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Navigating the Complex Interplay of Striatum in Parkinson's Disease: A Comprehensive Review

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a spectrum of motor and non-motor symptoms, primarily resulting from the progressive degeneration of dopaminergic neurons projecting to the striatum. This comprehensive review explores the intricate and multifaceted role of the striatum in the context of PD. The striatum, a pivotal component of the basal ganglia, is scrutinized for its anatomical subdivisions, microanatomy, neural connections, and blood supply. Detailed insights into the microcircuits, neurotransmitters, and neuronal populations within the striatum provide a holistic understanding of its functions, spanning motor control, reward processing, and decision-making. The paper elucidates the impact of alpha-synuclein pathology in the striatum, illuminating its role in PD pathogenesis and progression. Furthermore, the review underscores the therapeutic potential of growth factors and hormonal influences on striatal function in mitigating the debilitating effects of PD. In summary, this comprehensive review navigates the intricate interplay of the striatum in Parkinson's disease, offering valuable insights into its multifaceted contributions to both health and pathology.

Keywords: Basal ganglia, dopamine, Parkinsons disease, Striatum, alpha-synuclein

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1. Introduction

The striatum, a key component of the basal ganglia, is a highly intricate structure in the brain composed of several subregions, including the caudate nucleus and the putamen, that receives inputs from various brain regions, including the cortex and thalamus associated with a wide range of motor, cognitive, and affective functions. Its critical role in motor control has made it a focal point of research, particularly in the context of neurodegenerative disorders such as Parkinson's disease (PD). The primary neurotransmitter, dopamine, plays a pivotal role in modulating the balance of excitatory and inhibitory signals in the basal ganglia circuitry. The loss of dopamine-producing neurons in the substantia nigra pars compacta leads to disrupted striatal dopamine levels, resulting in the motor symptoms like bradykinesia, rigidity, resting tremors, and postural instability [1].

2. Subdivision of striatum and the associated circuits

The striatum is a complex brain structure composed of several subdivisions, each with unique functions and roles within neural circuits. The Caudate Nucleus, a major subdivision of the striatum, is intimately involved in motor control, cognitive processes, and learning. It plays a central role in planning and executing voluntary movements and belongs to the 'associative' or 'dorsal' striatum [2]. Adjacent to the caudate nucleus lies the Putamen, another substantial subdivision of the striatum that primarily governs motor control and regulates voluntary movements, working in conjunction with the caudate nucleus as part of the dorsal striatum. The Nucleus Accumbens, located within the ventral striatum, is a critical player in reward processing, motivation, and pleasure experience. It significantly influences behaviours related to addiction and motivation [3].

The Ventral Striatum, which includes the nucleus accumbens, is deeply involved in emotional and motivational processes. It integrates sensory and limbic information,

making it vital for decision-making and emotional responses. It exhibits extensive connectivity with various brain regions, including the amygdala and prefrontal cortex [4]. The Dorsal Striatum, composed of the caudate nucleus and putamen, primarily governs motor control and habit formation. It receives input from the cortex and actively participates in planning, executing, and regulating movements [5]. These subdivisions interact with diverse brain regions and pathways, influencing a wide range of functions. For example, the Corticostriatal Circuit links the cortex, including the motor cortex and prefrontal cortex, with the striatum, playing a critical role in motor planning, execution, and cognitive functions [6]. The Cortico-thalamo-striatal Circuit involves connections between the cortex, thalamus, and striatum, aiding in the regulation of motor activity and the integration of sensory information [7]. The Mesolimbic Reward Circuit prominently features the nucleus accumbens, receiving input from the ventral tegmental area (VTA) and mediating rewarding stimuli processing and feelings of pleasure and reward [8]. Within the broader framework, the Basal Ganglia Circuit, comprising the striatum, including both the caudate nucleus and putamen, along with structures like the globus pallidus, subthalamic nucleus, and substantia nigra, stands as a fundamental player in the control of motor movements [6].

3. Microanatomy of striatum

At the core of the striatum's microanatomy are the Medium Spiny Neurons (MSNs). These neurons dominate the striatal landscape, making up more than 90% of its neuronal population. MSNs, while numerous, exhibit diversity in their functions. They are further classified into two key subtypes: D1-expressing MSNs and D2-expressing MSNs [9]. These subtypes play pivotal roles in orchestrating the motor control and reward processing within the striatum. Complementing the MSNs are a variety of Interneurons. These interneurons, including fast-spiking interneurons (FSIs) and cholinergic interneurons, provide local inhibition and modulation of the striatal circuitry, fine-tuning the complex interactions that govern striatal function [10]. It is a structurally intricate region within the brain, and at the microanatomical level, it reveals a remarkable complexity of cell types, neural connections, and neurotransmitter systems that collectively underpin its multifaceted functions.

The striatum is, in essence, a hub of connectivity, and its microanatomy is defined by a network of neural connections that both originate within and project to this pivotal region. The Corticostriatal Pathway forms a critical link between the cortex, particularly the motor and prefrontal cortex, and the striatum. This pathway is the conduit through which motor plans are initiated and executed, as well as the bridge for higher cognitive functions that the striatum influences [6]. The Nigrostriatal Pathway, consisting of dopaminergic neurons from the substantia nigra pars compacta, projects to the striatum. This pathway, powered by dopamine, lies at the heart of motor control. Its degeneration is a defining feature of Parkinson's disease, illuminating the profound role of this neural connection [11]. The Striatopallidal Pathway and the Striatonigral Pathway involve the flow of signals from MSNs in the striatum to structures such as the globus pallidus and the substantia nigra pars reticulata. These pathways influence the regulation of motor activity and coordination, weaving the intricate tapestry of motor control [12].

Within this microanatomical landscape, neurotransmitters wield their influence: Dopamine, released by dopaminergic neurons, modulates the activity of MSNs in the striatum. The interplay between D1 and D2 receptor-expressing MSNs is central to functions related to motor control and reward [13]. Acetylcholine, released by cholinergic interneurons, further enriches the striatal microanatomy. Its effects on MSNs contribute to the regulation of attention, learning, and the integration of cognitive processes within this dynamic region [14]. At an even finer level of granularity, the striatum is host to intricate microcircuits. These circuits encompass a web of interactions between different cell types, involving both feedforward and feedback loops. These microcircuits are the gears that drive the processing of information related to motor control, reward, and cognitive functions within the striatum [15].

4. Blood supply of striatum

The striatum relies on a complex network of arteries for its vital blood supply, primarily from branches of two major cerebral arteries: the middle cerebral artery (MCA) and the anterior cerebral artery (ACA). The MCA, known for its intricate branching pattern, includes the lenticulostriate arteries, which are crucial for supplying oxygen and nutrients to the basal ganglia, particularly the striatum [16]. The ACA nourishes the frontal and superior brain regions and supplies the medial aspects of the striatum through the medial striate arteries. The Anterior Choroidal Artery, originating from the internal carotid artery, also supports the striatum's blood supply by extending into posterior regions. Another important contributor is the Recurrent Artery of Heubner, a branch of the ACA, ensuring the anterior and medial sectors of the striatum receive essential blood supply [17].

This intricate network of arteries is indispensable for meeting the metabolic requirements of neurons and glial cells within the striatum, enabling it to fulfill its pivotal roles in motor control, reward processing, and cognitive functions. Disturbances in this blood supply, such as ischemia or infarction, can lead to profound neurological consequences, potentially resulting in conditions like lacunar strokes [18].

5. Connections of Striatum

Striatum, is intricately connected to various brain regions, forming complex neural circuits that underlie essential functions in the brain. One of its primary connections is the corticostriatal pathway, which links the cortex, including the motor and prefrontal cortices, to the striatum [19]. This bidirectional pathway is pivotal for motor planning, execution, and cognitive functions, playing a central role in initiating voluntary movements and influencing decision-making processes. Another critical connection is the nigrostriatal pathway, which comprises dopaminergic neurons originating in the substantia nigra pars compacta (SNc) and projecting to the striatum. These neurons release dopamine and are essential for motor control. The degeneration of dopaminergic neurons in this pathway is a hallmark feature of Parkinson's disease, leading to motor deficits [20]. The striatopallidal and striatonigral pathways involve medium spiny neurons (MSNs) in the striatum projecting to structures such as the globus pallidus (GP) and the substantia nigra pars reticulata (SNr).

The striatopallidal pathway targets the external segment of the globus pallidus (GPe), while the striatonigral pathway projects to the internal segment of the globus pallidus (GPi) and the SNr. These pathways contribute to the regulation of motor activity and coordination. Additionally, the thalamostriatal pathway connects the thalamus, particularly the intralaminar and ventral anterior nuclei, with the striatum. This pathway is involved in integrating sensory information and regulating motor activity. The striatum, especially the nucleus accumbens in the ventral striatum, is a central component of the mesolimbic reward circuit. It receives input from the ventral tegmental area (VTA) and plays a critical role in processing rewarding stimuli, motivation, and pleasure.

Dysregulation of this circuit is associated with addiction and reward-related disorders. Furthermore, the striatum is intricately connected to limbic system structures, including the amygdala and the hippocampus, facilitating emotional processing, motivation, and the integration of emotional information into decision-making. Finally, the striatum is a core element of the basal ganglia loop, a circuitry that includes the globus pallidus, subthalamic nucleus, and substantia nigra. This circuit is essential for the control of motor movements and is disrupted in conditions such as Parkinson's disease and Huntington's disease [21]. These neural connections create complex circuits that regulate motor functions, reward processing, and cognitive processes. Dysfunction in these circuits can lead to a wide range of neurological and neuropsychiatric disorders.

6. Striatum and Decision making

The striatum plays a pivotal role in decision-making processes, closely tied to its functions in reward processing and reinforcement learning. Decision-making involves evaluating options, predicting outcomes, and selecting actions. The nucleus accumbens in the ventral striatum is central to reward processing, receiving input from dopaminergic neurons in the ventral tegmental area (VTA). It assesses potential rewards associated with choices and assigns values to options, aiding in the selection of actions that maximize rewards [22].

The striatum calculates prediction errors, indicating the variance between expected and actual rewards. These errors are essential for learning and adapting future decisions. Dopamine release in the striatum reinforces chosen actions when outcomes exceed expectations and prompts reevaluation when outcomes fall short. The dorsolateral striatum is involved in habitual behavior, while the ventral striatum and prefrontal cortex influence goal-directed behavior [23]. Additionally, the striatum assesses risk and uncertainty in decision-making, contributing to the balance between reward pursuit and risk minimization.

Dysregulation of the striatum can lead to issues such as impulsivity and decision-making disorders [24]. Conditions like addiction may result in compulsive reward-driven decision-making, while disorders like obsessive-compulsive disorder (OCD) can involve excessive habit formation and repetitive behaviors associated with the striatum [25].

7. Adult neurogenesis in Striatum

Adult neurogenesis has been traditionally associated with specific regions like the hippocampus and olfactory bulb, recent research suggests limited neurogenesis may also occur in the striatum, a component of the basal ganglia [26]. Unlike well-established neurogenesis in the hippocampus, the striatum's neurogenic potential is relatively restricted, primarily consisting of medium spiny neurons (MSNs), the predominant neuronal population. The source of newly generated striatal neurons remains under investigation. Some propose they originate within the striatum itself, while others suggest migration from other brain regions, like the subventricular zone (SVZ), may contribute [27]. Despite its limited extent, adult neurogenesis in the striatum is believed to play roles in motor learning, adaptation, and plasticity, as well as responding to environmental challenges.

Understanding the regulation of adult neurogenesis in the striatum is critical. Factors such as signalling pathways, growth factors, and environmental cues may influence neurogenesis rates. Unravelling these mechanisms is essential for potential therapeutic applications.

8. Striatal lesions in Parkinson’s Disease

Striatal lesions play a pivotal role in the pathophysiology of Parkinson's disease, a progressive neurodegenerative disorder. The disease's hallmark is the gradual loss of dopaminergic neurons in the substantia nigra pars compacta, which project to the striatum and release dopamine, a neurotransmitter critical for various brain functions, including motor control and reward processing [28]. As these dopaminergic neurons degenerate, there is a significant reduction in dopamine levels within the striatum, creating a profound imbalance in the basal ganglia circuitry. This disruption leads to the overactivity of the indirect pathway, resulting in excessive inhibition of motor commands. The most recognizable symptoms of Parkinson's disease are the motor impairments that include bradykinesia (slowness of movement), rigidity (muscle stiffness), resting tremors, and postural instability. The striatal lesions' impact on motor circuitry directly contributes to the inability to initiate and control voluntary movements, which characterizes the disease [29].

Beyond motor symptoms, striatal lesions also give rise to a range of non-motor symptoms in Parkinson's disease. These can encompass cognitive deficits, mood disturbances like depression and anxiety, sleep disturbances, and autonomic dysfunction. The striatum plays a role in cognition and emotion processing, and the loss of dopamine signaling in this region contributes to these non-motor manifestations. In terms of treatment, addressing the consequences of striatal lesions is a primary goal. Medications like levodopa, a dopamine precursor, are commonly prescribed to alleviate motor symptoms by restoring dopamine levels in the striatum. Deep brain stimulation (DBS) is another therapeutic approach that involves implanting electrodes in specific brain regions, including the subthalamic nucleus within the basal ganglia, to modulate activity and mitigate motor symptoms associated with striatal lesions.

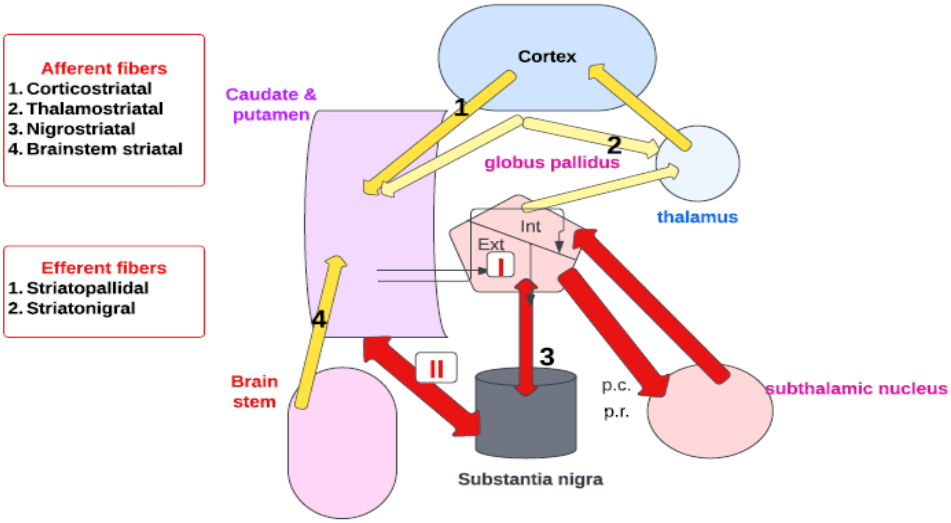

Figure 1. Afferent and Efferent Connections of Striatum

9. Striatal microglia in PD

In Parkinson's disease (PD), striatal microglia play a significant role in chronic neuroinflammation, which is a prominent feature of the condition [30]. Activation of microglia within the striatum is a critical contributor to this neuroinflammatory process. These microglia become activated in response to misfolded alpha-synuclein protein aggregates, characteristic of PD. When activated, striatal microglia release pro-inflammatory cytokines and reactive oxygen species (ROS), creating an inflammatory environment in the striatum that worsens both motor and non-motor symptoms [31].

This neuroinflammation in the striatum is closely linked to the degeneration of nearby dopaminergic neurons and their axonal terminals, contributing to the progressive nature of PD. Ongoing research aims to modulate striatal microglia to reduce neuroinflammation and protect dopaminergic neurons [32]. Potential therapeutic approaches include targeting specific microglial receptors and pathways involved in the inflammatory response. Promoting an anti-inflammatory or neuroprotective phenotype in striatal microglia is a promising avenue to slow the progression of PD. This approach may involve anti-inflammatory drugs or interventions encouraging neuroprotective microglial responses [33]. Advanced neuroimaging techniques, such as positron emission tomography (PET) with specific ligands, help visualize and quantify microglial activation in the striatum and other brain regions. These tools offer valuable insights into PD's neuroinflammation progression and the assessment of potential therapeutic strategies.

10. Growth factors and the Striatum

Growth factors play a crucial role in the development, maintenance, and function of the striatum, a key component of the basal ganglia. Brain-Derived Neurotrophic Factor (BDNF) supports the survival and growth of striatal neurons, particularly medium spiny neurons (MSNs), and fosters synaptic connections, ensuring proper neural circuit functioning. Nerve Growth Factor (NGF) also contributes to the growth and maintenance of specific striatal neuron populations. Glial-Derived Neurotrophic Factor (GDNF) is known for its neuroprotective properties, primarily acting on dopaminergic neurons but indirectly benefiting the striatum by preserving essential dopaminergic input [34].

Vascular Endothelial Growth Factor (VEGF) likely ensures proper vascularization of the striatum, maintaining the blood supply vital for striatal neurons and glial cells. Fibroblast Growth Factors (FGFs), like FGF2, have neurotrophic effects within the striatum, promoting neuron survival and differentiation. In neurodegenerative diseases like Huntington's and Parkinson's, dysregulation of growth factors, including BDNF, is implicated [35]. These conditions profoundly affect the striatum, making restoring normal growth factor signalling a focus of therapeutic research to enhance striatal function and resilience. Understanding this interplay is crucial for unravelling mechanisms governing striatal development, plasticity, and responses to injury or disease, offering potential therapeutic interventions.

11. Role of α-synuclein in Striatum

Alpha-synuclein, a protein present in neurons, plays a crucial role in the striatum, especially in neurodegenerative diseases like Parkinson's. In its normal state, it supports synaptic function, vesicle trafficking, and neurotransmitter release in the striatum. However, in neurodegenerative disorders like Parkinson's, it can misfold and form abnormal aggregates called Lewy bodies and Lewy neurites, found not only in the substantia nigra but also in the striatum.The accumulation of alpha-synuclein aggregates in the striatum disrupts dopaminergic transmission, crucial for motor control. As Lewy pathology spreads from the substantia nigra to the striatum, it impairs dopamine regulation and release, leading to motor symptoms like bradykinesia, rigidity, and tremors [36]. Recognizing the pivotal role of alpha-synuclein in the striatum has led to extensive research efforts to develop disease-modifying therapies.

12. Role of hormones on Striatum

Hormones, including estradiol and progesterone, exert notable effects on the striatum, for motor control, reward processing, and cognitive functions. Estradiol, has

demonstrated neuroprotective properties within the striatum, reducing neuronal damage and promoting cell survival, potentially offering defence against neurodegenerative conditions affecting this region. Estradiol also modulates dopamine signalling in the striatum, potentially enhancing dopamine release or receptor sensitivity, thereby influencing reward processing and motivation, with implications for mood disorders and addiction [37]. Progesterone also been associated with neuroprotection in the striatum. It has been explored as a potential therapeutic agent for conditions like traumatic brain injury. Additionally, progesterone can interact with the GABAergic system in the striatum, affecting inhibitory neurotransmission and potentially influencing motor control and behaviour [38].

Beyond estradiol and progesterone, other hormones play roles in striatal function. Testosterone, although primarily a male hormone, has behavioral effects that can involve the striatum, influencing motivation, aggression, and risk-taking behavior. Thyroid hormones, such as T4 and T3, indirectly affect striatal function through their regulation of overall brain metabolism [39]. Hormonal fluctuations, occurring during events such as the menstrual cycle, pregnancy, or menopause, can influence striatal function, potentially leading to changes in mood, cognition, and behaviour [40]. This intricate interplay between hormones and the striatum holds significance for understanding various neurological and neuropsychiatric conditions and may offer avenues for future therapeutic interventions.

13. Conclusion

In conclusion, the striatum is a complex and multifaceted brain structure with diverse functions, ranging from motor control to decision-making and emotional processing. Its intricate neural connections, microanatomy, and reliance on a well-regulated blood supply underscore its pivotal role in various aspects of brain function. The involvement of the striatum in neurodegenerative disorders like Parkinson's disease highlights the critical need to understand its anatomy and function. The subdivision of the striatum into regions like the caudate nucleus, putamen, and nucleus accumbens, each with distinct roles, emphasizes its versatility in coordinating motor movements, reward processing, and emotional responses. These functions are supported by intricate neural circuits, such as the corticostriatal and mesolimbic pathways, which provide a foundation for our understanding of decision-making and motivated behavior. The striatum's microanatomy, characterized by medium spiny neurons and various interneurons, adds another layer of complexity to its functionality. These neurons, along with neurotransmitters like dopamine and acetylcholine, contribute to the fine-tuning of neural circuits within the striatum.

The striatum's reliance on a robust blood supply, provided by arteries such as the middle cerebral artery and anterior cerebral artery, highlights the significance of vascular health in maintaining its functions. Any disruption in this blood supply can have profound neurological consequences. Furthermore, the role of growth factors, such as BDNF and GDNF, in supporting striatal neurons underscores their importance in neuroprotection and potential therapeutic applications in neurodegenerative diseases. Alpha-synuclein's involvement in the striatum highlights its role in Parkinson's disease and the urgency of developing treatments to address its pathogenic aggregation. Finally, the impact of hormones, including estradiol and progesterone, on the striatum adds a layer of complexity to our understanding of mood, cognition, and behavior regulation.

In summary, the striatum is a central hub within the brain, connecting various regions and orchestrating a wide array of functions. Its anatomical, functional, and biochemical intricacies make it a focal point of research with significant implications for neurology, psychiatry, and therapeutics. Understanding the striatum's role in health and disease is essential for advancing our knowledge of the brain's inner workings and developing innovative strategies to address neurological and neuropsychiatric conditions.

Conflict of interest

Authors declare no conflict of interest

References

[1] D.J. Surmeier. (2018). Determinants of dopaminergic neuron loss in Parkinson's disease. The FEBS journal. 285(19): 3657–3668.

[2] A. Tewari, R. Jog, M.S. Jog. (2016). The Striatum and Subthalamic Nucleus as Independent and Collaborative Structures in Motor Control. Frontiers in Systems Neuroscience. 10: 17.

[3] A.M. Klawonn, and R.C. Malenka. (2018). Nucleus Accumbens Modulation in Reward and Aversion. Cold Spring Harbor Symposia on Quantitative Biology. 83: 119–129.

[4] E.R. Pool, M.D. Tord, S. Delplanque, Y. Stussi, D. Cereghetti, P. Vuilleumier, and D. Sander. (2022). Differential Contributions of Ventral Striatum Subregions to the Motivational and Hedonic Components of the Affective Processing of Reward. The Journal of neuroscience: The Official Journal of the Society for Neuroscience. 42(13): 2716–2728.

[5] S. Cataldi, A.T. Stanley, M.C. Miniaci, and D. Sulzer. (2022). Interpreting the role of the striatum during multiple phases of motor learning. The FEBS Journal. 289(8): 2263–2281.

[6] S.N. Haber. (2016). Corticostriatal circuitry. Dialogues in Clinical Neuroscience. 18(1): 7–21.

[7] P. Fettes, L. Schulze, and J. Downar. (2017). Cortico-Striatal-Thalamic Loop Circuits of the Orbitofrontal Cortex: Promising Therapeutic Targets in Psychiatric Illness. Frontiers in Systems Neuroscience. 11: 25.

[8] S. Ikemoto. (2010). Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. Neuroscience and Biobehavioral Reviews. 35(2): 129–150.

[9] D. Gagnon, S. Petryszyn, M.G. Sanchez, C. Bories, J.M. Beaulieu, Y. De Koninck, A. Parent, and M. Parent. (2017). Striatal Neurons Expressing D1 and D2 Receptors are Morphologically Distinct and Differently Affected by Dopamine Denervation in Mice. Scientific Reports. 7: 41432.

theory. Neuroscience and Biobehavioral Reviews. 35(2): 129–150.

[10] J.K. O'Hare, H. Li, N. Kim, E. Gaidis, K. Ade, J. Beck, H. Yin, and N. Calakos. (2017). Striatal fast-spiking interneurons selectively modulate circuit

output and are required for habitual behavior. ELife. 6: e26231.

[11] R. Bourdy, M.J. Sánchez-Catalán, J. Kaufling, J.J. Balcita-Pedicino, M.J. Freund-Mercier, P. Veinante, S.R. Sesack, F. Georges, and M. Barrot. (2014). Control of the nigrostriatal dopamine neuron activity and motor function by the tail of the ventral tegmental area. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 39(12): 2788–2798.

[12] H. Sano, S. Chiken, T. Hikida, K. Kobayashi, and A. Nambu. (2013). Signals through the striatopallidal indirect pathway stop movements by phasic excitation in the substantia nigra. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 33(17): 7583–7594.

[13] S.X. Luo, E.J. Huang. (2016). Dopaminergic Neurons and Brain Reward Pathways: From Neurogenesis to Circuit Assembly. The American journal of pathology. 186(3): 478–488.

[14] M.R. Picciotto, M.J. Higley, and Y.S. Mineur. (2012). Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. Neuron. 76(1): 116–129.

[15] J. Cox, and I.B. Witten. (2019). Striatal circuits for reward learning and decision-making. Nature reviews. Neuroscience. 20(8): 482–494.

[16] E.M. Oo, K.E.E. Saw, H.N. Oo, T. Than and K. Thida. (2021). Variable Anatomy of the Middle Cerebral Artery from Its Origin to the Edge of the Sylvian Fissure: A Direct Fresh Brain Study. The Scientific World Journal. 6652676.

[17] H. El Falougy, P. Selmeciova, E. Kubikova, and Z. Haviarová. (2013). The variable origin of the recurrent artery of Heubner: an anatomical and morphometric study. BioMed Research International. 873434.

[18] S. Yaghi, E. Raz, D. Yang, S. Cutting, M.B. Grory, M.S. Elkind, and A. de Havenon. (2021). Lacunar stroke: mechanisms and therapeutic implications. Journal of Neurology, Neurosurgery, and Psychiatry. 326308.

[19] A. Mathai, and Y. Smith. (2011). The corticostriatal and corticosubthalamic pathways: two entries, one target. So what? Frontiers in Systems Neuroscience. 5: 64.

[20] E. Guatteo, N. Berretta, V. Monda, A. Ledonne, N.B. Mercuri. (2022). Pathophysiological Features of Nigral Dopaminergic Neurons in Animal Models of Parkinson's G. DeMaagd, and A. Philip. (2015). Parkinson's Disease and Its Management: Part 1: Disease Entity, Risk Factors, Pathophysiology, Clinical Presentation, and Diagnosis. P & T: A Peer-Reviewed Journal for Formulary Management, 40(8): 504–532.

[21] J.L. Lanciego, N. Luquin, and J.A. Obeso. (2012). Functional neuroanatomy of the basal ganglia. Cold Spring Harbor perspectives in medicine. 2(12): a009621.

[22] I.J. Bamford, and N.S. Bamford. (2019). The Striatum's Role in Executing Rational and Irrational Economic Behaviors. The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry.

[23] I A.M. Graybiel, and S.T. Grafton. (2015). The striatum: where skills and habits meet. Cold Spring Harbor Perspectives in Biology. 7(8): a021691.

[24] J.E. Grant, M. Isobe, and S.R. Chamberlain. (2019). Abnormalities of striatal morphology in gambling disorder and at-risk gambling. CNS Spectrums. 24(6): 609–615.

[25] E. Burguière, P. Monteiro, L. Mallet, G. Feng, and A.M. Graybiel. (2015). Striatal circuits, habits, and implications for obsessive-compulsive disorder. Current Opinion in Neurobiology. 30: 59–65.

[26] P. Leal-Galicia, M.E. Chávez-Hernández, F. Mata, J. Mata-Luévanos, L.M. Rodríguez-Serrano, A. Tapia-de-Jesús, and M.H. Buenrostro-Jáuregui. (2021). Adult Neurogenesis: A Story Ranging from Controversial New Neurogenic Areas and Human Adult Neurogenesis to Molecular Regulation. International Journal of Molecular Sciences. 22(21): 11489.

[27] F. Luzzati, S. De Marchis, R. Parlato, S. Gribaudo, G. Schütz, A. Fasolo, and P. Peretto. (2011). New striatal neurons in a mouse model of progressive striatal degeneration are generated in both the subventricular zone and the striatal parenchyma. PloS One. 6(9): e25088.

[28] M. Baydyuk, and B. Xu. (2014). BDNF signaling and survival of striatal neurons. Frontiers in Cellular Neuroscience. 8: 254.

[29] G. DeMaagd, and A. Philip. (2015). Parkinson's Disease and Its Management: Part 1: Disease Entity, Risk Factors, Pathophysiology, Clinical Presentation, and Diagnosis. P & T: A Peer-Reviewed Journal for Formulary Management, 40(8): 504–532.

[30] Q. Wang, Y. Liu, and J. Zhou. (2015). Neuroinflammation in Parkinson's disease and its potential as therapeutic target. Translational Neurodegeneration. 4: 19.

[31] S.A. Ferreira, and M. Romero-Ramos. (2018). Microglia Response During Parkinson's Disease: Alpha-Synuclein Intervention. Frontiers in Cellular Neuroscience. 12: 247.

[32] L. Muzio, A. Viotti, and G. Martino. (2021). Microglia in Neuroinflammation and Neurodegeneration: From Understanding to Therapy. Frontiers in Neuroscience. 15: 742065.

[33] S.R. Subramaniam, and H.J. Federoff. (2017). Targeting Microglial Activation States as a Therapeutic Avenue in Parkinson's Disease. Frontiers in Aging Neuroscience. 9: 176.

[34] R.E. Burke. (2006). GDNF as a candidate striatal target-derived neurotrophic factor for the development of substantia nigra dopamine neurons. Journal of Neural Transmission. S (70): 41–45.

[35] K.F. Azman, and R. Zakaria. (2022). Recent Advances on the Role of Brain-Derived Neurotrophic Factor (BDNF) in neurodegenerative diseases. International Journal of Molecular Sciences. 23(12): 6827.

[36] M. Gómez-Benito, N. Granado, P. García-Sanz, A. Michel, M. Dumoulin, and R. Moratalla. (2020). A.

Mathai, and Y. Smith. (2011). The corticostriatal and corticosubthalamic pathways: two entries, one target. So what? Frontiers in Systems Neuroscience. 5: 64.

[37] E. Brotfain, S.E. Gruenbaum, M. Boyko, R. Kutz, A. Zlotnik, and M. Klein. (2016). Neuroprotection by Estrogen and Progesterone in Traumatic Brain Injury and Spinal Cord Injury. Current Neuropharmacology. 14(6): 641–653.

[38] K.E. Yoest, J.A. Cummings, and J.B. Becker. (2014). Estradiol, dopamine, and motivation. Central Nervous System Agents in Medicinal Chemistry. 14(2): 83–89.

[39] R. Mullur, Y.Y. Liu, and G.A. Brent. (2014). Thyroid hormone regulation of metabolism. Physiological Reviews. 94(2): 355–382.

[40] Barth, C., Villringer, A., & Sacher, J. (2015). Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Frontiers in neuroscience, 9, 37.