

Ödül Değerinde  
KİMYASAL  
DOPAMİN VE  
İŞLEVLERİ

Yazar

Mahmud Esad PENÇE MD;PhD



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<b>ISBN</b>	<b>Sayfa ve Kapak Tasarımı</b>
978-625-399-476-1	Akademisyen Dizgi Ünitesi
<b>Kitap Adı</b>	<b>Yayıncı Sertifika No</b>
Ödül Değerinde Kimyasal Dopamin ve İşlevleri	47518
<b>Yazar</b>	<b>Baskı ve Cilt</b>
Mahmud Esad PENÇE MD;PhD ORCID iD: 0000-0002-8411-3138	Vadi Matbaacılık
<b>Yayın Koordinatörü</b>	<b>Bisac Code</b>
Yasin DİLMEN	OCC000000
	<b>DOI</b>
	10.37609/akya.3130

#### **Kütüphane Kimlik Kartı**

**Pençe, Mahmut Esad.**

Ödül Değerinde Kimyasal Dopamin ve İşlevleri / Mahmut Esad Pençe.

Ankara : Akademisyen Yayınevi Kitabevi, 2024.

138 s. : tablo, şekil. ; 135x210 mm.

Kaynakça var.

ISBN 9786253994761

**GENEL DAĞITIM**

**Akademisyen Kitabevi AŞ**

Halk Sokak 5 / A Yenışehir / Ankara

Tel: 0312 431 16 33

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*Sevgili eşime ...*

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## KAYNAKLAR

1. Carlsson A, Lindqvist M, Magnusson T. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature*. 1957;180(4596):1200. doi:10.1038/1801200a0.
2. Carlsson A. The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol Rev*. 1959;11(2):490-493.
3. Nagatsu T, Levitt M, Udenfriend S. Tyrosine hydroxylase: the initial step in norepinephrine biosynthesis. *J Biol Chem*. 1964;239:2910-2917. doi:10.1016/S0021-9258(18)93832-9.
4. Jung-Klawitter S, Richter P, Yuan Y, et al. Tyrosine hydroxylase variants influence protein expression, cellular localization, stability, enzymatic activity and the physical interaction between tyrosine hydroxylase and GTP cyclohydrolase I. *J Inher Metab Dis*. 2023;46(2):364-375. doi:10.1002/jimd.12690.
5. Kim T, Ha SH, Yoo D, Park KS, Ahn TB. A novel variant of GCH1 in dopa-responsive dystonia with oculogyric crises and intrafamilial phenotypic heterogeneity. *J Mov Disord*. 2023;16(3):199-205. doi:10.14802/jmd.23085.
6. Gjedde A, Reith J, Dyve S, et al. Dopa decarboxylase activity of the living human brain. *Proc Natl Acad Sci USA*. 1991;88(7):2721-2725. doi:10.1073/pnas.88.7.2721.
7. Wei F, Liu H, Zhang W, Wang J, Zhang Y. Drug inhibition and substrate alternating flipping mechanisms of human VMAT2. *bioRxiv*. 2024. doi:10.1101/2024.02.28.582500.
8. Takahashi N, Miner LL, Sora I, et al. VMAT2 knockout mice: heterozygotes display reduced amphetamine-conditioned reward, enhanced amphetamine locomotion, and enhanced MPTP toxicity. *Proc Natl Acad Sci USA*. 1997;94(18):9938-9943. doi:10.1073/PNAS.94.18.9938.
9. Shih JC, Chen K, Ridd MJ. Monoamine oxidase: from genes to behavior. *Annu Rev Neurosci*. 1999;22:197-217. doi:10.1146/annurev.neuro.22.1.197.
10. Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-O-methyltransferase, cognition, and psychosis: Val158Met and beyond. *Biol Psychiatry*. 2006;60(2):141-151. doi:10.1016/j.biopsych.2005.10.024.
11. Chen L, Zhuang X. Transgenic mouse models of dopamine deficiency. *Neuropsychopharmacology*. 2003;28(11):902-910. doi:10.1038/sj.npp.1300226.
12. Keibarian JW, Greengard P. Dopamine-sensitive adenylate cyclase: possible role in synaptic transmission. *Science*. 1971;174(4016):1346-1349. doi:10.1126/science.174.4016.1346.
13. Brown JH, Makman MH. Stimulation by dopamine of adenylate cyclase in retinal homogenates and of adenosine-3',5'-cyclic monophosphate

- formation in intact retina. *Proc Natl Acad Sci U S A.* 1972;69(2):539-543. doi:10.1073/pnas.69.2.539
14. Keabian JW, Petzold GL, Greengard P. Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to the 'dopamine receptor'. *Proceedings of the National Academy of Sciences.* 1972;69(8):2145-2149. doi:10.1073/pnas.69.8.2145
  15. Miller R, Horn AS, Iversen LL, Pinder RM. Effects of dopamine-like drugs on rat striatal adenylyl cyclase have implications for CNS dopamine receptor topography. *Nature.* 1974;250(5464):238-241. doi:10.1038/250238a0.
  16. Spano PF, Govoni S, Trabucchi M. Studies on the pharmacological properties of dopamine receptors in various brain areas of the rat. *Biochem Pharmacol.* 1978;27(4):431-437. doi:10.1016/0006-2952(78)90161-6.
  17. Trabucchi M, Longoni R, Fresia P, Spano PF. Sulpiride: a study of the effects on dopamine receptors in rat neostriatum and limbic forebrain. *Life Sci.* 1975;17(10):1551-1556. doi:10.1016/0024-3205(75)90176-9.
  18. Keabian JW, Calne DB. Multiple receptors for dopamine. *Nature.* 1979;277:93-96. doi:10.1038/277093a0.
  19. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. *Physiol Rev.* 1998;78(1):189-225. doi:10.1152/physrev.1998.78.1.189.
  20. Mansour A, Meador-Woodruff JH, Bunzow JR, Civelli O, Akil H, Watson SJ. Localization of dopamine D2 receptor mRNA and D1 and D2 receptor binding in the rat brain and pituitary: an in situ hybridization study. *Neuroscience.* 1990;35(3):607-624. doi:10.1016/0306-4522(90)90332-O.
  21. Herve D, Levi-Strauss M, Marey-Semper I, Verney C, Tassin JP, Glowinski J, Girault JA. G(olf) and Gs in rat basal ganglia: possible involvement of G(olf) in the coupling of dopamine D1 receptor with adenylyl cyclase. *J Neurosci.* 1993;13(5):2237-2248. doi:10.1523/JNEUROSCI.13-05-02237.1993.
  22. Herve D, Le Moine C, Corvol JC, et al. Galpha(olf) levels are regulated by receptor usage and control dopamine and adenosine action in the striatum. *J Neurosci.* 2001;21(12):4390-4399. doi:10.1523/JNEUROSCI.21-12-04390.2001.
  23. Sidhu A, Kimura K, Uh M, White BH, Patel S. Multiple coupling of human D5 dopamine receptors to G proteins in D1A receptor-expressing cells. *Mol Endocrinol.* 1998;12(4):534-542. doi:10.1210/mend.12.4.0110.
  24. Maurice N, Tkatch T, Meisler M, Sprunger LK, Surmeier DJ. D1/D5 dopamine receptor activation differentially modulates rapidly inactivating and persistent sodium currents in prefrontal cortex pyramidal

- neurons. *J Neurosci.* 2001;21(7):2268-2277. doi:10.1523/JNEUROSCI.21-07-02268.2001.
25. Sitek JD, Kuczeriszka M, Walkowska A, Kompanowska-Jezierska E, Dobrowolski L. Nonselective and A2a-selective inhibition of adenosine receptors modulates renal perfusion and excretion depending on the duration of streptozotocin-induced diabetes in rats. *Pharmaceuticals.* 2023;16(5):732. doi:10.3390/ph16050732.
  26. Bordelon-Glausier JR, Khan ZU, Muly EC. Quantification of D1 and D5 dopamine receptor localization in layers I, III, and V of *Macaca mulatta* prefrontal cortical area 9: coexpression in dendritic spines and axon terminals. *J Comp Neurol.* 2008;508(6):951-961. doi:10.1002/cne.21710.
  27. Sánchez-Soto M, Bonifazi A, Ro R, Cai NS, Ellenberger MP, Newman AH, Ferré S, Yano H. Evidence for noncanonical neurotransmitter activation: norepinephrine as a dopamine D2-like receptor agonist. *Mol Pharmacol.* 2016;89(4):457-466. doi:10.1124/mol.115.101808.
  28. Kiss B, Laszlovszky I, Krámos B, Visegrády A, Bobok A, Lévy G, Lendvai B, Román V. Neuronal dopamine D3 receptors: translational implications for preclinical research and CNS disorders. *Biomolecules.* 2021;11(1):104. doi:10.3390/biom11010104.
  29. Fuziwara S, Suzuki A, Inoue K, Denda M. Dopamine D2-like receptor agonists accelerate barrier repair and inhibit the epidermal hyperplasia induced by barrier disruption. *J Invest Dermatol.* 2005;125(4):783-789. doi:10.1111/j.0022-202X.2005.23873.x.
  30. O'Hara CM, Uhl GR, Smith AM, O'Malley KL, Todd RD. Inhibition of dopamine synthesis by dopamine D2 and D3 but not D4 receptors. *J Pharmacol Exp Ther.* 1996;277(1):186-192.
  31. Gonda X, Tarazi FI. Dopamine D3 receptors: From bench to bedside. *Neuropsychopharmacol Hung.* 2021;23(2):94-100.
  32. Khan ZU, Gutiérrez A, Martín R, Peñafiel A, Rivera A, De La Calle A. Differential regional and cellular distribution of dopamine D2-like receptors: An immunocytochemical study of subtype-specific antibodies in rat and human brain. *J Comp Neurol.* 1998;402(3):353-371. doi:10.1002/(SICI)1096-9861(19981221)402:3<353::AID-CNE5>3.0.CO;2-4.
  33. Ferraro L, Beggiano S, Tomasini MC, Antonelli T, Tanganelli S. Neurotensin NTS1-Dopamine D2 Receptor-Receptor Interactions in Putative Receptor Heteromers: Relevance for Schizophrenia. *Front Psychiatry.* 2016;7:35. doi:10.3389/fpsy.2016.00035.
  34. Neve KA, Robinson BG, Condon AF, et al. Autoreceptor Function of the Dopamine D2 Receptor Splice Variants D2S and D2L. *The FASEB Journal.* 2019;33(1\_supplement):502.2.
  35. Leysen JE, Gommeren W, Mertens J, et al. Comparison of in vitro bin-



- ding properties of a series of dopamine antagonists and agonists for cloned human dopamine D2S and D2L receptors and for D2 receptors in rat striatal and mesolimbic tissues, using [125I]2'-iodospiperone. *Psychopharmacology*. 1993;110(1-2):125-134. doi:10.1007/BF02246947.
36. Qi C, Lee D. Preand Postsynaptic Role of Dopamine D2 Receptor DD2R in Drosophila Olfactory Associative Learning. *Biology*. 2014;3(4):831-842. doi:10.3390/biology3040831.
  37. Purton T, Staskova L, Lane MM, et al. Prebiotic and probiotic supplementation and the tryptophankynurenine pathway: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*. 2021;123:98-109. doi:10.1016/j.neubiorev.2020.12.026.
  38. Nzila A, Chilengi R. Modulators of the efficacy and toxicity of drugs in malaria treatment. *Trends in Pharmacological Sciences*. 2010;31(6):290-297. doi:10.1016/j.tips.2010.03.002.
  39. Kehne JH, Cain CK. Therapeutic utility of non-peptidic CRF1 receptor antagonists in anxiety, depression, and stress-related disorders: Evidence from animal models. *Pharmacology & Therapeutics*. 2010;128(3):460-487. doi:10.1016/j.pharmthera.2010.08.011.
  40. Gründer G, Carlsson A, Wong DF. Cariprazine, an orally active D2/D3 receptor antagonist, for the potential treatment of schizophrenia, bipolar mania and depression. *Expert Opin Investig Drugs*. 2010;19(7):825-834. doi:10.1517/13543784.2010.485621.
  41. Van Tol HHM, Bunzow JR, Guan HC, et al. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature*. 1991;350(6319):610-614. doi:10.1038/350610a0.
  42. Lahti RA, Primus RJ, Gallagher DW, et al. Distribution of dopamine D4 receptor in human postmortem brain sections: Autoradiographic studies with [3H]-NGD-94-1. *Schizophrenia Research*. 1996;18(2-3):107-110. doi:10.1016/0920-9964(96)85548-4.
  43. Burström V, Ågren R, Berthari N, et al. Dopamine-induced arrestin recruitment and desensitization of the dopamine D4 receptor is regulated by G protein-coupled receptor kinase-2. *Frontiers in Pharmacology*. 2023;14:1087171. doi:10.3389/fphar.2023.1087171.
  44. Deth R, Muratore C, Benzecry J, et al. How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis. *NeuroToxicology*. 2008;29(1):163-175. doi:10.1016/j.neuro.2007.09.010.
  45. Miyauchi M, Neugebauer NM, Meltzer HY. Dopamine D4 receptor stimulation contributes to novel object recognition: Relevance to cognitive impairment in schizophrenia. *Journal of Psychopharmacology*. 2017;31(4):442-455. doi:10.1177/0269881117693746.
  46. El-Faddagh M, Laucht M, Maras A, Vöhringer L, Schmidt MH. As-

- sociation of dopamine D4 receptor (DRD4) gene with attention-deficit/hyperactivity disorder (ADHD) in a high-risk community sample: a longitudinal study from birth to 11 years of age. *Journal of Neural Transmission*. 2004;111(7):883-889. doi:10.1007/s00702-003-0054-2.
47. Russo SJ, Nestler EJ. The brain reward circuitry in mood disorders. *Nature Reviews Neuroscience*. 2013;14(9):609-625. doi:10.1038/nrn3381.
  48. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*. 1998;28(3):309-369. doi:10.1016/S0165-0173(98)00019-8.
  49. Moghaddam B, Javitt D. From Revolution to Evolution: The Glutamate Hypothesis of Schizophrenia and its Implication for Treatment. *Neuropsychopharmacology*. 2011;37(1):4-15. doi:10.1038/npp.2011.181.
  50. Mitrano DA, Schroeder JP, Smith Y, Cortright JJ, Bubula N, Veziņa P, Weinschenker D. Alpha-1 Adrenergic Receptors are Localized on Presynaptic Elements in the Nucleus Accumbens and Regulate Mesolimbic Dopamine Transmission. *Neuropsychopharmacology*. 2012;37(9):2161-2172. doi:10.1038/npp.2012.68.
  51. Sun N, Laviolette SR. Dopamine Receptor Blockade Modulates the Rewarding and Aversive Properties of Nicotine via Dissociable Neuronal Activity Patterns in the Nucleus Accumbens. *Neuropsychopharmacology*. 2015;40(3):791. doi:10.1038/npp.2014.289.
  52. Gotti C, Guiducci S, Tedesco V, Corbioli S, Zanetti L, Moretti M, Zanardi A, Rimondini R, Mugnaini M, Clementi F, Chiamulera C, Zoli M. Nicotinic Acetylcholine Receptors in the Mesolimbic Pathway: Primary Role of Ventral Tegmental Area  $\alpha 6\beta 2^*$  Receptors in Mediating Systemic Nicotine Effects on Dopamine Release, Locomotion, and Reinforcement. *The Journal of Neuroscience*. 2010;30(15):5311-5325. doi:10.1523/JNEUROSCI.5095-09.2010.
  53. Stahl SM. Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS Spectrums*. 2018;23(3):187-191. doi:10.1017/S1092852918001013.
  54. Nour MM, Dahoun T, Schwartenbeck P, Adams RA, FitzGerald THB, Coello C, Wall MB, Dolan RJ, Howes OD. S154. THE ROLE OF DOPAMINE IN PROCESSING THE MEANINGFUL INFORMATION OF OBSERVATIONS, AND IMPLICATIONS FOR THE ABERRANT SALIENCE HYPOTHESIS OF SCHIZOPHRENIA. *Schizophrenia Bulletin*. 2018;44(Suppl 1):S261. doi:10.1093/schbul/sby018.941.
  55. Estave PM, Spodnick MB, Karkhanis AN. KOR Control over Addiction Processing: An Exploration of the Mesolimbic Dopamine Pathway. In: Preedy VR, editor. *Neuroscience of Alcohol*. London: Academic Press; 2020. p. 463-473. doi:10.1016/B978-0-12-813125-1.00046-8.

56. Peters KZ, Oleson EB, Cheer JF. A Brain on Cannabinoids: The Role of Dopamine Release in Reward Seeking and Addiction. *Cold Spring Harbor Perspectives in Medicine*. 2020;11(1):a039305. doi:10.1101/cs-hperspect.a039305.
57. Howes OD, Kapur S. The Dopamine Hypothesis of Schizophrenia: Version III–The Final Common Pathway. *Schizophrenia Bulletin*. 2009;35(3):549-562. doi:10.1093/schbul/sbp006.
58. Gorelova N, Seamans JK. The Glutamatergic Component of the Mesocortical Pathway Emanating from Different Subregions of the Ventral Midbrain. *Cerebral Cortex*. 2011;22(2):327-336. doi:10.1093/cercor/bhr107.
59. Weinstein AM. Reward, motivation and brain imaging in human healthy participants – A narrative review. *Frontiers in Behavioral Neuroscience*. 2023;17:1123733. doi:10.3389/fnbeh.2023.1123733.
60. Brandl F, Knolle F, Avram M, Leucht C, Yakushev I, Priller J, Leucht S, Ziegler S, Wunderlich K, Sorg C. Negative symptoms, striatal dopamine and model-free reward decision-making in schizophrenia. *Brain*. 2022;146(2):593-606. doi:10.1093/brain/awac268.
61. Blesa J, Przedborski S. Parkinson's disease: animal models and dopaminergic cell vulnerability. *Frontiers in Neuroanatomy*. 2014;8:155. doi:10.3389/fnana.2014.00155.
62. Meredith GE, Rademacher DJ. MPTP Mouse Models of Parkinson's Disease: An Update. *Journal of Parkinson's Disease*. 2011;1(1):19-33. doi:10.3233/JPD-2011-11023.
63. Brichta L, Greengard P. Molecular determinants of selective dopaminergic vulnerability in Parkinson's disease: an update. *Frontiers in Neuroanatomy*. 2014;8:152. doi:10.3389/fnana.2014.00152.
64. Cepeda C, Murphy KPS, Parent M, Levine MS. The role of dopamine in Huntington's disease. *Progress in Brain Research*. 2014;211:235-254. doi:10.1016/B978-0-444-63425-2.00010-6.
65. Albin RL, Mink JW. Recent advances in Tourette syndrome research. *Trends in Neurosciences*. 2006;29(3):175-182. doi:10.1016/j.tins.2006.01.001.
66. Cosi C, Carilla-Durand E, Assié MB, Ormière AM, Maraval M, Leduc N, Newman-Tancredi A. Partial agonist properties of the antipsychotics SSR181507, aripiprazole, and bifeprunox at dopamine D2 receptors: G protein activation and prolactin release. *European Journal of Pharmacology*. 2006;535(1-3):135-144. doi:10.1016/j.ejphar.2006.01.051.
67. Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. *CNS Drugs*. 2014;28(5):421-453. doi:10.1007/s40263-014-0157-3.

68. Melkersson K, Dahl ML. Adverse metabolic effects associated with atypical antipsychotics. *Drugs*. 2004;64(7):701-723. doi:10.2165/00003495-200464070-00003.
69. Ungerstedt U. Stereotaxic mapping of the monoamine pathways in the rat brain. *Acta Physiologica Scandinavica Supplementum*. 1971;367:1-48. doi:10.1111/j.1365-201X.1971.tb10998.x.
70. Lindvall O, Björklund A. The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. *Acta Physiologica Scandinavica Supplementum*. 1974;412:1-48.
71. Thierry AM, Blanc G, Sobel A, Stinus L, Glowinski J. Dopaminergic Terminals in the Rat Cortex. *Science*. 1973;182(4111):499-501. doi:10.1126/science.182.4111.499.
72. Türk I, Turner S. Histochemical evidence for a catecholaminergic (presumably dopaminergic) projection from the ventral mesencephalic tegmentum to visual cortex in the cat. *Neuroscience Letters*. 1981;24(3):259-263. doi:10.1016/0304-3940(81)90159-2.
73. Lindvall O, Björklund A, Divac I. Organization of catecholamine neurons projecting to the frontal cortex in the rat. *Brain Research*. 1978;142(1):1-24. doi:10.1016/0006-8993(78)90173-7.
74. 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.
75. Wise RA. Catecholamine theories of reward: A critical review. *Brain Research*. 1978;152(2):215-247. doi:10.1016/0006-8993(78)90253-6.
76. Schultz W. Dopamine reward prediction-error signalling: a two-component response. *Nature Reviews Neuroscience*. 2016;17(3):183-195. doi:10.1038/nrn.2015.26.
77. Baimel C, Lau BK, Qiao M, Borgland SL. Projection-Target-Defined Effects of Orexin and Dynorphin on VTA Dopamine Neurons. *Cell Reports*. 2017;18(6):1346-1355. doi:10.1016/j.celrep.2017.01.030.
78. Tang YY, Posner MI, Rothbart MK, Volkow ND. Circuitry of self-control and its role in reducing addiction. *Trends in Cognitive Sciences*. 2015;19(8):439-444. doi:10.1016/j.tics.2015.06.007.
79. Saal D, Dong Y, Bonci A, Malenka RC. Drugs of Abuse and Stress Trigger a Common Synaptic Adaptation in Dopamine Neurons. *Neuron*. 2003;37(4):577-582. doi:10.1016/S0896-6273(03)00021-7.
80. Mazei-Robison MS, Koo JW, Friedman AK, Lansink CS, Robison AJ, Vinish M, Krishnan V, Kim S, Siuta MA, Galli A, Niswender KD, Appasani R, Horvath MC, Neve RL, Worley PF, Snyder SH, Hurd YL, Cheer JF, Han MH. Role for mTOR Signaling and Neuronal Ac-

- tivity in Morphine-Induced Adaptations in Ventral Tegmental Area Dopamine Neurons. *Neuron*. 2011;72(6):977-990. doi:10.1016/j.neuron.2011.10.012.
81. Nejati V, Salehinejad MA, Nitsche MA, Najian A, Javadi AH. Transcranial Direct Current Stimulation Improves Executive Dysfunctions in ADHD: Implications for Inhibitory Control, Interference Control, Working Memory, and Cognitive Flexibility. *Journal of Attention Disorders*. 2020;24(13):1791-1803. doi:10.1177/1087054717730611.
  82. Kerns JG, Cohen JD, MacDonald AW III, Cho RY, Stenger VA, Carter CS. Anterior Cingulate Conflict Monitoring and Adjustments in Control. *Science*. 2004;303(5660):1023-1026. doi:10.1126/science.1089910.
  83. MacDonald AW III, Cohen JD, Stenger VA, Carter CS. Dissociating the Role of the Dorsolateral Prefrontal and Anterior Cingulate Cortex in Cognitive Control. *Science*. 2000;288(5472):1835-1838. doi:10.1126/science.288.5472.1835.
  84. Ullsperger M, von Cramon DY. Neuroimaging of Performance Monitoring: Error Detection and Beyond. *Cortex*. 2004;40(4-5):593-604. doi:10.1016/S0010-9452(08)70155-2.
  85. Yun S, Reynolds RP, Masiulis I, Eisch AJ. Re-evaluating the link between neuropsychiatric disorders and dysregulated adult neurogenesis. *Nature Medicine*. 2016;22(11):1239-1247. doi:10.1038/nm.4218.
  86. Corrêa SAL, Hunter CJ, Palygin O, Wauters SC, Martin KJ, McKenzie C, McKelvey K, Morris RGM, Pankratov Y, Arthur JSC, Frenguelli BG. MSK1 Regulates Homeostatic and Experience-Dependent Synaptic Plasticity. *The Journal of Neuroscience*. 2012;32(38):13039-13051. doi:10.1523/JNEUROSCI.0930-12.2012.
  87. Wise RA. Neuroleptics and operant behavior: The anhedonia hypothesis. *Behavioral and Brain Sciences*. 1982;5(1):39-53. doi:10.1017/S0140525X00010372.
  88. Phillips AG, Fibiger HC. Decreased resistance to extinction after haloperidol: Implications for the role of dopamine in reinforcement. *Pharmacology Biochemistry and Behavior*. 1979;10(5):751-760. doi:10.1016/0091-3057(79)90328-9.
  89. Gray T, Wise RA. Effects of pimozide on lever pressing behavior maintained on an intermittent reinforcement schedule. *Pharmacology Biochemistry and Behavior*. 1980;12(6):917-923. doi:10.1016/0091-3057(80)90455-4.
  90. Wise RA. Action of drugs of abuse on brain reward systems. *Pharmacology Biochemistry and Behavior*. 1980;13(3):213-223. doi:10.1016/S0091-3057(80)80033-5.
  91. Saunders J, Showell GA, Baker R, Freedman SB, Hill D, McKnight AT, Er ., Newberry N, Salamone JD, Hirshfield J, Springer JP. Synthesis and

- characterization of all four isomers of the muscarinic agonist, 2'-methylspiro[1-azabicyclo[2.2.2]octane-3,4'-[1,3]dioxolane]. *Journal of Medicinal Chemistry*. 1987;30(6):959-967. doi:10.1021/jm00389a003.
92. Robbins T, Everitt BJ, Marston HM, Wilkinson J, Jones GH, Page K. Comparative effects of ibotenic acid and quisqualic acid-induced lesions of the substantia innominata on attentional function in the rat: further implications for the role of the cholinergic neurons of the nucleus basalis in cognitive processes. *Behavioural Brain Research*. 1989;35(3):221-240. doi:10.1016/S0166-4328(89)80143-3.
  93. Bindra D. A motivational view of learning, performance, and behavior modification. *Psychological Review*. 1974;81(3):199-213. doi:10.1037/h0036330.
  94. Grill HJ, Norgren R. The taste reactivity test. I. Mimetic responses to gustatory stimuli in neurologically normal rats. *Brain Research*. 1978;143(2):263-279. doi:10.1016/0006-8993(78)90568-1.
  95. Treit D, Berridge KC. A comparison of benzodiazepine, serotonin, and dopamine agents in the taste-reactivity paradigm. *Pharmacology Biochemistry and Behavior*. 1990;37(3):451-456. doi:10.1016/0091-3057(90)90011-6.
  96. Peciña S, Cagniard B, Berridge KC, Aldridge JW, Zhuang X. Hyperdopaminergic Mutant Mice Have Higher "Wanting" But Not "Liking" for Sweet Rewards. *The Journal of Neuroscience*. 2003;23(28):9395-9402. doi:10.1523/JNEUROSCI.23-28-09395.2003.
  97. Salamone JD, Steinpreis RE, McCullough LD, Smith P, Grebel D, Mahan K. Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure. *Psychopharmacology*. 1991;104(4):515-521. doi:10.1007/BF02245659.
  98. Salamone JD, Cousins MS, Bucher S. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behavioural Brain Research*. 1994;65(2):221-229. doi:10.1016/0166-4328(94)90108-2.
  99. Koch M, Schmid A, Schnitzler HU. Role of nucleus accumbens dopamine D1 and D2 receptors in instrumental and Pavlovian paradigms of conditioned reward. *Psychopharmacology*. 2000;152(1):67-73. doi:10.1007/s002130000505.
  100. Ostlund SB, Maidment NT. Dopamine Receptor Blockade Attenuates the General Incentive Motivational Effects of Noncontingently Delivered Rewards and Reward-Paired Cues Without Affecting Their Ability to Bias Action Selection. *Neuropsychopharmacology*. 2011;37(2):427-437. doi:10.1038/npp.2011.217.

101. Lex A, Hauber W. Dopamine D1 and D2 receptors in the nucleus accumbens core and shell mediate Pavlovian-instrumental transfer. *Learning & Memory*. 2008;15(7):483-491. doi:10.1101/lm.978708.
102. Baker TW, Florczyński MM, Beninger RJ. Differential effects of clozapine, metoclopramide, haloperidol and risperidone on acquisition and performance of operant responding in rats. *Psychopharmacology*. 2014;232(9):1569-1579. doi:10.1007/s00213-014-3789-6.
103. Wyvell CL, Berridge KC. Intra-Accumbens Amphetamine Increases the Conditioned Incentive Salience of Sucrose Reward: Enhancement of Reward “Wanting” without Enhanced “Liking” or Response Reinforcement. *The Journal of Neuroscience*. 2000;20(21):8122-8130. doi:10.1523/JNEUROSCI.20-21-08122.2000.
104. Ciccocioppo R, Sanna PP, Weiss F. Cocaine-predictive stimulus induces drug-seeking behavior and neural activation in limbic brain regions after multiple months of abstinence: Reversal by D1 antagonists. *Proceedings of the National Academy of Sciences*. 2001;98(4):1976-1981. doi:10.1073/pnas.98.4.1976.
105. Salamone JD, Correa M. The Mysterious Motivational Functions of Mesolimbic Dopamine. *Neuron*. 2012;76(3):470-485. doi:10.1016/j.neuron.2012.10.021.
106. McCullough LD, Cousins MS, Salamone JD. The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: A neurochemical and behavioral study. *Pharmacology Biochemistry and Behavior*. 1993;46(3):581-586. doi:10.1016/0091-3057(93)90547-7.
107. Schultz W. Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*. 1998;80(1):1-27. doi:10.1152/jn.1998.80.1.1.
108. Montague PR, Dayan P, Sejnowski TJ. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *The Journal of Neuroscience*. 1996;16(5):1936-1947. doi:10.1523/JNEUROSCI.16-05-01936.1996.
109. Schultz W, Dayan P, Montague PR. A Neural Substrate of Prediction and Reward. *Science*. 1997;275(5306):1593-1599. doi:10.1126/science.275.5306.1593.
110. Frank MJ. Dynamic Dopamine Modulation in the Basal Ganglia: A Neurocomputational Account of Cognitive Deficits in Medicated and Nonmedicated Parkinsonism. *Journal of Cognitive Neuroscience*. 2005;17(1):51-72. doi:10.1162/0898929052880093.
111. Yagishita S, Hayashi-Takagi A, Ellis-Davies GCR, Urakubo H, Ishii S, Kasai H. A critical time window for dopamine actions on the structural plasticity of dendritic spines. *Science*. 2014;345(6204):1616-1620. doi:10.1126/science.1255514.

112. Collins AGE, Frank MJ. Opponent actor learning (OpAL): Modeling interactive effects of striatal dopamine on reinforcement learning and choice incentive. *Psychological Review*. 2014;121(3):337-366. doi:10.1037/a0037015.
113. 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. doi:10.1016/j.neuron.2010.05.011.
114. Kravitz AV, Tye LD, Kreitzer AC. Distinct roles for direct and indirect pathway striatal neurons in reinforcement. *Nature Neuroscience*. 2012;15(6):816-818. doi:10.1038/nn.3100.
115. Yttri EA, Dudman JT. Opponent and bidirectional control of movement velocity in the basal ganglia. *Nature*. 2016;533(7603):402-406. doi:10.1038/nature17639.
116. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. *Neuroscience & Biobehavioral Reviews*. 2006;30(1):1-23. doi:10.1016/j.neubiorev.2005.03.024.
117. Frank MJ, Seeberger LC, O'Reilly RC. By Carrot or by Stick: Cognitive Reinforcement Learning in Parkinsonism. *Science*. 2004;306(5703):1940-1943. doi:10.1126/science.1102941.
118. Piray P, Zeighami Y, Bahrami F, Eissa AM, Hewedi DH, Moustafa AA. Impulse Control Disorders in Parkinson's Disease Are Associated with Dysfunction in Stimulus Valuation But Not Action Valuation. *Journal of Neuroscience*. 2014;34(23):7811-7821. doi:10.1523/JNEUROSCI.4063-13.2014.
119. Weismüller B, Ghio M, Logmin K, Hartmann C, Schnitzler A, Pollok B, Südmeyer M, Bellebaum C. Effects of feedback delay on learning from positive and negative feedback in patients with Parkinson's disease off medication. *Neuropsychologia*. 2018;117:102-109. doi:10.1016/j.neuropsychologia.2018.05.010.
120. Maia TV, Frank MJ. From reinforcement learning models to psychiatric and neurological disorders. *Nature Neuroscience*. 2011;14(2):154-162. doi:10.1038/nn.2723.
121. Piqueras CM, Herrera D, Latorre BA. First Report of High Boscalid Resistance in *Botrytis cinerea* Associated with the H272L Mutation in Grapevine in Chile. *Plant Disease*. 2014;98(10):1449. doi:10.1094/PDIS-05-14-0558-PDN.
122. Rigoli F, Rutledge RB, Chew B, Ousdal OT, Dayan P, Dolan RJ. Dopamine Increases a ValueIndependent Gambling Propensity. *Neuropsychopharmacology*. 2016;41(11):2658-2667. doi:10.1038/npp.2016.68.
123. van Holst RJ, Sescousse G, Janssen LK, Janssen M, Berry AS, Jagust WJ, Cools R. Increased Striatal Dopamine Synthesis Capacity in



- Gambling Addiction. *Biological Psychiatry*. 2018;83(12):1036-1043. doi:10.1016/j.biopsych.2017.06.010.
124. Harrison NA, Voon V, Cercignani M, Cooper EA, Pessiglione M, Critchley HD. A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards. *Biological Psychiatry*. 2016;80(1):73-81. doi:10.1016/j.biopsych.2015.07.018.
125. Cools R, Frank MJ, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M. Striatal Dopamine Predicts Outcome-Specific Reversal Learning and Its Sensitivity to Dopaminergic Drug Administration. *The Journal of Neuroscience*. 2009;29(5):1538-1543. doi:10.1523/JNEUROSCI.4467-08.2009.
126. Frank MJ, O'Reilly RC, Curran T. A mechanistic account of striatal dopamine function in human cognition: Psychopharmacological studies with cabergoline and haloperidol. *Behavioral Neuroscience*. 2006;120(3):497-517. doi:10.1037/0735-7044.120.3.497.
127. Boehme R, Deserno L, Gleich T, Katthagen T, Pankow A, Behr J, Buchert R, Roiser JP, Heinz A, Schlagenhauf F. Aberrant Salience Is Related to Reduced Reinforcement Learning Signals and Elevated Dopamine Synthesis Capacity in Healthy Adults. *Journal of Neuroscience*. 2015;35(28):10103-10111. doi:10.1523/JNEUROSCI.0805-15.2015.
128. Cools R. Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain*. 2001;124(12):2503-2512. doi:10.1093/brain/124.12.2503.
129. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, Compulsivity, and Top-Down Cognitive Control. *Neuron*. 2011;69(4):680-694. doi:10.1016/j.neuron.2011.01.020.
130. Volkow ND, Wise RA, Baler R. The dopamine motive system: implications for drug and food addiction. *Nature Reviews Neuroscience*. 2017;18(12):741-752. doi:10.1038/nrn.2017.130.
131. Oberlin BG, Dziedzic M, Tran SM, Soeurt CM, Albrecht DS, Yoder KK, Kareken DA. Beer Flavor Provokes Striatal Dopamine Release in Male Drinkers: Mediation by Family History of Alcoholism. *Neuropsychopharmacology*. 2013;38(9):1617-1624. doi:10.1038/npp.2013.91.
132. Clatworthy PL, Lewis SJG, Brichard L, Hong YT, Izquierdo D, Clark L, Cools R, Aigbirhio FI, Baron JC, Fryer TD, Robbins TW. Dopamine Release in Dissociable Striatal Subregions Predicts the Different Effects of Oral Methylphenidate on Reversal Learning and Spatial Working Memory. *The Journal of Neuroscience*. 2009;29(15):4690-4696. doi:10.1523/JNEUROSCI.3266-08.2009.
133. Dodds CM, Muller U, Clark L, van Loon A, Cools R, Robbins TW. Methylphenidate Has Differential Effects on Blood Oxygenation Level-Dependent Signal Related to Cognitive Subprocesses of Reversal Learning. *Journal of Neuroscience*. 2008;28(23):5976-5982. doi:10.1523/

- JNEUROSCI.1153–08.2008.
134. den Ouden HE, Daw ND, Fernandez G, Elshout JA, Rijpkema M, Hogman M, Franke B, Cools R. Dissociable Effects of Dopamine and Serotonin on Reversal Learning. *Neuron*. 2013;80(4):1090-1100. doi:10.1016/j.neuron.2013.08.030.
  135. Collins AG, Brown JK, Gold JM, Waltz JA, Frank MJ. Working Memory Contributions to Reinforcement Learning Impairments in Schizophrenia. *The Journal of Neuroscience*. 2014;34(41):13747-13756. doi:10.1523/JNEUROSCI.0989–14.2014.
  136. Zhang J, Berridge KC, Tindell AJ, Smith KS, Aldridge JW. A Neural Computational Model of Incentive Saliency. *PLoS Computational Biology*. 2009;5(7):e1000437. doi:10.1371/journal.pcbi.1000437.
  137. Gabriel DBK, Liley AE, Freels TG, Simon NW. Dopamine receptors regulate preference between high-effort and high-risk rewards. *Psychopharmacology*. 2021;238(4):1035-1045. doi:10.1007/s00213-020-05745-z.
  138. Hosking JG, Floresco SB, Winstanley CA. Dopamine Antagonism Decreases Willingness to Expend Physical, But Not Cognitive, Effort: A Comparison of Two Rodent Cost/Benefit Decision-Making Tasks. *Neuropsychopharmacology*. 2015;40(4):1005-1015. doi:10.1038/npp.2014.285.
  139. Hsiao SCB, Halladay LR. Complex response competition and dopamine blocking: choosing of high cost sucrose solution versus low cost water in rats. *The Chinese Journal of Physiology*. 1995;38(2):101-110.
  140. Manohar SG, Chong TTJ, Apps MA, Batla A, Stamelou M, Jarman PR, Bhatia KP, Husain M. Reward Pays the Cost of Noise Reduction in Motor and Cognitive Control. *Current Biology*. 2015;25(13):1707-1716. doi:10.1016/j.cub.2015.05.038.
  141. Westbrook A, Braver TS. Dopamine Does Double Duty in Motivating Cognitive Effort. *Neuron*. 2016;89(4):695-710. doi:10.1016/j.neuron.2015.12.029.
  142. Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F, Fowler JS, Zhu W, Logan J, Ma Y, Pradhan K, Wong C, Swanson JM. Evaluating Dopamine Reward Pathway in ADHD. *JAMA*. 2009;302(10):1084-1091. doi:10.1001/jama.2009.1308.
  143. Poeppel D, Mangun GR, Gazzaniga MS, Blakemore SJ. *Cognitive Neurosciences*. Cambridge, MA: MIT Press; 2020. ISBN 9780262356176.
  144. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum S, Hudspeth AJ. *Principles of Neural Science*. New York, NY: McGraw-Hill; 2013. ISBN 9780071390118.
  145. Scatton B, Rouquier L, Javoy-Agid F, Agid Y. Dopamine deficiency in

- the cerebral cortex in Parkinson disease. *Neurology*. 1982;32(9):1039-1040. doi:10.1212/wnl.32.9.1039.
146. Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y. Reduction of cortical dopamine, noradrenaline, serotonin, and their metabolites in Parkinson's disease. *Brain Research*. 1983;275(2):321-328. doi:10.1016/0006-8993(83)90993-9.
147. Chinaglia G, Alvarez F, Probst A, Palacios JM. Mesostriatal and mesolimbic dopamine uptake binding sites are reduced in Parkinson's disease and progressive supranuclear palsy: A quantitative autoradiographic study using [3H]mazindol. *Neuroscience*. 1992;49(2):317-327. doi:10.1016/0306-4522(92)90099-n.
148. Rakshi JS, Uema T, Ito K, Bailey DL, Morrish PK, Ashburner J, Dagher A, Jenkins IH, Friston KJ, Brooks DJ. Frontal, midbrain, and striatal dopaminergic function in early and advanced Parkinson's disease: A 3D [18F]dopa-PET study. *Brain*. 1999;122(9):1637-1650. doi:10.1093/brain/122.9.1637.
149. Chaudhuri KR, Schapira AHV. Non-motor symptoms of Parkinson's disease: Dopaminergic pathophysiology and treatment. *The Lancet Neurology*. 2009;8(5):464-474. doi:10.1016/S1474-4422(09)70068-7.
150. Egerton A, Mehta MA, Montgomery AJ, Lappin JM, Howes OD, Reeves SJ, Cunningham VJ, Grasby PM. The dopaminergic basis of human behaviors: A review of molecular imaging studies. *Neuroscience & Biobehavioral Reviews*. 2009;33(7):1109-1132. doi:10.1016/j.neubio-rev.2009.05.005.
151. Witkovsky P. Dopamine and retinal function. *Documenta Ophthalmologica*. 2004;108(1):17-40. doi:10.1023/B:DOOP.0000019487.88486.0a.
152. Dowling JE, Ehinger B. Synaptic Organization of the Amine-Containing Interplexiform Cells of the Goldfish and Cebus Monkey Retinas. *Science*. 1975;188(4185):270-273. doi:10.1126/science.804181.
153. Frederick JM, Rayborn ME, Laties AM, Lam DMK, Hollyfield JG. Dopaminergic neurons in the human retina. *Journal of Comparative Neurology*. 1982;210(1):65-79. doi:10.1002/cne.902100108.
154. Straschill M, Perwein J. The inhibition of retinal ganglion cells by catecholamines and yaminobutyric acid. *Pflügers Archiv European Journal of Physiology*. 1969;312(3):173-181. doi:10.1007/BF00588530.
155. Wollner B, Yahr MD. Measurements of Visual Evoked Potentials in Parkinson's Disease. *Brain*. 1978;101(4):661-671. doi:10.1093/brain/101.4.661.
156. Nguyen-Legros J. Functional neuroarchitecture of the retina: Hypothesis on the dysfunction of retinal dopaminergic circuitry in Parkinson's disease. *Surgical and Radiologic Anatomy*. 1988;10(2):137-144. doi:10.1007/BF02307822.

157. Bulens C, Meerwaldt JD, Van der Wildt GJ, Van Deursen JBP. Effect of levodopa treatment on contrast sensitivity in Parkinson's disease. *Annals of Neurology*. 1987;22(3):365-369. doi:10.1002/ana.410220313.
158. Harnois C, Di Paolo T. Decreased dopamine in the retinas of patients with Parkinson's disease. *Investigative Ophthalmology & Visual Science*. 1990;31(11):2473-2475.
159. Hutton JT, Morris JL, Elias JW. Levodopa Improves Spatial Contrast Sensitivity in Parkinson's Disease. *Archives of Neurology*. 1993;50(7):721-724. doi:10.1001/archneur.1993.00540070041012.
160. Weil RS, Schrag AE, Warren JD, Crutch SJ, Lees AJ, Morris HR. Visual dysfunction in Parkinson's disease. *Brain*. 2016;139(11):2827-2843. doi:10.1093/brain/aww175.
161. Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson's disease: Prevalence and characteristics. *Pain*. 2009;141(1):173-177. doi:10.1016/j.pain.2008.12.004.
162. Juri C, Rodriguez-Oroz M, Obeso JA. The pathophysiological basis of sensory disturbances in Parkinson's disease. *Journal of the Neurological Sciences*. 2010;289(1-2):60-65. doi:10.1016/j.jns.2009.08.018.
163. Seppi K, Chaudhuri KR, Coelho M, Fox SH, Katzenschlager R, Lloret SP, Weintraub D, Sampaio C. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. *Movement Disorders*. 2019;34(2):180-198. doi:10.1002/mds.27602.
164. Wood PB. Role of central dopamine in pain and analgesia. *Expert Review of Neurotherapeutics*. 2008;8(5):781-797. doi:10.1586/14737175.8.5.781.
165. Fleetwood-Walker SM, Hope PJ, Mitchell R, El-Yassir N, Molony V. The influence of opioid receptor subtypes on the processing of nociceptive inputs in the spinal dorsal horn of the cat. *Brain Research*. 1988;451(1-2):261-273. doi:10.1016/0006-8993(88)90766-4.
166. Saadé NE, Jabbur SJ. Nociceptive behavior in animal models for peripheral neuropathy: Spinal and supraspinal mechanisms. *Progress in Neurobiology*. 2008;86(1):22-47. doi:10.1016/j.pneurobio.2008.06.002.
167. Scott DJ, Heitzeg MM, Koepp RA, Stohler CS, Zubieta JK. Variations in the Human Pain Stress Experience Mediated by Ventral and Dorsal Basal Ganglia Dopamine Activity. *The Journal of Neuroscience*. 2006;26(42):10789-10795. doi:10.1523/JNEUROSCI.2577-06.2006.
168. Brefel-Courbon C, Payoux P, Thalamas C, Ory F, Quelven I, Chollet F, Montastruc JL, Rascol O. Effect of levodopa on pain threshold in Parkinson's disease: A clinical and positron emission tomography study. *Movement Disorders*. 2005;20(12):1557-1563. doi:10.1002/mds.20629.
169. Schestatsky P, Kumru H, Valls-Solé J, Valldeoriola F, Marti MJ, Tolosa E, Chaves ML. Neurophysiologic study of central pain in patients with

- Parkinson disease. *Neurology*. 2007;69(23):2162-2169. doi:10.1212/01.wnl.0000295669.12443.d3.
170. Javoy-Agid F, Agid Y. Is the mesocortical dopaminergic system involved in Parkinson disease? *Neurology*. 1980;30(12):1326-1330. doi:10.1212/wnl.30.12.1326.
171. Braak H, Braak E. Morphological criteria for the recognition of Alzheimer's disease and the distribution pattern of cortical changes related to this disorder. *Neurobiology of Aging*. 1994;15(3):355-362. doi:10.1016/0197-4580(94)90032-9.
172. Harding AJ, Lakay B, Halliday GM. Selective hippocampal neuron loss in dementia with Lewy bodies. *Annals of Neurology*. 2001;51(1):125-128. doi:10.1002/ana.10071.
173. Tessitore A, Hariri AR, Fera F, Smith WG, Chase TN, Hyde TM, Weinberger DR, Mattay VS. Dopamine Modulates the Response of the Human Amygdala: A Study in Parkinson's Disease. *The Journal of Neuroscience*. 2002;22(20):9099-9103. doi:10.1523/JNEUROSCI.22-20-09099.2002.
174. Cummings JL. Depression and Parkinson's disease: A review. *American Journal of Psychiatry*. 1992;149(4):443-454. doi:10.1176/ajp.149.4.443.
175. Goldman-Rakic PS. The Cortical Dopamine System: Role in Memory and Cognition. In: Bloom FE, editor. *Advances in Pharmacology*. Vol. 42. San Diego, CA: Academic Press; 1997. p. 707-711. doi:10.1016/s1054-3589(08)60846-7.
176. Miguez A, Gomis C, Vila C, Monguió-Tortajada M, Fernández-García S, Bombau G, Galofré M, García-Bravo M, Sers P, Fernández-Medina H, Poquet B, Salado-Manzano C, Roura S, Alberch J, Segovia JC, Allen ND, Borràs FE, Canals JM. Soluble mutant huntingtin drives early human pathogenesis in Huntington's disease. *Cellular and Molecular Life Sciences*. 2023;80(8):192. doi:10.1007/s00018-023-04882-W.
177. Jiang A, Hadley RR, Lehnert K, Snell RG. From Pathogenesis to Therapeutics: A Review of 150 Years of Huntington's Disease Research. *International Journal of Molecular Sciences*. 2023;24(16):1613021. doi:10.3390/ijms241613021.
178. Reynolds DS, Carter RJ, Morton AJ. Dopamine Modulates the Susceptibility of Striatal Neurons to 3-Nitropropionic Acid in the Rat Model of Huntington's Disease. *The Journal of Neuroscience*. 1998;18(23):10116-10127. doi:10.1523/JNEUROSCI.18-23-10116.1998.
179. Joyce JN, Lexow N, Bird E, Winokur A. Organization of dopamine D1 and D2 receptors in human striatum: Receptor autoradiographic studies in Huntington's disease and schizophrenia. *Synapse*. 1988;2(5):546-557. doi:10.1002/syn.890020511.
180. Schwab L, Mason S, Begeti F, Barker R. J16 The Effect Of Dopamine

- Blockade On Cognition In Huntington's Disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 2014;85(Suppl 1):A63. doi:10.1136/JNNP-2014-309032.199.
181. Kourosch-Arami M, Komaki A, Zarrindast MR. Dopamine as a Potential Target for Learning and Memory: Contributing to Related Neurological Disorders. *CNS & Neurological Disorders - Drug Targets*. 2023;22(4):472-484. doi:10.2174/1871527321666220418115503.
  182. Nittari G, Roy P, Martinelli I, Bellitto V, Tomassoni D, Traini E, Tayebati SK, Amenta F. Rodent Models of Huntington's Disease: An Overview. *Biomedicines*. 2023;11(12):3331. doi:10.3390/biomedicines11123331.
  183. Creus-Muncunill J, Ehrlich ME. Cell-Autonomous and Non-cell-Autonomous Pathogenic Mechanisms in Huntington's Disease: Insights from In Vitro and In Vivo Models. *Neurotherapeutics*. 2019;16(4):1080-1092. doi:10.1007/s13311-019-00782-9.
  184. Bartlett DM, Cruickshank TM, Hannan AJ, Eastwood PR, Lazar AS, Ziman MR. Neuroendocrine and neurotrophic signaling in Huntington's disease: Implications for pathogenic mechanisms and treatment strategies. *Neuroscience & Biobehavioral Reviews*. 2016;71:444-454. doi:10.1016/j.neubiorev.2016.09.006.
  185. Johnson MA, Rajan V, Miller CE, Wightman RM. Dopamine release is severely compromised in the R6/2 mouse model of Huntington's disease. *Journal of Neurochemistry*. 2006;97(3):737-746. doi:10.1111/j.1471-4159.2006.03762.x.
  186. Björkqvist M, Wild EJ, Thiele J, Silvestroni A, Andre R, Lahiri N, Raibon E, Lee RV, Benn CL, Soulet D, Magnusson A, Woodman B, Landles C, Pouladi MA, Hayden MR, Khalili-Shirazi A, Lowdell MW, Brundin P. A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. *The Journal of Experimental Medicine*. 2008;205(8):1869-1877. doi:10.1084/jem.20080178.
  187. Shenderov E, De Marzo AM, Lotan TL, Wang H, Chan S, Lim SJ, Ji H, Allaf ME, Chapman C, Moore PA, Chen F, Sorg K, White AM, Church SE, Hudson B, Fields PA, Hu S, Denmeade SR, Pienta KJ. Neoadjuvant enoblituzumab in localized prostate cancer: a single-arm, phase 2 trial. *Nature Medicine*. 2023;29(4):598-606. doi:10.1038/s41591-023-02284-w.
  188. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, Nance M, Ross CA, Scahill RI, Wetzel R, Wild EJ, Tabrizi SJ. Huntington disease. *Nature Reviews Disease Primers*. 2015;1:15005. doi:10.1038/nrdp.2015.5.
  189. Blair U, Leslie U. A message from the Editors-in-Chief on the 10th Anniversary of the *Journal of Huntington's Disease*. *Journal of Huntington's Disease*. 2022;11(1):1-2. doi:10.3233/JHD-229001.

190. Coyle JT, Schwarcz R. Lesion of striatal neurons with kainic acid provides a model for Huntington's chorea. *Nature*. 1976;263(5574):244-246. doi:10.1038/263244a0.
191. 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.
192. Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ Jr, Sibley DR. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science*. 1990;250(4986):1429-1432. doi:10.1126/science.2147780.
193. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends in Neurosciences*. 1990;13(7):281-285. doi:10.1016/0166-2236(90)90110-v.
194. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends in Neurosciences*. 1989;12(10):366-375. doi:10.1016/0166-2236(89)90074-X.
195. Calabresi P, Picconi B, Tozzi A, Ghiglieri V, Di Filippo M. Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends in Neurosciences*. 2007;30(5):211-219. doi:10.1016/j.tins.2007.03.001.
196. Jakel RJ, Maragos WF. Neuronal cell death in Huntington's disease: a potential role for dopamine. *Trends in Neurosciences*. 2000;23(6):239-245. doi:10.1016/S0166-2236(00)01568-x.
197. Plotkin JL, Surmeier DJ. Corticostriatal synaptic adaptations in Huntington's disease. *Current Opinion in Neurobiology*. 2015;33:53-62. doi:10.1016/j.conb.2015.01.020.
198. Marti M, Mela F, Bianchi C, Beani L, Morari M. Striatal dopamine-NMDA receptor interactions in the modulation of glutamate release in the substantia nigra pars reticulata in vivo: opposite role for D1 and D2 receptors. *Journal of Neurochemistry*. 2002;83(3):635-644. doi:10.1046/j.1471-4159.2002.01169.x.
199. Morari M, Marti M, Sbrenna S, Fuxe K, Bianchi C, Beani L. Review Article Reciprocal dopamine-glutamate modulation of release in the basal ganglia. *Neurochemistry International*. 1998;33(5):383-397. doi:10.1016/S0197-0186(98)00052-7.
200. Reiner A, Albin RL, Anderson KD, D'Amato CJ, Penney JB, Young AB. Differential loss of striatal projection neurons in Huntington disease. *Proceedings of the National Academy of Sciences*. 1988;85(15):5733-5737. doi:10.1073/pnas.85.15.5733.
201. Kleppner SR, Tobin AJ. GABA signalling: therapeutic targets for epilepsy, Parkinson's disease and Huntington's disease. *Emerging Therapeutic Targets*. 2001;5(2):219-239. doi:10.1517/14728222.5.2.219.