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REVIEW

Impulse control disorders in Parkinson's disease: seeking a roadmap toward a better understanding

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Abstract The development of an impulse control disorder (ICD) is now recognized as a potential nonmotor adverse effect of dopamine replacement therapy in Parkinson's disease (PD). Here, recent epidemiological, neurophysiological and genetic advances are summarized to outline potential mechanisms involved. It is safe to say that dopaminergic drugs, particularly dopamine agonists, are able to induce ICDs only in a minority of patients, while the majority are somehow protected from this adverse effect. While it seems clear that men with early-onset PD are more vulnerable, other predisposing factors, such as various current or pre-PD personality traits, are a matter of debate. In terms of neurophysiological advances, one may find striking analogies to the addiction literature suggesting a causal chain beginning with certain predisposing conditions of striatal dopamine synapses, an "unnatural" increase of dopamine stimulation and a characteristic pattern of resulting functional changes in remote networks of appetitive drive and impulse control. Future prospects include potential add-on medications and the possible identification of genetic predispositions at a genome-wide scale. Functional imaging of pharmacogenetic interactions (imaging pharmacogenomics) may be an important tool on that road.

Keywords Imaging · Gambling · Addiction · Impulsive · Compulsive · Dopamine agonist

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Introduction

Impulse control disorders (ICDs), such as pathological gambling, compulsive shopping, binge eating and hypersexuality may develop as nonmotor adverse effects of dopamine replacement therapy in patients with Parkinson's disease (PD) (Driver-Dunckley et al. 2003; Seedat et al. 2000). In this review, we aim to summarize promising recent advances in characterizing (1) circumstances under which these behavioral disturbances appear, (2) neurobiological trigger mechanisms that may be involved and (3) possible neurophysiologic and genetic makeups that may help explain why some individuals are more vulnerable than others. For the sake of focus, certain types of impulsive and repetitive behavior that are observed in PD will not be discussed in this review. While there is growing evidence that electric stimulation of the subthalamic nucleus blocks the so-called 'hyperdirect' pathway of the basal ganglia, which may in turn produce a certain type of impulsivity (Frank et al. 2007), the exact relationship between subthalamic stimulation in PD and ICDs is unclear, as these abnormal behaviors may either follow neurostimulation (Lim et al. 2009; Volkmann et al. 2010) or resolve after dopaminergic dose reduction associated with successful surgery (Ardouin et al. 2006; Bandini et al. 2007; Witjas et al. 2005). It is therefore conceivable that subthalamic stimulation and dopaminergic medication may both lead to impulsivity, yet by different neurobiological

mechanisms (Dalley et al. 2011). Although compulsive anti-Parkinsonian drug use—commonly referred to as dopamine dysregulation syndrome (DDS)—is sometimes associated with the development of ICDs in PD, epidemiological findings regarding DDS are markedly different from ICDs insofar as DDS usually develops as a complication of long-term dopaminergic therapy in advanced PD (O'Sullivan et al. 2009). Sometimes associated with DDS are repetitive, complex stereotyped behaviors (e.g., collectionism), described as punding (Evans et al. 2004). Even though punding certainly has elements of compulsions, it is felt to lie outside of the ICD spectrum (Evans et al. 2009).

Clinical observations

Epidemiology of ICDs in PD

A recent blinded, multi-center cross-sectional study with over 3,000 patients in North America constitutes the strongest effort yet to gather scientific evidence about the circumstances, in which ICDs in PD may occur (Weintraub et al. 2010). Similar to epidemiological studies in other PD populations (Lee et al. 2010), one or more forms of ICD was found in 13.6% of medicated PD patients. Moreover, the risk to develop an ICD appeared to increase threefold when dopamine agonists (DAAs) were part of the therapeutic regimes. This finding was independent of the type of DAA used, but combinational use with levodopa was found to be a contributing factor. Interestingly, ICDs have also been identified with similar or even higher frequencies in other DAA-treated conditions such as restless-legs syndrome, prolactinoma or fibromyalgia (Cornelius et al. 2010; Grosset et al. 2007; Holman 2009). Although this certainly is a strong indication for a specific pharmacological trigger mechanism of DAAs, it has to be noted that the prevalence of ICDs in PD patients on dopaminergic medication excluding DAAs was still found to be much higher than in the general population (Crockford et al. 2008). One of the most interesting findings of this cross-sectional study was the absence of a significant dose relationship for DAAs, despite the fact that in the individual patient with a DAA-induced ICD, a dose threshold does sometimes feel quite palpable (Weintraub et al. 2010). Of note, a different epidemiological study showed that such a dose relationship may indeed be found, when clinical parameters including risk factors (see below) are taken into account (Lee et al. 2010). This indicates that the development of ICDs may stem from an interaction of a specific pharmacological trigger with intrinsic neurobiological vulnerability factors.

Apart from unusual manifestations of ICDs (Bienfait et al. 2010; Bonfanti and Gatto 2010; Odiyoor et al. 2009; Pinggera et al. 2009), pathological gambling, compulsive shopping, binge eating and hypersexuality seem to be equally common in DAA-medicated PD (Fig. 1). However, men seem to be more prone to develop pathological gambling or hypersexuality, while women have higher rates of compulsive shopping and binge eating. It is yet unclear how much of these differences may stem from differences in the mesocorticolimbic reward system (Hoeft et al. 2008; Munro et al. 2006) or reporting biases due to social acceptance.

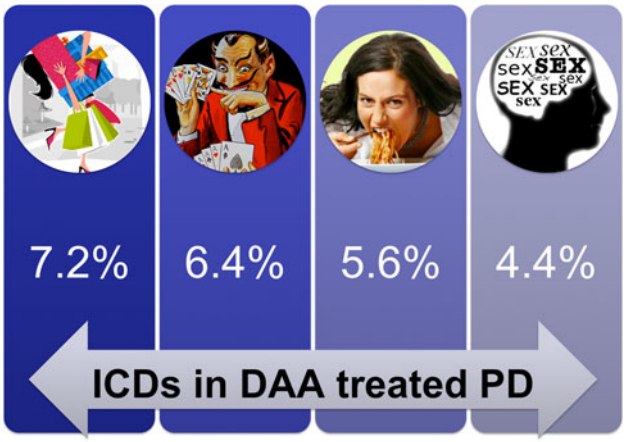

Fig. 1 Prevalence of the most frequent impulse control disorders (ICDs) in PD patients on dopamine agonists (DAA) according to the DOMINION study (Weintraub et al. 2010). From *left* to *right*: compulsive shopping, pathological gambling, binge eating and hypersexuality

Factors of individual predisposition

Male gender, early-onset PD, current or pre-PD personality traits characterized by high impulsivity and novelty-seeking personality traits, family or personal history of ICD symptoms or substance abuse (including current smoking) may all be regarded as considerable risk factors (Weintraub et al. 2010). The mechanisms of male preponderance are unclear, but imaging studies comparing men with women after exposure to rewarding stimuli have shown higher release of dopamine in the ventral striatum (Munro et al. 2006) and increased activation of the mesocorticolimbic system in men (Hoeft et al. 2008). Compared to the general population, a previous history of ICDs or substance abuse is less frequent in PD patients developing ICDs after the initiation of dopamine replacement therapy (Gallagher et al. 2007). More recently, the akinetic-rigid phenotype has been suggested to be more prone to impulsive responses and risk taking than tremor-dominant phenotype (Singh-Curry et al. 2010). An increased prevalence of executive dysfunctions in PD patients with ICD behaviors

Table 1 Genes involved in impulse control disorders, substance addiction and associated traits in PD and non-PD populations

Transmitter system	Protein	Gene/allele	Population	ICDs/addiction	References
Dopamine	DAT	SLCA3	Non-PD	ICDs (BE, HS), substance abuse, reward sensitivity and impulsivity	Muramatsu and Higuchi 1995; Shinohara et al. 2004; Kreek et al. 2005; Guo et al. 2007; Forbes et al. 2009; Hahn et al. 2010
	DRD1	800 T/C	Non-PD	ICDs (PG), substance abuse	Comings et al. 1997; da Silva et al. 2007
	DRD2/ ANKK1	TaqlA	Non-PD	ICDs (PG, BE), alcohol and nicotine abuse	Blum et al. 1995; Comings et al. 1996; Neville et al. 2004; Gelernter et al. 2006; Yang et al. 2007; Haile et al. 2007
	DRD3	p-S9G	Non-PD, PD	ICDs, alcohol abuse and risk taking	Kreek et al. 2005; Lee et al. 2009
	DRD4	Exon III; 7-repeat allele	Non-PD	ICDs (PG, BE), substance abuse and novelty seeking	Perez de Castro et al. 1997; Gelernter et al. 1997; Comings et al. 1999; Levitan et al. 2004; Rogers et al. 2004; Eisenegger 2010
Catecholaminergic	COMT	Val158Met	Non-PD	ICDs (BE), substance abuse and reward sensitivity	Kreek et al. 2005; Hersrud et al. 2009; Lohoff et al. 2008; Dreher et al. 2009
	MAD-A	Promoter: 3-repeat allete	Non-PD	ICDs (PG)	Ibanez et al. 2000; Petez de Castro et al. 2002
Serotonergic	Serotonin transporter	SLC6A4	Non-PD	ICDs (PG, CS, TM), substance abuse	Perez de Castro et al. 1999 and 2002; Devor et al. 1999; Hemmings et al. 2006
	Tryptophan hydroxylase	TPH1	Non-PD	ICDs (PG), substance abuse	Comings et al. 2001; Kreek et al. 2005; Nielsen et al. 2008
Glutamatergic	NMDA receptor 2B	GRIN2B	Non-PD, PD	ICDs, alcohol abuse	Kim et al. 2006; Lee et al. 2009
Opioid	μ/K receptors	OPRM1; OPRK1	Non-PD	Substance abuse, impulsivity	Kreek et al. 2005; Olmstead et al. 2009

ANKK1 ankyrin repeat and kinase domain containing-1 gene, *BE* binge eating, *CS* compulsive shopping, *COMT* catechol-O-methyl-transferase, *DAT* dopamine transporter, *DRD* dopamine receptor gene, *HS* hypersexuality, *ICDs* impulse control disorders, *MAO-A* monoamine oxidase A, *NMDA* N-methyl-D-aspartate, *PG* pathological gambling, *SERT* serotonin transporter, *TM* trichotillomania

is controversial, as found in the study of Santangelo et al. (Santangelo et al. 2009), while no differences in frontal lobe functions between gamblers versus non-gamblers have been reported in other studies (Siri et al. 2010; Voon et al. 2007). Further studies are needed to assess cognitive profiles of large samples of PD patients with and without ICDs, particularly focusing on frontal lobe functions while reliably eliminating potential biases such as age differences.

In the non-parkinsonian population, there seems to be a close association between individual vulnerability to risk-taking behaviors and genetically determined variants in different neurotransmitter systems, mainly the dopaminergic mesocorticolimbic circuit (Brewer and Potenza 2008; Forbes et al. 2009; Haile et al. 2007). The mesolimbic dopaminergic transmission is centrally involved in the motivational salience of stimuli and appetitive or reward-dependent behaviors (Berridge and Robinson 2003). In particular, distinct differences in magnitude and pattern of dopamine release in the ventral striatum have been linked to disorders involving enhanced reward seeking, such as addiction and ICDs (Hyman et al. 2006).

In Table 1, we provide an overview of genetic findings in non-parkinsonian individuals with ICDs, focusing on dopamine transmission but not without taking a glance at other neurotransmitter systems.

Neurobiological hypotheses in the non-parkinsonian population

In the last few years, ICDs such as pathological gambling have been increasingly regarded as a 'behavioral addiction' (Goudriaan et al. 2004; Potenza 2008; Tamminga and Nestler 2006). Many of the diagnostic criteria for ICDs share features with those for substance use disorders, underscoring its classification as 'behavioral addiction' in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM, American Psychiatric Association, 1994). The main features of substance use disorders include: (a) enhanced salience attribution to drug-related stimuli in comparison to other natural rewards, (b) failure to inhibit the urge to obtain the drug, (c) withdrawal symptoms including cue-induced craving and (d) continued engagement in maladaptive risk-

taking behaviors despite negative future consequences (Goldstein and Volkow 2002; Kalivas and Volkow 2005). Several of these common features are modulated by dopamine and are therefore of great interest, as they may constitute possible mediators of ICDs in subjects chronically treated with dopaminergic drugs and will thus be reviewed in the following paragraphs.

Although we focus on dopamine, other neurotransmitters (e.g., serotonin and opioids) may also be involved in the development of impulse control and addictive disorders. Serotoninergic neurons project form the raphe nucleus to mesocorticolimbic areas including prefrontal/orbitofrontal cortex, amygdala and hippocampus and are known to modulate delay discounting and reversal learning (Clarke et al. 2004; Rogers 2011). Moreover, forebrain serotonin levels were found to be negatively correlated with measures of impulsivity (Brewer and Potenza 2008) and risk-taking behavior (Potenza 2001; Moreno et al. 2010). The mu-opioid system is activated in response to gambling behavior (Shinohara et al. 2004) and is involved in the processing of hedonic responses and incentive motivation by modulating the nucleus accumbens and the ventral globus pallidum, either directly (Smith et al. 2009) or indirectly, via gamma-aminobutyric acid input to the mesolimbic dopamine pathway (Ikemoto et al. 1997; Grant et al. 2003; Olmstead et al. 2009).

DA-mediated mechanisms leading to (drug-related and behavioral) addiction

Exposure to rewards, including drugs of abuse and behaviors (such as gambling, sex or eating), induce phasic dopamine release from the ventral tegmental area into the nucleus accumbens, a process that is associated with reinforcement effects underlying stimulus–response conditioned learning and amplify salience attribution to the specific reward (Volkow et al. 2008). Repeated exposure to the reward—drug or behavior—may result in over-activation of the reward and motivational circuits (including the medial orbitofrontal cortex, OFC) while decreasing the top–down control of inhibitory cortical areas (including the ACC) (Potenza 2008). Pathologically increased saliency attribution to a particular reward produces an irresistible and increasingly compulsive drive toward that reward and away from other reinforcers, finally leading to withdrawal symptoms and craving, similar to substance use disorders (Hyman 2005; Robinson and Berridge 1993) and which has been hypothesized to be mediated by changes in dopamine and glutamate functioning (Kalivas and Volkow 2005).

Personality, behavior and cognition

The role of personality measures in the development of ICDs, such as sensation seeking and extraversion, is still controversial (Brand et al. 2005; Goudriaan et al. 2009; Jimenez-Murcia et al. 2010; Leiserson and Pihl 2007). Cognitive functions in non-parkinsonian subjects with PG demonstrated reduced decision-making abilities and executive dysfunction compared to controls (Alessi and Petry 2003; Brand et al. 2005; Forbush et al. 2008; Goudriaan et al. 2005; Kalechstein et al. 2007; Labudda et al. 2007; Lakey et al. 2006; Marazziti et al. 2008). In particular, non-parkinsonian gamblers show enhanced impulsivity together with impaired cognitive flexibility with higher rates of perseveration and impaired response inhibition. This is in consistence with studies in substance abuse (Forbush et al. 2008; Goudriaan et al. 2004; Kalechstein et al. 2007; Kertzman et al. 2008). Notably, decision-making impairment in pathological gamblers mainly includes reduced response shifting after losses (Goudriaan et al. 2006), supporting the hypothesis of impaired sensitivity to negative reinforcers and thus affecting the so-called 'win–stay–lose–shift' heuristic.

Neuroimaging findings

Studies using functional neuroimaging in healthy subjects demonstrated that rewarding events increase activity in the medial OFC, amygdala and ventral striatum (Hampton et al. 2007; Knutson and Cooper 2005; Yacubian et al. 2006), while increased brain activity in the ventrolateral prefrontal cortex (vlPFC), ACC and ventral striatum is generally associated with decision making under risk (Hewig et al. 2009; Hollander et al. 2005; Rao et al. 2008; Tom et al. 2007).

Resting state brain metabolism of pathological gamblers was found to be higher than matched controls in the medial OFC and other medial prefrontal cortical areas (Hollander et al. 2008). Similarly, in subjects with Internet game overuse, increased glucose metabolism in the medial OFC, the caudate and the insula was associated with greater impulsiveness compared to controls (Park et al. 2010). Reduced activation of the ventral striatum and the ventral prefrontal cortex during non-specific rewarding and punishing events has been shown in non-parkinsonian pathological gamblers, subjects with eating disorders and drug abusers compared to normal controls (de Ruiter et al. 2009; Potenza 2008; Reuter et al. 2005), suggesting a blunted response to rewards as well as to losses. On the other hand, also in pathological gamblers, lower vlPFC activity was found during monetary loss (de Ruiter et al. 2009), which is consistent with a diminished sensitivity to negative reinforcers (Goudriaan et al. 2005).

To say it in one grossly simplified sentence: neuroimaging evidence in the non-parkinsonian population points toward a reduced engagement of brain areas involved in the prevention of negative outcomes via inhibitory circuits

(e.g., vlPFC) and an amplified engagement of areas mediating goal-directed behavior via motivational circuits (e.g., medial OFC).

Possible pathophysiologic pathways fostering ICDs in PD

Dopaminergic depletion in PD involves not only the nigrostriatal 'motor' loop, but also, though to a lesser degree, the mesocorticolimbic circuit, affecting the nucleus accumbens, OFC, ACC, amygdala and the hippocampus (Kish et al. 1988; Ouchi et al. 1999). All these regions are critically involved in the modulation of behavior in positive/negative reinforcement learning, motivation, inhibitory control and decision making (Frank et al. 2004; Schultz 2002; Tremblay and Schultz 1999). Thus, it is tempting to think that these brain regions must be—in one way or another—implicated in the development of ICDs. Moreover, the fact that in PD, mesocortical and mesolimbic circuitries are relatively intact, yet may undergo the same pharmacologic effect of dopaminergic treatment than the motor loop has led to the intuitive proposition of an 'overdosing' of the mesolimbic dopaminergic system (Cools and Robbins 2004). This mental concept is analogous to the 'overdose theory' of the frontal lobes, which we may ascribe to C. David Marsden's mastermind (Gotham et al. 1988). Note, however, that only a minority of PD patients on dopaminergic medication actually develop ICDs. Therefore, this concept—however intuitively convincing—does not give a sufficient answer to the most crucial questions associated with DAA-induced ICDs in PD: how do dopaminergic drugs generally alter limbic brain functions? What is different in the brain of susceptible PD patients? And what exactly happens in their brain that does not happen in the majority of PD patients? Recent imaging studies have begun to shed some light on those questions.

General drug-mediated changes in reward processing and reinforcement learning

Several lines of evidence point toward a reduced sensitivity of the reward system as a key feature in drug addiction and pathological gambling in the non-parkinsonian population (Goldstein et al. 2007; Potenza 2008; Reuter et al. 2005). In line with this notion, Riba et al. found that DAA leads to blunted neuronal responses to unexpected financial wins in the ventral striatum of healthy subjects (Riba et al. 2008). Extending this result to PD patients and comparing DAA and levodopa medication effects, van Eimeren et al. found that both medications reduced reward sensitivity in the ventral striatum, but only DAA greatly diminished reward sensitivity in the OFC (van Eimeren et al. 2009).

Moreover, there is ample evidence that DAAs disrupt appropriate feedback from negative outcomes in reinforcement learning. Behaviorally, PD patients are less able to learn from negative feedback when medicated with DAA (Bodi et al. 2009; Cools et al. 2006; Frank et al. 2004). Neurophysiologically, DAAs seem to prevent decreases in DA transmission that occur with negative feedback (van Eimeren et al. 2009). Indeed, abnormalities found in reward and punishment sensitivity could generally result in aberrant expectations of reward and loss and, consequently, to a pathological 'over-optimism', contributing to the continuation of behaviors such as pathological gambling. Yet, more studies are definitely needed to disentangle general (all patients) from specific (only vulnerable patients) DAA effects on reward and reinforcement learning.

Characteristic features of dopaminergic mesolimbic synapses

In a recent [11C]-raclopride PET study, (Steeves et al. 2009) compared levels of D2-receptor availability in PD patients with and without DAA-induced ICD behavior. Reduced availability of striatal D2-receptors was found to be a distinctive feature of the vulnerable patient group. This result is well in accordance with equivalent findings in drug addiction, in which decreased D2 receptor availability in combination with impaired OFC and ACC metabolism has been found (Volkow et al. 2001). A reduction in D2 receptor availability possibly constitutes a vulnerability that is genetically determined (see Table 1). In healthy volunteers, this genetically driven reduction in D2-receptors leads to impaired recruitment of the ACC and the right lateral OFC in negative feedback learning (Jocham et al. 2009). Note that reduced D2-receptor availability—as measured by [11C]-raclopride PET—can have three possible origins: reduced density of post-synaptic D2-receptors, increased levels of synaptic dopamine or both. In this respect, it is important to take into account another recent study measuring striatal dopamine transporter density with single photon emission tomography (Cilia et al. 2010). PD patients with DAA-induced ICD—as compared to patients without—demonstrated reduced levels of dopamine transporters specifically in the ventral striatum. Dopamine transporters are the single most important way to eliminate dopamine from the synaptic cleft. Therefore, it is tempting to infer increased levels of synaptic dopamine in vulnerable PD patients, which could also help explain the finding of reduced D2-receptor availability.

Characteristic patterns of neuronal activity

Similar to findings in the non-PD population (see "Neurobiological hypotheses in the non-parkinsonian

population"), ICDs in PD patients seem to be associated with functional changes in circuitries that evaluate or mediate rewarding outcomes and/or evaluate risks during decision making. During rest and on regular dopaminergic medication, PD patients with active ICD behavior showed relatively increased blood flow in the OFC, the amygdala and globus pallidum indicative of a relative overactivity of those areas in an "idle" state (i.e., without engagement in a specific task) (Cilia et al. 2008). A recent fMRI study focused on the ventral striatum as a region of interest and found decreased resting blood flow together with reduced modulation of activity during risk taking in the ventral striatum of medicated PD patients with active ICDs (Rao et al. 2010). Another fMRI study investigated DAA-induced changes during a feedback learning task (Voon et al. 2010). In the ventral striatum, DAA medication specifically induced increased activation in relation to expected gains, while DAA medication diminished reactivity associated with expected losses in PD patients with active ICDs (Voon et al. 2010). Although these results may generally underscore the involvement of reward processing areas, the interpretation of activation data in this study is complicated by the fact that DAA medication also differentially modulated task performance in patients with and without ICD behavior. Investigating DAA-induced changes in regional brain activity during a card selection game with predetermined probabilistic outcomes, another recent imaging study found that only in vulnerable PD patients, DAA medication led to a deactivation of areas implicated in response inhibition and impulse control (vlPFC, ACC, amygdala, internal globus pallidus) (van Eimeren et al. 2010). It is interesting to note that most of the participants of this study were previously investigated with [11C]-raclopride PET and showed reduced availability of striatal D2-receptors (Steeves et al. 2009). In good accordance with a differential modulation of corticostriatal inhibitory networks, a functional disconnection has been recently found between the ACC and the striatum in PD patients with ICDs (Cilia et al. 2011). This disconnection may be involved in the failure of loss-related behavioral shifts due to an inability to disengage from reward-seeking behaviors that previously gained abnormal salience via dopamine-mediated positive reinforcements (Baler and Volkow 2006). Future neuroimaging studies in PD patients may help to confirm and extend these hypotheses by specifically focusing on differential and potential additive effects of various types of DAA and levodopa (Dewey 2010). Taking all available findings together, however, we may observe a striking analogy to the existing addiction literature that suggest a causal chain beginning with certain predisposing conditions of striatal dopamine synapses, an "unnatural" increase of dopamine stimulation and a characteristic pattern of resulting functional changes in remote networks of appetitive drive and impulse control (Potenza 2008; Volkow et al. 2001).

The Yin and Yang of appetitive drive and inhibitory control: attempt of a unified hypothesis

As mentioned before, DAA may increase appetitive drive (novelty seeking and impulsivity) while hampering negative feedback learning and behavioral inhibition. However, only a minority of PD patients actually develop ICD behaviors, suggesting an individual predisposition. One can only speculate on the underlying pharmacophysiologic–psychological interactions that drive behavioral change in susceptible patients. On the assumption of a relatively increased synaptic dopamine level in the striatum of vulnerable PD patients, we derive hypotheses based and an established model of the effects of tonic and phasic dopamine release on cortical connections with the direct and indirect pathways of the basal ganglia (Fig 2a). Decision making is believed to involve interactions of inhibitory and motivational inputs to the ventral striatum that are modified by convergent dopaminergic innervation from the ventral tegmental area (Goto et al. 2007). Phasic dopamine release, via D1 receptor activation, has been shown to facilitate inputs from motivational areas (e.g., medial OFC, frontopolar cortex) and thereby strengthens the influence of the direct or 'Go' pathway on executive areas (Goto and Grace 2005). Conversely, a transient reduction of tonic dopamine release, via D2-receptor inactivation, increases inputs from inhibitory areas (e.g., vlPFC and ACC) and thereby strengthens the influence of the indirect or 'NoGo' pathway on areas of executive control (Goto and Grace 2005).

Dopaminergic depletion in the ventral striatum of PD patients regularly decreases tonic D2-receptor stimulation. In susceptible patients on the other hand, a constitutionally increased tonic dopamine level would lead to a relatively normal level of tonic D2-receptor stimulation in the ventral striatum. According to the above-mentioned model, therapeutic use of DAA would further increase D2-receptor stimulation to the point of an "overdose" situation, leading to a hampered engagement of inhibitory cortical areas and increased influence of appetitive drive areas (Fig. 2b). This model would be in good accordance with findings in vulnerable PD patients, who showed reduced involvement of vlPFC and ACC and increased resting activity of the medial OFC in association with an increased tonic D2-receptor stimulation (Cilia et al. 2008, 2010, 2011; Steeves et al. 2009; van Eimeren et al. 2010). While this hypothesis may be intuitively convincing, it will have to be tested in further studies involving genetic, behavioral and neuroimaging methods.

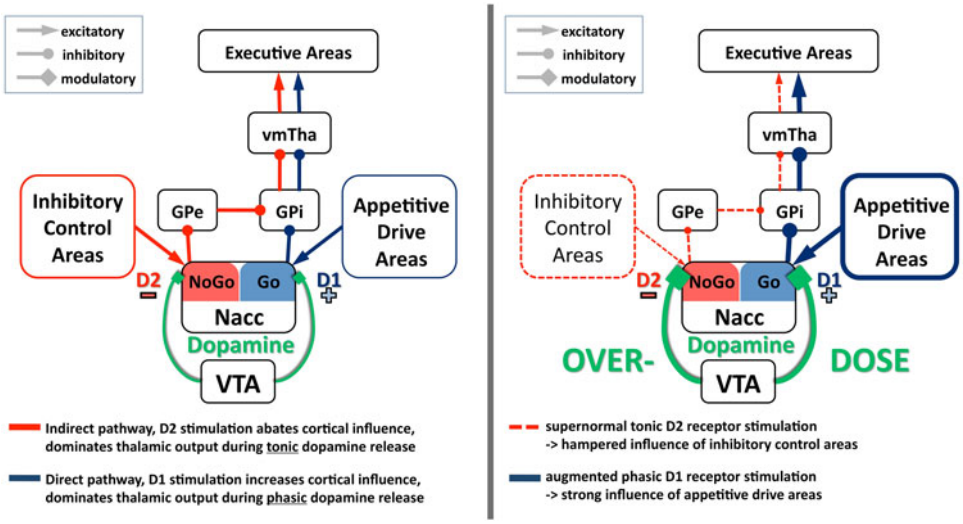

Fig. 2 The Yin-and-Yang model of appetitive drive and inhibitory control. *Left* The effects of tonic and phasic dopamine release on cortical connections with the direct and indirect pathways of the basal ganglia (here nucleus accumbens (Nacc) and ventral tegmental area (VTA), modified model after Goto and Grace 2005). *Right* In a majority of the patients with PD, dopaminergic depletion decreases tonic D2-receptor stimulation in the ventral striatum/Nacc. In susceptible patients on the other hand, a constitutionally increased tonic dopamine level leads to relatively normal levels of tonic D2-receptor stimulation in the ventral striatum/Nacc. Therapeutic use of DAA further increases D2-receptor stimulation to the point of an "overdose" situation, leading to a hampered engagement of inhibitory cortical areas and increased influence of appetitive drive areas

Future directions in pharmacology, imaging and genomics

The management options of ICDs in PD are not entirely satisfactory. While there are no evidence-based treatment strategies available, the most common form of therapeutic intervention in DA-induced ICDs in PD is the tapering and substitution of DAA (Galpern and Stacy 2007). It might be worth trying another type of DAA, if the clinical effect of DAA is otherwise deemed superior to alternatives. Moreover, the notion of the so-called DAA withdrawal syndrome (DAWS)—defined as psychological (e.g., anxiety, panic attacks, depression) or physical (e.g., diaphoresis, orthostatic hypotension) symptoms caused by the tapering of DAAs (Rabinak and Nirenberg 2010; Schlesinger et al. 2010)—underscores an urgent need for more therapeutic options for the clinician. Although case reports suggest possible roles for subthalamic stimulation (Bandini et al. 2007; Halbig et al. 2009) (but see Moro 2009), enteral carbidopa/levodopa infusions, amantadine, zonisamide, carbamazepine or clozapine (Bach et al. 2009; Bermejo et al. 2010; Gerschlager and Bloem 2009; Rotondo et al. 2010; Thomas et al. 2010), none of these potential add-on medications have been tested in prospective, randomized controlled trials. It is also worth mentioning that SSRI medications are commonly used in the treatment of non-parkinsonian ICDs and that opioid antagonists also seem to be effective (Leung and Cottler 2009), probably by increasing punishment sensitivity (Petrovic et al. 2008). Future neuroimaging studies may contribute to direct attention to potential add-on medications by evaluating the influence of certain drugs (e.g., amantadine) on motivational and inhibitory circuitries.

Moreover, a steady flow of new neuroimaging studies will continue to increase our understanding of dopaminergic modulation of human behavior. It will be important to follow recent developments and to test hypotheses in clinically realistic circumstances (dopaminergic medication in parkinsonian populations). While most neuroimaging studies, for obvious reasons, will focus on the dopaminergic system, it will also be important to illuminate potentially crucial contributions of other neurotransmitter systems (as discussed above).

In the non-parkinsonian population, genetic factors of individual predisposition have been indentified (see Table 1). In the next few years, we need to systematically test genetic variances in large PD populations to potentially describe genetic makeups that may predict socially devastating side effects of anti-parkinsonian treatment. What we need is a better understanding of genetic determinants of pharmacologic effects on brain function. Functional imaging of pharmacogenetic interactions (imaging pharmacogenomics) will be an important tool to this end.

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