thwarts this process. In the case of repeated L-dopa or amphetamine, an abnormally large dopamine system activation to stimuli would occur. The impact of such an overactivation relates to the modulatory effects of dopamine in the limbic system. The ventral striatum including the nucleus accumbens receives two prominent excitatory inputs: the prefrontal cortex and the ventral hippocampus subiculum. The prefrontal cortex input enables behavioral flexibility, or the ability to shift behavioral focus as task contingencies change.[70,71] The subiculum is a context-dependent structure[72,73] that is believed to keep an organism focused on a task. These two processes are regulated in opposite manners by the dopamine system. Stimulation of D2 dopamine receptors will inhibit prefrontal cortex input, whereas D1 receptor stimulation will potentiate hippocampal input.[70,71] Thus, reward-related activation of the dopamine system would keep the individual focused on the task through D1-mediated potentiation of the subiculum, and D2-mediated inhibition of prefrontal cortex.[74] If a behavioral response fails to produce a reward, a resultant dip in dopamine neuron activity[67] will remove subiculum potentiation and prefrontal cortex inhibition, enabling the prefrontal cortex to shift task focus. If the system is disrupted, such as after repeated dopamine agonist administration, then overstimulation of the dopamine system would occur and a persistent focus on a single task to the exclusion of prefrontal cortex-drive goal-directed behavior. Such a condition could relate to DDS seen with L-dopa administration.[75] Because both repeated L-dopa

TABLE 1. Genes associated with ICD in PD and in the general population

Transmitter System	Protein	Gene/Allele	General Population	PD	References
Dopamine	DAT	*SLCA3*/VNTR	+	-	*Vallelunga et al., 2012*[88]
	DRD1	800 T/C	+	ND	
	DRD2	Taq1A	+	-	*Lee et al., 2012*[86]; *Vallelunga et al., 2012*[88]
	DRD3	P-S9G	+	+	
	DRD4	Exon3	+	ND	
Dopamine metabolism	COMT	Val158Met	+	-	*Vallelunga et al., 2012*[88]
	MAO-A	Promoter	+	ND	
Serotonin	Transporter	*SLC6A4*	+	-	*Lee et al., 2012*[86]
	Tryptophan hydroxylase	*TPH1*	+	ND	
	5HT2A receptor	*HTR2A*	+ (impulsivity)	+/− (trend)	*Lee et al., 2009*[88]
Glutamate	NMDA receptor	*GRIN2B*	+	+	*Lee et al., 2012*[87]

+, significant association with ICD; −, no significant association with ICD was found; ND, no data.

and repeated amphetamine/withdrawal[64] increase dopamine neuron population activity and lead to addictive behavior, this parameter may indeed be related to addiction-like dopamine dysregulation syndrome. A very different effect has been observed with direct-acting dopamine agonists, for example, repeated administration of quinpirole decreases burst firing,[76] an event that also could lead to increased reward-seeking behavior. In the case of both repeated L-dopa and repeated quinpirole, a down-regulation of dopamine neuron autoreceptor function occurs,[63,77] which could increase the responsiveness of the dopamine neurons to stimuli. Possibly these pathophysiological processes underpin impulsive, nonadaptive behavioral processes that are associated with chronic dopamine therapy in PD patients.

Genetic Vulnerabilities Associated With Impulse Control Disorders in Parkinson's Disease

The fact that virtually all PD patients are treated with dopaminergic drugs, but only a minority of them develop ICDs, suggests predisposing or protecting factors, potentially of genetic origin. Indeed, vulnerability to ICD is a complex trait with substantial genetic influences that were documented by data from family, adoption, and twin studies.[78] High rates (45% to 63%) of alcohol dependence and other substance use disorders are found among pathological gamblers,[79] which suggest a common underlying vulnerability.[80] Twin studies estimated that genetic factors account for 33% to 54% of the overall variance in the risk of development of pathological gambling behavior.[81,82]

Candidate genes encoding receptors or metabolic enzymes of neurotransmitter pathways, particularly monoamines, have been found associated with ICD susceptibility or impulsivity traits in the general population (Table 1). Dopamine, serotonin, and norepinephrine genes have been shown to contribute approximately equally to the risk of pathological gambling.[83,84] However, these genetic factors only explained 15% to 21% of the inheritance, and a large number of unknown genes are yet to be discovered.[83] Only one genome-wide association study has been performed on pathological gambling[85] In this study, although 1,312 individuals from 894 families were analyzed, no single-nucleotide polymorphism achieved genome-wide significance. Interestingly, none of the previously validated candidate genes were part of the top gene list, suggesting that monoamine pathways account for only a small part of ICD susceptibility.

In PD, some inheritance also has been suggested by the association of ICD with familial history of ICD, alcoholism, drug addiction, or mood disorders.[2] In a study comparing 58 PD patients with ICD with 346 PD patients without ICD, a significant association was found with the D3 dopamine receptor (*DRD3*) and the NMDA glutamate receptor 2B subunit (*GRIN2B*).[86] Subsequent analyses in the same cohort identified a trend toward a dose-dependent association with the serotonin 2A receptor gene (*HTR2A*).[87] By contrast to the general population, no association was found with the dopamine D2 receptor (*DRD2*), the C-O-methyltransferase (*COMT*), or the serotonin transporter (*SLC64A*), a result confirmed in an independent study performed in 41 PD patients with ICD with 48 matched controls (Table 1).[88] However, the small number of patients in these studies and the lack of replication does not allow for definitive conclusions.

In overview, several genes from the monoamine pathways have been associated with ICD in the general population, whereas in PD only the *DRD3* and the *GRIN2B* genes were found to be associated. This

apparent discrepancy may be related to the exposure to dopamine agonists in PD that may trigger the association toward the drug response rather than ICD genetic susceptibility.

Summary and Conclusions

The phenomenon of ICDs in PD continues to be an untoward side effect of dopaminergic therapy with potentially devastating consequences to a significant number of patients.[89] The past decade has witnessed impressive advances not only in the recognition of ICDs but also in understanding the neurobiological and genetic associations: Human imaging has aided in mapping the neuroanatomical substrates that are engaged during active phases of ICDs, and in providing insights in those regions that are altered during PD with ICDs. These substrates map onto those that are described at the cellular and circuit levels in studies with laboratory animals. New animal models that recapitulate critical features of PD with ICDs are being developed. Genetic constructs that may be unique to ICDs in PD are being identified. These all provide exciting new venues in which the causes of ICD side effects of dopamine therapy in PD can be identified, and ultimately provide new therapies that can improve the motor pathology of PD but are devoid of ICD side effects. To accomplish this goal, the new animal models could be exploited to help identify the ICD potential of putative therapies. Future work also needs to include large case-control studies on genetic susceptibility to confirm these current results and ultimately identify genes that may be predictive of ICD development. ∎

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