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General

The Role of Dopamine in Impulsivity and Substance Abuse: A Narrative Review

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Substance use disorder (SUD), based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is defined by symptoms caused by utilizing a substance that a person continues taking despite its negative effects. Impulsive decision making is commonly defined as a reduced ability to choose a delayed large reward instead of a small immediate reward. Dopamine has been implicated as a prominent neurotransmitter implicated in the development and pattern of addiction and impulsivity, especially in regard to substance use disorder. Discovery as a key player in the development of addiction dates to the 1950s, with a study performed by Olds and Milner on rats placed in a Skinner box. Their original discovery is part of the beginning of what would become the search into the main mechanistic source of addiction, and how exactly it works at a cellular, physiological, and psychological level. The dopaminergic pathways of our brains are well-studied. It is well established that most of the dopaminergic neurons of the brain are located in the ventral mid-brain and consists of four main pathways: mesocortical, mesolimbic, nigrostriatal, and tuberoinfundibular pathways. Dopamine acts various receptors, with dopamine (D) receptors 1, 2, and 3 playing a major role in motor function and receptors D1 and D2 playing a major role in reward. There are additional studies warranted, especially finding ways to manipulate the dopaminergic system to treat addiction disorders of all varieties. The focus of the present investigation is to delve into the current literature regarding dopamine and its clinical implications in substance use disorder and impulsive behavior.

INTRODUCTION

Dopamine has been shown to be a key player in the cycle of addictive behavior since it was initially discovered to play a role in subsequent studies following a study done in the 1950s by Olds and Milner. Their initial study showed that rats would use the process of positive reinforcement by repeatedly self-stimulating parts of their brain that consisted of dopaminergic neurons by pressing a lever after being placed in a Skinner Box.[1] Many subsequent studies following this breakthrough discovery were focused on studying dopamine specifically as a key player in reward and impulsiveness pathways. Some of these studies showed that blocking the dopaminergic pathways with neuroleptic drugs leads to the lack of positive reinforcement in rats and primates, showing dopamine's essential role in the development of addiction and reward behaviors.[2] Since these discoveries, immense research has been undertaken in the hopes of understanding fully how dopamine works in the addiction process to find potential treatments for addiction.

Addiction is a growing problem in our society, whether it involves a substance, internet, or activity. It can be prevalent in up to 30% of cases seen in a primary care setting and 50% in patients with a pre-existing psychiatric illness. Unfortunately, it is often missed or undiagnosed by physicians, whether that is due to inadequate screening or bias.[3, 4] According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a substance use disorder (SUD) is defined by symptoms caused by utilizing a substance that a person continues taking despite its negative effects. Based on decades of research, DSM-5 definition of substance abuse disorder includes 11 criteria that can arise from substance misuse. These criteria categorized into four categories — impaired control, physical dependence, social problems, and risky use. These criteria include using a substance longer than directed, trying to cut down on use, withdrawals, tolerance, neglecting responsibilities, continued use in the face of relationship issues, neglecting important or desirable social events, use in risky settings, and continued use despite physical and mental health consequences.

There are many addictive substances that are commonly used in today's society and trigger the dopaminergic system to release dopamine and result in addiction. These substances include cocaine, amphetamines, alcohol, opiates, nicotine, caffeine, benzodiazepines, and barbiturates to name a few. Other activators of dopaminergic effects include things such as foods, internet usage, and gambling.[5] There are varying direct effects and withdrawal symptoms that exist among the different forms of addictive drugs that exist. However, among all of these drugs, the common theme of dopaminergic activation and the brain reward system are the common denominator among them. The pathways in which dopaminergic activation and the downstream effects of reward and pleasure are well-studied, albeit vast and complex. In this study, therefore, we review the latest literature regarding dopamine physiology and cellular pathways including the downstream effects of individual dopamine receptors and the significance of their correlation to substance abuse disorder, reward, motivation, and impulsivity.

DOPAMINERGIC PATHWAYS

DOPAMINE

Dopamine (3-hydroxytyramine) is the prominent catecholaminergic neurotransmitter in the central nervous system where it is produced in the ventral tegmental area and in the substantia nigra, extending into the hypothalamus, striatum (caudate-putamen), cortex, and limbic system of the brain.[6] Dopamine is also produced in the peripheral nervous system specifically in the kidney and intestines.[7] Most of dopamine is synthesized directly from tyrosine, which is actively transported from the liver, but it can also be processed indirectly from phenylalanine.[7,8] Through a series of reactions involving tyrosine hydroxylase, L-dopa is formed which is converted by dopa decarboxylase to dopamine.

DOPAMINE RECEPTORS

For dopamine to be effective it binds to specific transmembrane G protein-coupled receptors (GPCRS) which are divided into two major groups: D_1-like receptors (D_1 and D_5) generally have a stimulating effect and D_2-like receptors (D_2-D_4) are associated with inhibitory actions.[9] Dopamine receptors are prevalent in the brain, especially subtypes D_1 and D_2. D_1-like receptors are predominantly located in the frontal and temporal cortex, striatum, substantia nigra pars reticulata, nucleus accumbens, olfactory bulb, hippocampus, amygdala, and hypothalamus. D_2-like receptors are largely present in basal ganglia, striatum, nucleus accumbens, ventral tegmental area, hippocampus, pituitary, hypothalamus, and frontal cerebral cortex.[7,8]

DOPAMINE RECEPTOR FUNCTIONS

Dopamine is involved in a variety of central nervous system functions such as motor abilities, sleep, attention, emotion, and reward and it has an effect peripherally on the cardiovascular, renal, immune, endocrine, and renal systems as well.[10,11] D_1, D_2, and D_3 are the major receptors which control locomotion while D_4 and D_5 have a minimal role in motor function. Involvement of D_1 and D_2 in the processes of reward and reinforcement has strong implications for addictive behaviors since research indicates that the manipulation of these receptors can alter one's response to drug addiction.[10,11] Additional activities which are influenced by means of dopamine receptors include learning, working memory, impulse control, and decisions.[7] The response dopamine evokes depends on the specific receptor it binds to and activates. A majority of the dopamine downstream signaling involves GPCRs which experience continuous regulation after binding occurs. For example, with drug addiction, there is an upregulation of D1 while D2 is downregulated. This can result in a downstream effect of neuronal death.[7]

DOPAMINERGIC PATHWAYS

Dopamine neurons innervate various portions of the brain and most of them are located in the midbrain's ventral aspect which is where three of four main dopaminergic pathways originate.[7,12] The mesocortical pathway originates from the ventral tegmental area and extends to the prefrontal cortex, nucleus accumbens, amygdala, and hippocampal area.[13] This pathway mediates emotions and cognition (working memory, attention). An imbalance in dopamine levels, particularly in the prefrontal cortex, has a negative effect on memory. When dopamine receptors are blocked in this pathway by antipsychotic drugs, negative symptoms of schizophrenia exacerbate.[14,15] The mesolimbic pathway also originates from the ventral tegmental area and extends to the nucleus accumbens, prefrontal cortex, amygdala, and lateral septal nuclei. This system is involved with reward and motivation and the release of dopamine mediates the pleasure which is experienced.[8,14,15] The nigrostriatal pathway which is associated with habit development and control/learning of voluntary motor function projects from the substantia nigra to the basal ganglia (caudate nucleus and putamen). A breakdown in this pathway results in Parkinson's Disease. When dopamine receptors in this path are blocked, extrapyramidal symptoms ensue. Originating from the hypothalamus and extending to the pituitary is the tuberoinfundibular pathway. Dopamine neurons which form this system are responsible for the inhibition of prolactin release.[7,8]

PREFRONTAL CORTEX, DOPAMINE AND ADDICTION

As mentioned, the mesolimbic pathway is associated with the experience of pleasure. When pleasure activates this system such as that experienced with drug addiction, there is a release of dopamine especially in the prefrontal cortex and nucleus accumbens. This release of dopamine is a key factor in substance abuse because it elicits immediate pleasure and the desire to continue to seek pleasure via the abuse of drugs. The mesolimbic pathway is considered to have a significant role in addictive behaviors.[14,15]

INFLUENCE OF DOPAMINE ON IMPULSIVITY

Impulsive decision making is commonly defined as a reduced ability to choose a delayed large reward instead of a small immediate reward.[16] The effects of dopamine have long been postulated to contribute to impulsive behavior in human beings. Impulsive behavior is implicated in addiction,[17] Attention deficit disorder (ADHD),[18] and Parkinson's disease (PD).

Impulsive decision making is a prominent characteristic of ADHD; amphetamines are a mainstay of therapy and work primarily by influencing neurotransmission of dopamine, norepinephrine, and serotonin.[19] Methylphenidate (MPH) inhibits reuptake of Norepinephrine and dopamine in the CNS. A 2022 study found that administration of MPH reduced choice impulsivity and is associated with increased striatal activity and fronto-striatal connectivity, suggesting dopamine modulation following MPH administration may reduce impulsive choices by increasing fronto-striatal connectivity.[20] Conversely, a randomized clinical controlled trial found that the dopamine D2/D3 antagonist amisulpride, reduced reward impulsivity in a cohort of 41 patients compared to a placebo group.[21]

Pharmacologic agents that modulate dopaminergic receptor/dopaminergic metabolism are associated with impulsive behaviors. Impulse control disorders occur in around 17% patients treated with dopamine agonists.[22] Ropinirole, a D3 receptor agonist, was proven to reduce proactive inhibition in a double blinded placebo controlled trial.[23] Tolcapone inhibits catechol-O-methyltransferase (COMT) from metabolizing catecholamines in the CNS and PNS. Tolcapone has been associated with improvement of pathologic gambling symptoms and statistically significant reductions in PG-Yale Brown Obsessive compulsiveness scale scores.[24] Dopamine's influence on impulsive behavior is implicated in addiction. Clinical trial data demonstrates that 15-day administration of the D3 dopamine receptor agonist Pramipexole produced two-fold increases in positive subjective effect rating following cocaine administration in a cohort of cocaine users.[25]

The influence of dopaminergic neural pathways on impulsive behavior is also evidenced by PD patients. The crux of PD treatment involves pharmacologic replacement of dopamine (DRT) , modulation of CNS dopamine receptors, and deep brain stimulation (DBS) (Grant et al., 2013). Impulsive behavior/impulse control disorders (ICD) have long been associated with dopamine replacement therapy and include pathologic gambling, hypersexuality, binge eating, and compulsive shopping.[26] A prospective cohort study found that incident rates of ICD and related behaviors increased by 8% at 1 year, 18% at 2 years, and 25% at 3 years following DRT.[27] Conversely, the incidence ICD symptoms decreased in PD patients not receiving DRT.

Evidence for the association with DBS and impulsive behaviors is poorly characterized. Neuropsychiatric side effects of impulsivity and mania following subthalamic DBS are postulated to arise as sequalae of modulatory effects through differential recruitment of frontostriatal networks.[28] A 2021 clinical trial found that PD patients had significantly higher scores on the TCI dimension Novelty-Seeking following implantation of DBS than before at baseline suggesting that increased dopamine activity in the subthalamic nucleus (STN) and globus pallidus internus (GPi) is associated with an increase in impulsive behavior.[29] Data from a 2018 study evaluating ICD in 61 PD patients at 1 and 7 years following DBS treatment found that all preoperative ICDs disappeared after DBS therapy; but 11% of PD patients developed a subsequent ICD in the following 7 years after receiving DBS therapy.[30] This data suggests that modulation of dopamine level in the CNS of PD patients contributes to both improvement and development of impulsive behavior.

IMPLICATION OF DOPAMINE IN SUBSTANCE ABUSE

MOTIVATION AND REWARD

At a behavioral level, the drive, motivation, reward, and impulsivity of drug abuse are similar to behaviors such as eating, defending oneself, or copulation. What all these behaviors share is an extrinsic stimulus of both past and present experiences leading to the cycle of cellular excitability response intrinsically motivating future behavior. Based on both experience and prior reward cycles of these extrinsic stimuli, the impetus for a behavioral response is intrinsically motivated. At the cellular level, this reinforcing reward-driven behavioral cycle is a direct product of the degree of dopamine response at the cerebral location responsible for that behavioral stimulus' reward. This relationship of developed dopamine response to behavioral modifications is referred to as the dopamine motive system. The dopamine motive system also suggests that repeated exposure to a dopamine-releasing stimulus causes progressive downregulation of the excitatory dopamine response to that stimulus as well as other dopamine-releasing stimuli, leading to decreased self-regulation and the emergence of impulsive and compulsive reactions to these stimuli. Therefore, the dopamine motive system can contribute to addiction when compromised and, therefore, must be rebalanced between stimulus-response and reward to alleviate these impulsive and compulsive behaviors.[31-33]

IMPLICATIONS OF DOPAMINE IN SUBSTANCE ABUSE

At the cellular and synaptic level, the dopamine motive system begins with the dopamine synthesizing neurons in the ventral tegmental area (VTA) and the substania nigra. Once synthesized, the dopamine will be stored within the vesicles of the neuron axon terminals of the VTA and substantia nigra for future release from neurons projecting to the nucleus accumbens (NAc) and dorsal striatum, respectively.[31] Once the VTA and substantia nigra neurons receive an excitatory action potential caused by stimuli like food, sex, and drug use, the dopamine stored within these vesicles is released into the synaptic cleft. Once in the synaptic cleft, dopamine binds to either dopamine receptors, transmitting this action potential to the neurons of the NAc and dor-

sal striatum. Once bound to the post-synaptic dopamine receptors, dopamine elicits changes within the postsynaptic neuron, leading to altered neuron excitability. The release of dopamine by the presynaptic neurons of the VTA to the postsynaptic neurons of the NAc is correlated with rewarding stimuli, signaling the stimuli behavior as desirable and should be pursued. On the other hand, the excitability of the dopaminergic neurons in the substantia nigra, which project to the dorsal striatum, are correlated with converting reward signals into habitual actions based on prior experience. Over time, this habitual reward-associated behavior causes a decreased regulatory input from the prefrontal cortex to the dorsal striatum, causing decreased cognitive regulation of addiction-like behaviors.[32] The VTA and NAc neural circuit is considered the major reward pathway of the central nervous system where rewarding stimuli promote the release of dopamine from the VTA into the NAc, reenforcing impulsive reward-seeking behavior, which is habitually complemented by action forming input of the substantia nigra and dorsal striatum.[6,34] Chronic exposure to addictive drugs compromises this dopamine motive system by both forming habitual downregulation of behavioral response and by initiating adaptive changes through altering the D1, D2, and D3 dopamine receptor density, distribution, and sensitivity in the NAc. This means that fewer receptors are available to bind dopamine, leading to reduced sensitivity to dopamine release. Therefore, increasing amounts of the inciting stimulus are required to achieve the same level of dopamine-induced reward or pleasure.[32,35]

This relationship of this dopamine release adaptation response to drive, motivation, reward, and impulsivity in drug abuse is well supported by animal and clinical patient studies. One example of the many homeostatic compensatory mechanisms for the downregulation of dopamine reward-response cycles in mice studies occurs by upregulation of leptin response at the post-synaptic neurons on the NAc, therefore downregulating dopamine-dependent cocaine reinforcement.[36] Another demonstrated mechanism of dopamine response adaptation shows that optogenetic activation of both D_1 and D_2 neurons in the NAc enhances motivation-orientated activity in mice models; conversely, optogenetic inhibition of D2 neurons in the NAc decreases motivation. This D2 inhibitory effect is also seen in chronic addictive drug use due to the downregulation of the dopaminergic response of D2 receptors in the NAc.[37] In another mouse model study, developmental overexpression of the D_2 receptor in striatal spiny projection neurons resulted in a population of mice that had a reduction in motivation, working memory, and cognitive flexibility.[38] Several behavioral, pharmacologic studies on rodents have demonstrated that antagonizing dopamine receptors or depleting dopamine levels in the ventral striatum correlate with diminished motivation.[39] Fluctuation in dopamine levels also contributes to motivation levels/apathy, as demonstrated by humans with Parkinson's disease, a pathology defined by decreased dopamine production related to the loss of dopamine-producing neurons. These apathetic and decreased motivational symptoms of Parkinson's disease are suggested to be largely related to the dopamine production deficit, and the symptoms are often pharmaceutically counteracted by dopamine receptor agonists. For example, chronic subthalamic nucleus deep brain stimulation in rodent models results in motivational deficits; the deficits were fully reversed by treatment with the D_2 and D_3 receptor agonist pramipexole.[40] Further rodent studies also suggest an increase in both impulsivity and inattention in a dose-dependent manner when dopaminergic dysfunction is simulated by the administration of dopamine receptor antagonists.[41] Therefore, the direct downregulation of the dopamine motive system elicited by chronic exposure to addictive drugs is suggested to elicit the symptoms of decreased drive, motivation, reward, and increased impulsivity as a product of acquired dopamine tolerance related to various compensatory mechanisms of decreased dopamine receptor response (Table 1).[31,32,42]

CONCLUSION

The various systems and pathways involving dopamine in our body are vast and very complex, making understanding difficult and therapeutic interventions challenging. Since its discovery many years ago, extensive research has been taken to understand dopamine and how it influences bodily systems, functions, motives, and actions. Even with our extensive understanding of the dopaminergic pathways in our brain, there is still much more to learn. Studies that dive deeper into the mediation or modulation of these pathways as a potential treatment for addiction and substance use disorder are warranted in the future, especially with how prevalent addiction and substance is currently in our world. Substance use disorder and addiction, in general, remain major issues and can include many matters other than drugs, including internet use, pornography, alcohol, and many more. Even with the major advances and insight scientists and clinicians have made throughout the years into how dopamine influences these behaviors, it is still important to continue to strive for clinical advancements to help potentially treat these addictions pharmacologically. With ADHD also becoming more prominent in recent decades, the study of correlations of internet use and ADHD rates could also be a potential area for more research as to ascertain how dopamine plays a direct and substantial role.

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COMPETING INTERESTS

None

AUTHOR CONTRIBUTIONS

All authors listed have made a direct and intellectual contribution to the work and approved for publication.

Table 1. Clinical Trails Demonstrating the Influence of Dopamine on Impulsivity and Substance Abuse

Author (Year)	Methodology	Results and Findings	Conclusions
Weber S (2016)	A randomized double-blind study comparing cue-induced responding and reward impulsivity with a delay discounting task on participants who received amisulpride, naltrexone, or placebo.	Amisulpride was associated with statistically significantly suppressed reward impulsivity compared to the placebo group (t(78)=2.58 P<0.01).	Data suggests that D2/D3 dopamine antagonist amisulpride may show promise in the treatment of addiction in individuals with heightened drug cue activity and elevated reward impulsivity.
Pham U (2021)	A prospective randomized study comparing Novelty seeking, Self Directness, Cooperativity, and Social Conformity scores in Parkinson patients one year after STN-DBS therapy.	Parkinson's disease patients who underwent STN-DBS had significantly higher novelty seeking and lower persistence scores (-0.8 +/- 3; P<0.01) than comparative norms.	The study found higher baseline level of impulsivity in patients who underwent STN-DBS therapy, suggesting that treatment may affect a patient's personality by increasing components of impulsivity.
Grant J (2013)	24 individuals with Pathological Gambling disorder were given 8 week course of tolcapone and assessed with score on PG-Yale Brown Obcessive Compulsive Scale (PG-YBPCS) and pre- and post-treatment fMRI.	Treatment with Tolcapone was associated with significantly significant reductions in PG-YBPCS (Visit one score 23.63 +/- 4.49 vs Visit 5 score 10.50 +/-7.02; P<0.001).	Pathological gambling symptoms improved significantly in the majority of subjects treated with the COMT inhibitor Tolcapone, and the magnitude of improvement was associated with val/val COMT polymorphism.
Newton T (2015)	A randomized double-blind, placebo-controlled trial examining the effects of pramipexole treatment on the subjective effects produced by cocaine in a cohort of individuals with cocaine use disorder.	Pramipexole treatment enhances the positive subjective effects of cocaine; Pramipexole is associated with increased diastolic blood pressure and heart rate and produces upwards of two-fold increases in positive subjective effects of following cocaine administration. Post-hoc comparisons revealed significantly greater ratings from participants treated with pramipexole (3 mg) compared to placebo (pramipexole 0 mg) following 20 mg cocaine ($p < 0.001$)	Chronic activation of the D3 receptor increases subjective positive effects following the administration of cocaine in individuals with cocaine use disorder. Pramipexole should be prescribed with caution to individuals with the potential for cocaine abuse.
Daood M (2022)	A randomized double-blind placebo-controlled trial. Fifty seven health participants participated and completed delayed discounting task twice during fMRI scans after administration of methylphenidate (20mg) or placebo.	Methylphenidate was associated with a significant improvement in choice impulsivity compared to placebo during the delayed discounting task. ($t_{[56]} = 2.336$, $p = .023$; *%Now choices:* placebo session = 43.69%; MPH session = 41.63%)	Acute methylphenidate administration is associated with increased striatal activity, fronto striatal connectivity and reduced choice impulsivity.

COMPLIANCE WITH ETHICAL GUIDELINES

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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REFERENCES

1. Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology*. 1954;47(6):419-427. doi:10.1037/h0058775

2. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. *Psychological Review*. 1987;94(4):469-492. doi:10.1037/0033-295X.94.4.469

3. Johnson TP, Booth AL, Johnson P. Physician beliefs about substance misuse and its treatment: findings from a U.S. survey of primary care practitioners. *Subst Use Misuse*. 2005;40(8):1071-1084. doi:10.1081/JA-200030800

4. Clay S. A Review of Addiction. *Postgrad Med*. 2008;120(2). doi:10.3810/pgm.2008.07.1802

5. Wise RA, Robble MA. Dopamine and Addiction. *Annu Rev Psychol*. 2020;71(1):79-106. doi:10.1146/annurev-psych-010418-103337

6. Baik JH. Dopamine Signaling in reward-related behaviors. *Front Neural Circuits*. 2013;7. doi:10.3389/fncir.2013.00152

7. Klein MO, Battagello DS, Cardoso AR, Hauser DN, Bittencourt JC, Correa RG. Dopamine: Functions, Signaling, and Association with Neurological Diseases. *Cell Mol Neurobiol*. 2019;39(1):31-59. doi:10.1007/s10571-018-0632-3

8. Ayano G. Dopamine: Receptors, Functions, Synthesis, Pathways, Locations and Mental Disorders: Review of Literatures. *J Ment Disord Treat*. 2016;2(2). doi:10.4172/2471-271X.1000120

9. Pivonello R, Ferone D, Lombardi G, Colao A, Lamberts SWJ, Hofland LJ. Novel insights in dopamine receptor physiology. *eur j endocrinol*. 2007;156(suppl_1):S13-S21. doi:10.1530/eje.1.02353

10. Beaulieu JM, Gainetdinov RR. The Physiology, Signaling, and Pharmacology of Dopamine Receptors. Sibley DR, ed. *Pharmacol Rev*. 2011;63(1):182-217. doi:10.1124/pr.110.002642

11. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine Receptors: From Structure to Function. *Physiological Reviews*. 1998;78(1):189-225. doi:10.1152/physrev.1998.78.1.189

12. Kim S, Kwok S, Mayes LC, Potenza MN, Rutherford HJV, Strathearn L. Early adverse experience and substance addiction: dopamine, oxytocin, and glucocorticoid pathways. *Annals of the New York Academy of Sciences*. 2017;1394(1):74-91. doi:10.1111/nyas.13140

13. Ruiz-Tejada A, Neisewander J, Katsanos CS. Regulation of Voluntary Physical Activity Behavior: A Review of Evidence Involving Dopaminergic Pathways in the Brain. *Brain Sciences*. 2022;12(3):333. doi:10.3390/brainsci12030333

14. Christine CW, Aminoff MJ. Clinical differentiation of parkinsonian syndromes: Prognostic and therapeutic relevance. *The American Journal of Medicine*. 2004;117(6):412-419. doi:10.1016/j.amjmed.2004.03.032

15. Björklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. *Trends in Neurosciences*. 2007;30(5):194-202. doi:10.1016/j.tins.2007.03.006

16. van Gaalen MM, van Koten R, Schoffelmeer ANM, Vanderschuren LJMJ. Critical Involvement of Dopaminergic Neurotransmission in Impulsive Decision Making. *Biological Psychiatry*. 2006;60(1):66-73. doi:10.1016/j.biopsych.2005.06.005

17. Bickel WK, Koffarnus MN, Moody L, Wilson AG. The behavioral- and neuro-economic process of temporal discounting: A candidate behavioral marker of addiction. *Neuropharmacology*. 2014;76:518-527. doi:10.1016/j.neuropharm.2013.06.013

18. Mechler K, Banaschewski T, Hohmann S, Häge A. Evidence-based pharmacological treatment options for ADHD in children and adolescents. *Pharmacol Ther*. 2022;230:107940. doi:10.1016/j.pharmthera.2021.107940

19. Luethi D, Liechti ME. Designer drugs: mechanism of action and adverse effects. *Arch Toxicol*. 2020;94(4):1085-1133. doi:10.1007/s00204-020-02693-7

20. Daood M, Peled-Avron L, Ben-Hayun R, et al. Fronto-striatal connectivity patterns account for the impact of methylphenidate on choice impulsivity among healthy adults. *Neuropharmacology*. 2022;216:109190. doi:10.1016/j.neuropharm.2022.109190

21. Weber SC, Beck-Schimmer B, Kajdi ME, Müller D, Tobler PN, Quednow BB. Dopamine D2/3- and μ-opioid receptor antagonists reduce cue-induced responding and reward impulsivity in humans. *Transl Psychiatry*. 2016;6(7):e850. doi:10.1038/tp.2016.113

22. Voon V, Napier TC, Frank MJ, et al. Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. *The Lancet Neurology*. 2017;16(3):238-250. doi:10.1016/S1474-4422(17)30004-2

23. Rawji V, Rocchi L, Foltynie T, Rothwell JC, Jahanshahi M. Ropinirole, a dopamine agonist with high D3 affinity, reduces proactive inhibition: A double-blind, placebo-controlled study in healthy adults. *Neuropharmacology*. 2020;179:108278. doi:10.1016/j.neuropharm.2020.108278

24. Grant JE, Odlaug BL, Chamberlain SR, Hampshire A, Schreiber LRN, Kim SW. A proof of concept study of tolcapone for pathological gambling: Relationships with COMT genotype and brain activation. *European Neuropsychopharmacology*. 2013;23(11):1587-1596. doi:10.1016/j.euroneuro.2013.07.008

25. Newton TF, Haile CN, Mahoney JJ, et al. Dopamine D3 receptor-preferring agonist enhances the subjective effects of cocaine in humans. *Psychiatry Res*. 2015;230(1):44-49. doi:10.1016/j.psychres.2015.07.073

26. Corvol JC, Artaud F, Cormier-Dequaire F, et al. Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology*. 2018;91(3):e189-e201. doi:10.1212/WNL.0000000000005816

27. Smith KM, Xie SX, Weintraub D. Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. *J Neurol Neurosurg Psychiatry*. 2016;87(8):864-870. doi:10.1136/jnnp-2015-311827

28. Mosley PE, Paliwal S, Robinson K, et al. The structural connectivity of subthalamic deep brain stimulation correlates with impulsivity in Parkinson's disease. *Brain*. 2020;143(7):2235-2254. doi:10.1093/brain/awaa148

29. Pham U, Skogseid IM, Pripp AH, Bøen E, Toft M. Impulsivity in Parkinson's disease patients treated with subthalamic nucleus deep brain stimulation-An exploratory study. *PLoS One*. 2021;16(3):e0248568. doi:10.1371/journal.pone.0248568

30. Kim A, Kim YE, Kim HJ, et al. A 7-year observation of the effect of subthalamic deep brain stimulation on impulse control disorder in patients with Parkinson's disease. *Parkinsonism Relat Disord*. 2018;56:3-8. doi:10.1016/j.parkreldis.2018.07.010

31. Volkow ND, Wise RA, Baler R. The dopamine motive system: implications for drug and food addiction. *Nat Rev Neurosci*. 2017;18(12):741-752. doi:10.1038/nrn.2017.130

32. Volkow ND, Michaelides M, Baler R. The Neuroscience of Drug Reward and Addiction. *Physiological Reviews*. 2019;99(4):2115-2140. doi:10.1152/physrev.00014.2018

33. Botticelli L, Micioni Di Bonaventura E, Del Bello F, et al. Underlying Susceptibility to Eating Disorders and Drug Abuse: Genetic and Pharmacological Aspects of Dopamine D4 Receptors. *Nutrients*. 2020;12(8):2288. doi:10.3390/nu12082288

34. Becker-Krail DD, Walker WH, Nelson RJ. The Ventral Tegmental Area and Nucleus Accumbens as Circadian Oscillators: Implications for Drug Abuse and Substance Use Disorders. *Front Physiol*. 2022;13:886704. doi:10.3389/fphys.2022.886704

35. Solinas M, Belujon P, Fernagut PO, Jaber M, Thiriet N. Dopamine and addiction: what have we learned from 40 years of research. *J Neural Transm*. 2019;126(4):481-516. doi:10.1007/s00702-018-1957-2

36. You ZB, Wang B, Liu QR, Wu Y, Otvos L, Wise RA. Reciprocal Inhibitory Interactions Between the Reward-Related Effects of Leptin and Cocaine. *Neuropsychopharmacol*. 2016;41(4):1024-1033. doi:10.1038/npp.2015.230

37. Soares-Cunha C, Coimbra B, David-Pereira A, et al. Activation of D2 dopamine receptor-expressing neurons in the nucleus accumbens increases motivation. *Nat Commun*. 2016;7(1):11829. doi:10.1038/ncomms11829

38. Simpson EH, Gallo EF, Balsam PD, Javitch JA, Kellendonk C. How changes in dopamine D2 receptor levels alter striatal circuit function and motivation. *Mol Psychiatry*. 2022;27(1):436-444. doi:10.1038/s41380-021-01253-4

39. Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology*. 2007;191(3):461-482. doi:10.1007/s00213-006-0668-9

40. Vachez Y, Carcenac C, Magnard R, et al. Subthalamic Nucleus Stimulation Impairs Motivation: Implication for Apathy in Parkinson's Disease. *Movement Disorders*. 2020;35(4):616-628. doi:10.1002/mds.27953

41. Klem L, Nielsen MM, Gestsdóttir SB, Frandsen SL, Prichardt S, Andreasen JT. Assessing attention and impulsivity in the variable stimulus duration and variable intertrial interval rodent continuous performance test schedules using dopamine receptor antagonists in female C57BL/6JRj mice. *Psychopharmacology*. 2023;240(8):1651-1666. doi:10.1007/s00213-023-06387-7

42. Wise RA, Robble MA. Dopamine and Addiction. *Annu Rev Psychol*. 2020;71(1):79-106. doi:10.1146/annurev-psych-010418-103337