HHS Public Access

Author manuscript

Semin Neurol. Author manuscript; available in PMC 2018 May 16.

Published in final edited form as:

Semin Neurol. 2017 April ; 37(2): 186–192. doi:10.1055/s-0037-1601887.

Impulse Control Disorders and Related Complications of Parkinson's Disease Therapy

Alexander M. Lopez, MS[1], **Daniel Weintraub, MD**[2], and **Daniel O. Claassen, MD, MS**[3]

[1]Department of Medicine, Meharry Medical College, Nashville, Tennessee

[2]Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

[3]Department of Neurology, Vanderbilt University, Nashville, Tennessee

Abstract

Impulsive and compulsive behaviors in Parkinson's disease (PD) patients are most often attributed to dopamine agonist therapy; dysregulation of the mesocorticolimbic system accounts for this behavioral phenotype. The clinical presentation is commonly termed *impulse control disorder* (ICD): Behaviors include hypersexuality, compulsive eating, shopping, pathological gambling, and compulsive hobby participation. However, not all PD individuals taking dopamine agonists develop these behavioral changes. In this review, the authors focus on the similarities between the phenotypic presentation of ICDs with that of other reward-based behavioral disorders, including binge eating disorder, pathological gambling, and substance use disorders. With this comparison, we emphasize that the transition from an impulsive to compulsive behavior likely follows a ventral to dorsal striatal pattern, where an altered dopaminergic reward system underlies the emergence of these problematic behaviors. The authors discuss the neurobiological similarities between these latter disorders and ICDs, emphasizing similar pathophysiological processes and discussing treatment options that have potential for translation to PD patients.

Keywords

Parkinson's disease; dopamine agonist; impulse control disorder; striatum

Within the last decade, an increased recognition of clinically signifigcant impulsive and compulsive behaviors in Parkinson's disease (PD) patients has resulted in a greater emphasis on the study of nonmotor dopamine effects on cognition and behavior.[1–4] Despite the clinical efficacy of dopaminergic therapy for motor symptoms, certain PD patients experience alterations in the pursuit of reward or incentive-based behavior, commonly referred to as *impulse control disorder* (ICD).[5] The clinical phenotype of ICD is a repetitive participation in reward-driven activities, which can include a combination of different pursuits related to sexuality, eating, shopping, gambling.[6] In addition, patients can spend hours on hobbies instead of attending to daily living activities.[1,4,5] There exist similar

Address for correspondence Daniel O. Claassen, MD, MS, Department of Neurology, Vanderbilt University, 1161 21st Avenue South, A-0118 Medical Center North, Nashville, TN 37232-2551 (Daniel.claassen@vanderbilt.edu).

phenotypic behaviors in non-PD populations, and the neurobiologic bases for these behaviors offer insights into why certain patients are susceptible to these symptoms. In this review, we focus on the neurobiology of impulsive compulsive behaviors in both PD and non-PD populations.

Parkinson's Disease: Personality and Dopamine

The neurodegenerative process in PD clinically manifests with motor symptoms linked to nigral-striatal pathology and dopaminergic disruption. Motor symptoms, such as resting tremor and bradykinesia, are often exquisitely responsive to exogenous dopaminergic therapy. Unfortunately, this same therapy can adversely impact key aspects of cognition and behavioral function in patients, leading to ICD.[4] Symptoms are characterized by a compulsive reward-seeking behavior, and likely reflect dopamine effects on the mesolimbic and mesocortical networks, which receive dopaminergic inputs from the ventral tegmental area- (VTA-)associated networks.[7–10] Second-generation nonergot dopamine agonists are the most common risk factor for ICD, and the preferential selectivity for D2-like receptors (D3 and D2 receptors), which are co-localized to the mesocorticolimbic system, likely explains the unique side-effect profile for this class of medication.[11]

Even before receiving dopamine therapy, PD patients may develop changes in personality, which may reflect changes to this mesocorticolimbic system. Descriptions such as "harm-avoidant," "introverted," and "meek" often are attributed to the PD-personality phenotype. These descriptions are generated from cross-sectional studies and are difficult to experimentally replicate, but overall, PD patients are thought to display increased caution and be risk aversive prior to diagnosis.[12] Termed as *Parkinson's disease personality*, these characteristics are certainly not predictive of a patient developing PD, as others have not replicated this personality as a risk factor or precursor for PD in larger longitudinal cohorts.[13]

In contrast to the risk-averse PD-personality description, patients with impulsive and compulsive behaviors are more likely to pursue risks, make poorly informed decisions without foresight, and compulsively pursue certain reward-based activities. Another clinically troubling symptom that contrasts the PD-personality phenotype is dopamine dysregulation syndrome (DDS). This is characterized by a patient's compulsive desire to take and increase dopaminergic medication dosage to maintain their "high" (when in "on" state) or avoid the "lows" (when in "off" state) associated with the nonmotor fluctuations commonly encountered with levodopa therapy.[14] Although the clinical symptoms of ICD and DDS contrast in presentation, the biological link appears to be the mesocorticolimbic network, where improper regulation of the reward pathways account for these symptoms.[15,16]

Biologically, dopamine receptors are differentiated by their mechanism of action, where D1-type receptors (subtypes D1 and D5) modify gamma-aminobutyric acid (GABA) transmission directly to the globus pallidus interna and subsequently the substantia nigra pars reticulata. Dopaminergic D2 type (subtypes D2, D3, D4) receptors modify substantia nigra pars reticulata activity in a different manner. These receptors send inhibitory

projections to the globus pallidus externa, then excitatory glutamatergic signaling via the subthalamic nucleus to converge at the globus pallidus interna and substantia nigra pars reticulata. D1-type and D2-type receptors are thus responsible for inhibitory and excitatory signaling, respectively. These two receptor families have contrasting roles with regards to reward-based decision making, where D1-type receptors localize to the direct pathway reward-based behaviors, and D2-type the indirect pathway.[17] The direct pathway is associated with cue-based reward responses. When an unexpected reward occurs, D1-receptor-mediated phasic signaling results in a "positive" response through an increased stimulation of striatal projections to the nucleus accumbens (NAc)/ventral striatum. On the other hand, it is thought that D2 receptors play an opposing role to the D1 receptors, where they signal aversive or negative behavior and elicit suppression of the cortico-accumbens network. [6,18–20] An imbalance between these pathways could lead to altered reward signaling and subsequent behavioral changes.[6]

Unlike D1 receptors, which cannot be easily imaged with conventional imaging techniques, D2 receptors are visualized by various positron emission tomography (PET) ligands. For instance, a comparison [^{11}C]raclopride (competitive D2-receptor ligand) PET study with PD patients with and without ICD showed that during a gambling task, PD patients with ICD had reduced binding to D2 receptors in the ventral, but not the dorsal striatum, illustrating that they might have difficulty relating negative valence to actions. Impulsive choice correlates to reduced D2 receptor expression on the ventral striatum, where an unopposed stimulation of the direct pathway and D1 receptors, and stimulation of the dorsal striatum, may bias reward-based choice.[21]

Mesocorticolimbic Network: From Stimulus to Compulsion

Two important brain dopaminergic pathways are the mesolimbic and mesocortical pathways. These circuits are responsible for reward learning and executive decision making, respectively, with dysregulation of the mesolimbic reward network underlying the clinical manifestation of impulsive and compulsive behaviors. The mesocorticolimbic dopaminergic network links key cortical and subcortical regions, especially the prefrontal cortex (PFC), ventral striatum, VTA, and amygdala.[22] Cue incentive actions are encoded by the VTA and project to the ventral striatum, more specifically the NAc. Unlike the anatomically well-defined NAc in rodents, this region is not well-defined in humans; thus, the ventral striatum and NAc are interchangeable terms when describing clinically relevant behaviors in human studies). The NAc plays a crucial role in learning reinforcement. Conversely, aversive actions localize through the VTA's projection to the NAc, ventral pallidum, amygdala, and lateral habenula. These regions receive GABA-ergic stimulation from the NAc, resulting in a negative stimulus response.[23–25]

The mesocortical pathway is important for executive function, as the prefrontal cortex projects to the ventral striatum.[26–28] The ventral striatum also receives reciprocal inputs from the VTA, and striatal changes appear to account for the translation from impulsive action into compulsive addiction.[29–31] In this case, the dorsal striatum is responsible for habitual and addictive behaviors. For instance, dopamine blockade of the dorsal, but not ventral striatum can alter compulsive cocaine use and addiction behavior.[27,32]

Although ICD development in PD patients appears largely drug-induced, the presentation and behavioral pattern mirrors pathological ICD in the general (i.e., non-PD) population. Similar changes to dopaminergic pathways seen in PD-ICD patients also occur in patients with binge eating disorder (BED), pathological gambling (PG), and substance use disorders. Study of these disorders can offer insight into the neurobiological basis for ICD manifestation in PD patients, and vice versa. In addition, various therapeutic treatments used for non-PD ICD inform novel treatment strategies for PD ICD symptoms.

Like substance use disorders, ICD behaviors emerge after exposure to certain rewards, which over time become compulsive in nature.[29] During the first instance of a reward, there isan "unexpected" activationof the ventral striatum, eliciting a strong emotional response, and an increase in ventral striatal dopamine.[19] After this action is repeated, the behavior starts to become a "habit," and may be associated with craving.[22] This is thought to localize initially at the ventral striatum, then later behaviors are reinforced by the dorsal striatum, illustrating a Pavlovian conditioning.[33] For instance, a [11C]raclopride study in cocaine-addicted subjects showed that patients had a greater release of dopamine from the dorsal, but not ventral striatum. This finding has not been replicated in PD-associated reward behaviors, but deserves further study. The compulsion to keep performing a task stems from the dorsal striatum, as it is used in the maintenance of drug-seeking behaviors with little activity by the NAc.[32] This shows the transition of how an action can become a compulsive behavior as the shift from the ventral to dorsal striatum occurs.[29]

Neurobiology and Treatments of Other Impulsive and Compulsive Behaviors

Binge eating disorder, included as a psychiatric disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*,[34] is characterized by bouts of increased food consumption beyond comfort, with an inability to stop or control food in take. It can lead to excessive weight gain, causing self-loathing and resulting in further binge eating. Binge eating disorder is the most prevalent eating disorder in the United States.[35] An impairment in the dopamine signaling in the reward circuit can result in the progression of BED.[36] There exist similar neuropathological changes between patients with BED and PD-ICD patients who note symptoms of compulsive eating.[37] The manifestation of BED is linked to changes of dopamine regulation in the ventral striatum and associated alterations to dopamine receptor biology. In a comparison functional magnetic resonance imaging (fMRI) study between obese BED and obese non-BED individuals, there was a decrease in ventral striatal activation to reward cues in BED participants.[38] This may be due to atrophy of the ventral striatum in BED individuals.[39] These findings are associated with reduced D2-receptor availability in obese BED patients. Dopamine receptor polymorphisms on allele A1, located within the *ANKK1* gene and lying downstream of the dopamine receptor *D2* gene, is also associated with reduced D2-receptor density in obese BED patients, causing an increasein the D1/D2 ratio.[40] Also, polymorphisms in the dopamine transporter gene (*DAT1*; 9-repeat allele) are associated with BED, and increased synaptic dopamine and reduced transporter function may result in important changes to mesolimbic biology and appetite stimulation.[41]

Treatments for BED in the general population range from psychotherapy to psychopharmacology, including serotonin selective reuptake inhibitors (SSRI), anticonvulsants, and stimulants. Cognitive–behavioral therapy (CBT) seeks to improve inhibitory control over appetite, but suffers from a high relapse rate and has little effect on changing weight.[41] A placebo-controlled trial of fluoxetine did not appear to improve symptoms.[42,43] In addition, fluoxetine with CBT had no additive effect when used together.[42] Topiramate, an anticonvulsant, can decrease appetite and is associated with weight loss, and appears to decrease weight in patients with BED.[44] Topiramate increases the synaptic transmission of GABA, blocking voltage-gated-sodium channels.[45] Although the mechanism of how topiramate reduces weight and improves appetite is poorly understood, altering GABA levels may ultimately improve inhibitory ability through the D2-mediated indirect pathway. The most recent treatment for BED involves the prescription of amphetamines to inhibit monoamine oxidase, the same enzyme that breaks down dopamine.[46] This treatment significantly improved symptoms by reducing the number of binge- eating days per week.

Pathological gambling is considered a behavioral impulse control disorder, with the individual unable to resist urges to gamble. Within the United States and Canada, the prevalence of PG is 1.6% in a normal population and 2.2 to 7% in the dopamine agonist-treated PD population.[47,48] In the general population, there is an association between the development of PG and premorbid alcohol abuse, anxiety, and depression.[49,50] In fMRI studies with non-PD-PGs, the activity of ventromedial prefrontal cortex and ventral striatum are diminished in PG individuals, suggesting a loss of higher order input to the limbic system.[51,52] Individuals with more severe cases of PG tended to have greater reductions of network activation in these areas.[53] Studies of receptor polymorphisms in PG emphasize similar pathways as in BED.[54] Pathological gambling patients have an increased prevalence of allelic variations in D2-receptors, as well as in polymorphisms in dopamine transporter (DAT1), mono-amine oxidase (MAO) A and B, suggesting that alterations to dopamine turnover may be associated with developing PG.[55–58] Increased MAO-B and MAO-A polymorphisms are more prominent in severe male PG.[59,60]

Treatment for PG also includes nonpharmacological and pharmacological therapies. Cognitive–behavioral therapy is not especially effective in helping PG individuals.[61] For pharmacological treatment, PG individuals taking opioid antagonists, such as nalmefene and naltrexone, had a significant decrease in the severity of PG symptoms.[48,62,63] In addition, topiramate and carbamazepine, GABA receptor agonists, helped in improving mood in PG patients.[63,64] Modafinil, a dopamine reuptake inhibitor, improved PG outcome by increasing synaptic dopamine and activating D2-receptors, thus reducing impulsivity.[66,67] N-acetyl cysteine treatment increases glutamate concentration in the NAc, and experimentally diminished PG severity in patients.[68]

Cocaine is a drug of abuse that acts by blocking dopamine reuptake channels. Cocaine use results in a “rush” of energy, euphoria, increased heart rate, self-confidence, and alertness. However, this feeling only lasts for a few minutes and is followed by a period of lethargy and depression. This negative reaction tends to make the person crave to try to maintain the “positive” sensations associated with cocaine. However, despite continued use, the original

"high" is never reattained. This results in the individual developing compulsive cravings for cocaine. What was once used for recreation turns into a drug of abuse. Studies of cocaine addiction point to biological changes in the mesocorticolimbic system. Cocaine largely impacts dopamine concentrations in the NAc/ventral striatum.[69] Strong "pleasurable" feelings with drug administration are likely from increased connectivity between the NAc and amygdala.[70] Prolonged cocaine use has the potential to change various dopamine receptors inthestriatum. Dopamine-release PET studies show a reduction in D2-like receptor activity in the ventral striatum; fMRI imaging illustrate that changes to the dorsal striatum are associated with compulsive behavior.[32] In addition, the dorsal striatum is seen to be engaged more often in rodent models of chronically administered cocaine use.[71]

The treatment for cocaine addiction starts with detoxification of the patient and managing the accompanying symptoms. Some patients may suffer signs of withdrawal such as abdominal pain, nausea, drenching sweats, and seizures, and should be treated accordingly. Reduced synaptic release of dopamine is seen with prolonged cocaine use. Careful therapeutic dosing of dopamine agonists, such as bromocriptine, have been proposed as therapeutic interventions to improve diminished dopamine transmission.[72] However, studies have shown that bromocriptine has no efficacy on cocaine dependence.[73] By slowly reducing the activation of dopamine receptors, this approach would help reduce excessive withdrawals. However, due to bromocrip-tine's ability to stimulate dopamine receptors, this drug can actually induce cocaine cravings, resulting in relapse if drug concentrations are inappropriately administered. Other forms of treatment include using GABA agonists and β-adrenoceptor antagonists such as topiramate and propranolol, respectively.[74] Vigabatrin, a gamma-vinyl GABA, is an irreversible inhibitor of GABA transamidase that increases GABA concentrations.[75,76] This medication has been shown to block the expression of cocaine seeking behavior and sensitization to cocaine. Nonpharmacological therapy such as CBT is useful in helping patients develop control over their own actions, and is useful in preventing relapse: A combination of medication and psychosocial therapy may be the best treatment.[77,78]

Overall, the aforementioned disorders share a similar dys-regulation of the mesocorticolimbic network, manifesting as similar behavioral changes (Table 1). Decreased activation of the D2-receptors in the ventral striatum and increased stimulation of the dorsal striatum seem to be hallmark traits of compulsive behaviors. In addition, these syndromes share an alteration to dopamine transmission by decreased reuptake, increased dopamine metabolism, or synthesis at the level of the synapse. These variations could result in an improper balance of the direct pathway, with treatments focusing on alleviating cravings, and GABA-targeted therapy, thereby improving indirect pathway activation.

Managing PD-ICD Patients

Studies of risk factors for ICD suggest that a family history of alcoholism may place a PD individual at risk for this behavior.[79] One biological reason for this is alteration to serotonin levels, as reduced levels of tryptophan, an amino acid necessary for making serotonin, is associated with alcoholism. Individuals with low levels of the serotonin (5-HT) metabolite, HIAA, have greater impulsivity characteristics and early signs of alcoholism.[80,81]

Experimentally, primate models of 5-HT depletion result in increased impulsivity and risk behavior.[82,83] In general, using SSRIs to treat impulsivity and ICD has not shown efficacy.[84,85] In PD, SSRI use has shown minimal improvement in ICD behaviors.[86]

Interestingly, opioid antagonists have been looked at as another form of therapy for their ability to modulate dopa-mine in the VTA. Opioid receptor antagonists, such as naltrexone and nalmefene, were effective in case studies treating compulsive sexual behavior, alcoholism, and compulsive buying in non-PD patients. In addition, a randomized trial using naltrexone in PD-ICD suggested that concomitant use of naltrexone could reduce the severity of ICD behaviors, even though this trial failed to meet its primary endpoint.[63]

Deep brain stimulation (DBS) is thought to improve ICD symptoms largely through reduction in dopaminergic requirements. The subthalamic nucleus (STN) plays a key role in the frontostriatothalamocortical loop, which is involved in motor and cognitive function.[87] It is hypothesized that the stimulation of the subthalamic nucleus enhances the inhibitory effect in the indirect dopamine pathway, resulting in an increase in reward-driven behaviors in certain patients. Furthermore, the lead placement in the dorsal and ventral STN may result in a sensorimotor and executive/associative circuit, respectively.[88–90] However, STN-targeted DBS can result in new-onset ICD behavior.[91] Deep brain stimulation treatment can be used to replace the use of dopamine agonist treatment to treat motor symptom, and s as a result, theoretically reduce the risk of developing dopamine agonist-induced ICD. However, in one report, individuals with STN-DBS were just as likely to develop ICD as patients on dopamine agonists.[92]

Overall, the most useful treatment for PD-ICD remains reduction in dopamine agonist treatment. Dopamine agonist withdrawal syndrome and worsening motor symptoms remain the greatest side effects of this reduction. No studies have convincingly shown that add-on therapy can improve ICD symptoms in PD.

Conclusions

Patients suffering from BED, PG, and cocaine abuse appear to have similar neurobiological changes of increased dopaminergic activity in the dorsal striatum, where compulsive behaviors localize. A shared risk factor between these three non-PD behavioral phenotypes is an altered regulation of dopamine at the synaptic level. Themes ocorticolimbic changes seen in ICD in PD may progress in a similar manner, where initial ventral-striatal-associated reward responses transition to compulsive behaviors via decreased ventral-striatal activation and increased dorsal-striatal activity. Future studies localizing neurobiological mechanisms and improved treatment options for PD patients suffering from maladaptive behaviors are necessary.

References

1. Voon V, Gao J, Brezing C, et al. Dopamine agonists and risk: impulse control disorders in Parkinson’s disease. Brain. 2011; 134(Pt 5):1438–1446. [PubMed: 21596771]
2. Voon V, Mehta AR, Hallett M. Impulse control disorders in Parkinson’s disease: recent advances. Curr Opin Neurol. 2011; 24(4):324–330. [PubMed: 21725242]

3. Macmahon D, Macphee G. Dopamine agonists and impulse control disorders in Parkinson's disease. Prog Neurol Psychiatry. 2008; 12(9):5–9.
4. Claassen DO, Kanoff K, Wylie SA. Dopamine agonists and impulse control disorders in Parkinson's disease. US Neurol. 2013; 9(2):13–16.
5. Lim S-Y, Evans AH, Miyasaki JM. Impulse control and related disorders in Parkinson's disease: review. Ann N Y Acad Sci. 2008; 1142:85–107. [PubMed: 18990123]
6. Shimo Y, Hattori N. Underlying mechanisms of impulse control disorders and dopamine agonist withdrawal syndrome in Parkinson's disease. J Neurol Disord Stroke. 2014; 2(3):1–4.
7. Ranaldi R. Dopamine and reward seeking: the role of ventral tegmental area. Rev Neurosci. 2014; 25(5):621–630. [PubMed: 24887956]
8. Yun IA, Wakabayashi KT, Fields HL, Nicola SM. The ventral tegmental area is required for the behavioral and nucleus accum-bens neuronal firing responses to incentive cues. J Neurosci. 2004; 24(12):2923–2933. [PubMed: 15044531]
9. Luo AH, Tahsili-Fahadan P, Wise RA, Lupica CR, Aston-Jones G. Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. Science. 2011; 333(6040):353–357. [PubMed: 21764750]
10. Uhl GR, Hedreen JC, Price DL. Parkinson's disease: loss of neurons from the ventral tegmental area contralateral to therapeutic surgical lesions. Neurology. 1985; 35(8):1215–1218. [PubMed: 4022359]
11. Garcia-Ruiz PJ, Martinez Castrillo JC, Alonso-Canovas A, et al. Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. J Neurol Neurosurg Psychiatry. 2014; 85(8):840–844. [PubMed: 24434037]
12. Menza MA, Golbe LI, Cody RA, Forman NE. Dopamine-related personality traits in Parkinson's disease. Neurology. 1993; 43(3 Pt 1):505–508. [PubMed: 8450991]
13. Arabia G, Grossardt BR, Colligan RC, et al. Novelty seeking and introversion do not predict the long-term risk of Parkinson disease. Neurology. 2010; 75(4):349–357. [PubMed: 20660865]
14. Dagher A, Robbins TW. Personality, addiction, dopamine: insights from Parkinson's disease. Neuron. 2009; 61(4):502–510. [PubMed: 19249271]
15. Rabinak CA, Nirenberg MJ, CAR. Dopamine agonist withdrawal syndrome in Parkinson disease. Arch Neurol. 2010; 67(1):58–63. [PubMed: 20065130]
16. Evans AH, Pavese N, Lawrence AD, et al. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. Ann Neurol. 2006; 59(5):852–858. [PubMed: 16557571]
17. Keeler JF, Pretsell DO, Robbins TW. Functional implications of dopa-mine D1 vs. D2 receptors: A 'prepare and select' model of the striatal direct vs. indirect pathways. Neuroscience. 2014; 282:156–175. [PubMed: 25062777]
18. West AR, Grace AA. Opposite influences of endogenous dopamine D1 and D2 receptor activation on activity states and electrophys-iological properties of striatal neurons: studies combining in vivo intracellular recordings and reverse microdialysis. J Neurosci. 2002; 22(1):294–304. [PubMed: 11756513]
19. Hikida T, Kimura K, Wada N, Funabiki K, Nakanishi S. Distinct roles of synaptic transmission in direct and indirect striatal pathways to reward and aversive behavior. Neuron. 2010; 66(6):896–907. [PubMed: 20620875]
20. Beninger RJ, Miller R. Dopamine D1-like receptors and reward-related incentive learning. Neurosci Biobehav Rev. 1998; 22(2):335–345. [PubMed: 9579323]
21. Steeves TDL, Miyasaki J, Zurowski M, et al. Increased striatal dopamine release in Parkinsonian patients with pathologicalgambling: a [11C] raclopride PET study. Brain. 2009; 132(Pt 5):1376–1385. [PubMed: 19346328]
22. Cardinal RN, Parkinson JA, Hall J, Everitt BJ. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev. 2002; 26(3):321–352. [PubMed: 12034134]
23. Proulx CD, Hikosaka O, Malinow R. Reward processing by the lateral habenula in normal and depressive behaviors. Nat Neurosci. 2014; 17(9):1146–1152. [PubMed: 25157511]

24. Lawson RP, Seymour B, Loh E, et al. The habenula encodes negative motivational value associated with primary punishment in humans. Proc Natl Acad Sci U S A. 2014; 111(32):11858–11863. [PubMed: 25071182]
25. Carlezon WAJ Jr, Thomas MJ. Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis. Neuropharmacology. 2009; 56(Suppl 1):122–132. [PubMed: 18675281]
26. Pujara MS, Philippi CL, Motzkin JC, Baskaya MK, Koenigs M. Ventromedial prefrontal cortex damage is associated with decreased ventral striatum volume and response to reward. J Neurosci. 2016; 36(18):5047–5054. [PubMed: 27147657]
27. Behan B, Stone A, Garavan H. Right prefrontal and ventral striatum interactions underlying impulsive choice and impulsive responding. Hum Brain Mapp. 2015; 36(1):187–198. [PubMed: 25158155]
28. Beck A, Schlagenhauf F, Wüstenberg T, et al. Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. Biol Psychiatry. 2009; 66(8):734–742. [PubMed: 19560123]
29. Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci. 2005; 8(11):1481–1489. [PubMed: 16251991]
30. Everitt BJ, Belin D, Economidou D, Pelloux Y, Dalley JW, Robbins TW. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Philos Trans R Soc London B Biol Sci. 2008; 363(1507):3125–3135. [PubMed: 18640910]
31. Burton AC, Nakamura K, Roesch MR. From ventral-medial to dorsal-lateral striatum: neural correlates of reward-guided decision-making. Neurobiol Learn Mem. 2015; 117:51–59. [PubMed: 24858182]
32. Volkow ND, Wang GJ, Telang F, et al. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J Neurosci. 2006; 26(24):6583–6588. [PubMed: 16775146]
33. Vollstädt-Klein S, Wichert S, Rabinstein J, et al. Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. Addiction. 2010; 105(10):1741–1749. [PubMed: 20670348]
34. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5. DSM Library. American Psychiatric Association; 2013. Feeding and eating disorders.
35. Hudson JI, Hiripi E, Pope HGJ Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007; 61(3):348–358. [PubMed: 16815322]
36. Manwaring JL, Green L, Myerson J, Strube MJ, Wilfley DE. Discounting of various types of rewards by women with and without binge eating disorder: evidence for general rather than specific differences. Psychol Rec. 2011; 61(4):561–582. [PubMed: 24039301]
37. Kessler RM, Hutson PH, Herman BK, Potenza MN. The neurobio-logical basis of binge-eating disorder. Neurosci Biobehav Rev. 2016; 63:223–238. [PubMed: 26850211]
38. Balodis IM, Kober H, Worhunsky PD, et al. Monetary reward processing in obese individuals with and without binge eating disorder. Biol Psychiatry. 2013; 73(9):877–886. [PubMed: 23462319]
39. Woolley JD, Gorno-Tempini M-L, Seeley WW, et al. Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. Neurology. 2007; 69(14):1424–1433. [PubMed: 17909155]
40. Yang B-Z, Kranzler HR, Zhao H, Gruen JR, Luo X, Gelernter J. Association of haplotypic variants in DRD2, ANKK1, TTC12 and NCAM1 to alcohol dependence in independent case control and family samples. Hum Mol Genet. 2007; 16(23):2844–2853. [PubMed: 17761687]
41. Davis C, Levitan RD, Kaplan AS, et al. Dopamine transporter gene (DAT1) associated with appetite suppression to methylphenidate in a case-control study of binge eating disorder. Neuropsychopharmacology. 2007; 32(10):2199–2206. [PubMed: 17314918]
42. Grilo CM, Masheb RM, Wilson GT. Efficacy of cognitive behavioral therapy and fluoxetine for the treatment of binge eating disorder: a randomized double-blind placebo-controlled comparison. Biol Psychiatry. 2005; 57(3):301–309. [PubMed: 15691532]
43. Pearlstein T, Spurell E, Hohlstein LA, et al. A double-blind, placebo-controlled trial of fluvoxamine in binge eating disorder: a high placebo response. Arch Women Ment Health. 2003; 6(2):147–151.

44. McElroy SL, Arnold LM, Shapira NA, et al. Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. Am J Psychiatry. 2003; 160(2): 255–261. [PubMed: 12562571]
45. Mula M, Cavanna AE, Monaco F. Psychopharmacology of top-iramate: from epilepsy to bipolar disorder. Neuropsychiatr Dis Treat. 2006; 2(4):475–488. [PubMed: 19412496]
46. Citrome L. Lisdexamfetamine for binge eating disorder in adults: a systematic review of the efficacy and safety profile for this newly approved indication - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract. 2015; 69(4):410–421. [PubMed: 25752762]
47. Goudriaan AE, Oosterlaan J, de Beurs E, Van den Brink W. Pathological gambling: a comprehensive review of biobehavioral findings. Neurosci Biobehav Rev. 2004; 28(2):123–141. [PubMed: 15172761]
48. Santangelo G, Barone P, Trojano L, Vitale C. Pathological gambling in Parkinson's disease. A comprehensive review. Parkinsonism Relat Disord. 2013; 19(7):645–653. [PubMed: 23490464]
49. Welte JW, Barnes GM, Wieczorek WF, Tidwell M-CO, Parker JC. Risk factors for pathological gambling. Addict Behav. 2004; 29(2):323–335. [PubMed: 14732420]
50. Rizeanu S. Pathological gambling and depression. Procedia Soc Behav Sci. 2013; 78:501–505.
51. Potenza MN, Leung H-C, Blumberg HP, et al. An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. Am J Psychiatry. 2003; 160(11):1990–1994. [PubMed: 14594746]
52. Reuter J, Raedler T, Rose M, Hand I, Gläscher J, Büchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci. 2005; 8(2):147–148. [PubMed: 15643429]
53. Balodis IM, Kober H, Worhunsky PD, Stevens MC, Pearlson GD, Potenza MN. Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. Biol Psychiatry. 2012; 71(8):749–757. [PubMed: 22336565]
54. Santangelo G, Vitale C, Trojano L, Verde F, Grossi D, Barone P. Cognitive dysfunctions and pathological gambling in patients with Parkinson's disease. Mov Disord. 2009; 24(6):899–905. [PubMed: 19205072]
55. Blaszczynski A, Nower L. A pathways model of problem and pathological gambling. Addiction. 2002; 97(5):487–499. [PubMed: 12033650]
56. Blum K, Sheridan PJ, Wood RC, et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med. 1996; 89(7):396–400. [PubMed: 8774539]
57. Blanco C, Orensanz-Muñoz L, Blanco-Jerez C, Saiz-Ruiz J. Pathological gambling and platelet MAO activity: a psychobiological study. Am J Psychiatry. 1996; 153(1):119–121. [PubMed: 8540570]
58. Comings DE, Gade-Andavolu R, Gonzalez N, et al. The additive effect of neurotransmitter genes in pathological gambling. Clin Genet. 2001; 60(2):107–116. [PubMed: 11553044]
59. Ibañez A, Perez de Castro I, Fernandez-Piqueras J, Blanco C, Saiz-Ruiz J. Pathological gambling and DNA polymorphic markers at MAO-A and MAO-B genes. Mol Psychiatry. 2000; 5(1):105–109. [PubMed: 10673777]
60. Ibáñez A, Blanco C, Perez de Castro I, Fernandez-Piqueras J, Sáiz-Ruiz J. Genetics of pathological gambling. J Gambl Stud. 2003; 19(1):11–22. [PubMed: 12635538]
61. Ladouceur R, Jacques C, Ferland F, Giroux I. Prevalence of problem gambling: a replication study 7 years later. Can J Psychiatry. 1999; 44(8):802–804. [PubMed: 10566111]
62. Grant JE, Potenza MN, Hollander E, et al. Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. Am J Psychiatry. 2006; 163(2):303–312. [PubMed: 16449486]
63. Papay K, Xie SX, Stern M, et al. Naltrexone for impulse control disorders in Parkinson disease: a placebo-controlled study. Neurology. 2014; 83(9):826–833. [PubMed: 25037206]
64. Dannon PN, Lowengrub K, Gonopolski Y, Musin E, Kotler M. Topiramate versus fluvoxamine in the treatment of pathological gambling: a randomized, blind-rater comparison study. Clin Neuropharmacol. 2005; 28(1):6–10. [PubMed: 15711432]

65. Black DW, Shaw MC, Allen J. Extended release carbamazepine in the treatment of pathological gambling: an open-label study. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(5):1191–1194. [PubMed: 18436362]
66. Zack M, Poulos CX. Effects of the atypical stimulant modafinil on a brief gambling episode in pathological gamblers with high vs. low impulsivity. J Psychopharmacol. 2009; 23(6):660–671. [PubMed: 18583430]
67. Leung KS, Cottler LB. Treatment of pathological gambling. Curr Opin Psychiatry. 2009; 22(1):69–74. [PubMed: 19122538]
68. Grant JE, Kim SW, Odlaug BL. N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biol Psychiatry. 2007; 62(6):652–657. [PubMed: 17445781]
69. Hernandez L, Hoebel BG. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci. 1988; 42(18):1705–1712. [PubMed: 3362036]
70. Di Ciano P, Everitt BJ. Direct interactions between the basolateral amygdala and nucleus accumbens core underlie cocaine-seeking behavior by rats. J Neurosci. 2004; 24(32):7167–7173. [PubMed: 15306650]
71. Everitt BJ, Robbins TW. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. Neurosci Biobehav Rev. 2013; 37(9 Pt A):1946–1954. [PubMed: 23438892]
72. Dackis CA, Gold MS. Pharmacological approaches to cocaine addiction. J Subst Abuse Treat. 1985; 2(3):139–145. [PubMed: 3912517]
73. Gorelick DA, Wilkins JN. Bromocriptine treatment for cocaine addiction: association with plasma prolactin levels. Drug Alcohol Depend. 2006; 81(2):189–195. [PubMed: 16051446]
74. Sofuoglu M, Kosten TR. Novel approaches to the treatment of cocaine addiction. CNS Drugs. 2005; 19(1):13–25. [PubMed: 15651902]
75. Brodie JD, Figueroa E, Laska EM, Dewey SL. Safety and efficacy of gamma-vinyl GABA (GVG) for the treatment of metham-phetamine and/or cocaine addiction. Synapse. 2005; 55(2):122–125. [PubMed: 15543630]
76. Brodie JD, Figueroa E, Dewey SL. Treating cocaine addiction: from preclinical to clinical trial experience with gamma-vinyl GABA. Synapse. 2003; 50(3):261–265. [PubMed: 14515344]
77. Aharonovich E, Nunes E, Hasin D. Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. Drug Alcohol Depend. 2003; 71(2):207–211. [PubMed: 12927659]
78. Potenza MN, Sofuoglu M, Carroll KM, Rounsaville BJ. Neuroscience of behavioral and pharmacological treatments for addictions. Neuron. 2011; 69(4):695–712. [PubMed: 21338880]
79. Heiden P, Heinz A, Romanczuk-Seiferth N. Pathological gambling in Parkinson's disease: what are the risk factors and what is the role of impulsivity? Eur J Neurosci. 2017; 45(1):67–72. [PubMed: 27623191]
80. Soloff PH, Lynch KG, Moss HB. Serotonin, impulsivity, and alcohol use disorders in the older adolescent: a psychobiological study. Alcohol Clin Exp Res. 2000; 24(11):1609–1619. [PubMed: 11104107]
81. Hinckers AS, Laucht M, Schmidt MH, et al. Low level of response to alcohol as associated with serotonin transporter genotype and high alcohol intake in adolescents. Biol Psychiatry. 2006; 60(3):282–287. [PubMed: 16497275]
82. Ferrari PF, Palanza P, Parmigiani S, de Almeida RMM, Miczek KA. Serotonin and aggressive behavior in rodents and nonhuman primates: predispositions and plasticity. Eur J Pharmacol. 2005; 526(1–3):259–273. [PubMed: 16289029]
83. Seo D, Patrick CJ, Kennealy PJ. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. Aggress Violent Behav. 2008; 13(5):383–395. [PubMed: 19802333]
84. Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. Neuroscience. 2012; 215:42–58. [PubMed: 22542672]
85. Rinne T, van den Brink W, Wouters L, van Dyck R. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. Am J Psychiatry. 2002; 159(12):2048–2054. [PubMed: 12450955]

86. Weintraub D, Taraborelli D, Morales KH, Duda JE, Katz IR, Stern MB. Escitalopram for major depression in Parkinson's disease: an open-label, flexible-dosage study. J Neuropsychiatry Clin Neurosci. 2006; 18(3):377–383. [PubMed: 16963587]

87. Demetriades P, Rickards H, Cavanna AE. Impulse control disorders following deep brain stimulation of the subthalamic nucleus in Parkinson's disease: clinical aspects. Parkinsons Dis. 2011; 2011:658415. [PubMed: 21403902]

88. Brunenberg EJL, Moeskops P, Backes WH, et al. Structural and resting state functional connectivity of the subthalamic nucleus: identification of motor STN parts and the hyperdirect pathway. PLoS One. 2012; 7(6):e39061. [PubMed: 22768059]

89. Greenhouse I, Gould S, Houser M, Aron AR. Stimulation of contacts in ventral but not dorsal subthalamic nucleus normalizes response switching in Parkinson's disease. Neuropsychologia. 2013; 51(7):1302–1309. [PubMed: 23562963]

90. Rodriguez-Oroz MC, López-Azcárate J, Garcia-Garcia D, et al. Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. Brain. 2010; 134:36–49. [PubMed: 21059746]

91. Wylie SA, Ridderinkhof KR, Elias WJ, et al. Subthalamic nucleus stimulation influences expression and suppression of impulsive behaviour in Parkinson's disease. Brain. 2010; 133(12): 3611–3624. [PubMed: 20861152]

92. Hälbig TD, Tse W, Frisina PG, et al. Subthalamic deep brain stimulation and impulse control in Parkinson's disease. Eur J Neurol. 2009; 16(4):493–497. [PubMed: 19236471]

Table 1

Similarities in the neurobiology and treatment of various neurobehavioral disorders

Syndrome	Mesocorticolimbic system localization	Dopamine-based polymorphisms	Treatment
Binge eating disorder	Decreased D2-receptor activation in ventral striatum during reward cue tasks Increased dorsal striatal activity seen with compulsive behaviors[38]	D2 receptor & DAT polymorphisms[40,41]	Increase in GABA (topiramate)[45] & inhibition of monoamine oxidase (amphetamines)[46]
Pathological gambling	Ventromedial prefrontal and ventral striatum in an fMRI study are diminished.[51,52]	D2, DAT, MAO polymorphisms[55–58]	Opioid antagonist (naltrexone),[62] increase GABA (topiramate/ carbamazepine),[64,65] dopamine reuptake inhibitor (modafinil),[66,67] ventral striatal glutamate (N-acetyl cysteine)[68]
Cocaine abuse	Reduction in D2-like receptors in the ventral striatum and changes in the dorsal striatum are associated with compulsive behaviors.[32]	DAT polymorphism[41]	Increase in GABA (topiramate),[74] inhibit GABA transamidase and increase GABA (vigabatrin)[75,76]
DA- induced ICD in PD	Reduced D2-receptor stimulation in the ventral striatum and maintained D2-receptor activation in the dorsal striatum appears related to compulsive behaviors.[21]	To be determined	Reduction in dopamine agonist levels

Abbreviations: DAT, dopamine transporter gene; ICD, impulse control disorder; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; MAO, monoamine oxidase.