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BASAL GANGLIA

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Abstract: This article provides an overview of the anatomical and neurochemical components of the basal ganglia, its historical development, and its involvement in various neurological and psychiatric disorders. The basal ganglia's intricate circuitry, involving the striatum, globus pallidus, substantia nigra, and subthalamic nucleus, is discussed, emphasizing its role in action selection and motor control. The historical journey from early anatomical observations to modern neuroscience techniques is traced, highlighting key contributors and breakthroughs. The article delves into the cortico-basal ganglia-thalamo-cortical loop, the direct and indirect pathways, and the modulation of basal ganglia activity by dopamine. A detailed analysis of the basal ganglia's involvement in Parkinson's disease and Huntington's disease is provided, elucidating the disruptions in circuit connections leading to characteristic motor and cognitive symptoms. Overall, this comprehensive exploration enhances our understanding of the basal ganglia's intricate workings and its significance in health and disease.

Key words: Basal ganglia, Dopamine, Direct pathway, Cortico-basal ganglia-thalamo-cortical loop, Circuit connections, Globus pallidus, Huntington’s disease, Indirect pathway, Neuroanatomy, Parkinson’s disease, Striatum, Substantia nigra, Subthalamic nucleus.

Research objective: To understand the role of basal ganglia in the organism by analyzing the structure and functions of basal ganglia.

Vol. 2 No. 1 (2023)
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Introduction: The basal ganglia (BG), also known as basal nuclei, constitutes a cluster of subcortical nuclei present in the brains of vertebrates. Variations between humans and certain primates primarily exist in the division of the globus pallidus into external and internal regions, as well as in the division of the striatum. Positioned at the base of the forebrain and the upper part of the midbrain, these nuclei establish robust connections with the cerebral cortex, thalamus, brainstem, and other brain regions. The basal ganglia are implicated in diverse functions, encompassing the regulation of voluntary motor movements, procedural learning, habit formation, conditional learning, eye movements, cognition, and emotion. The primary functional constituents of the basal ganglia encompass the striatum, which includes both the dorsal striatum (comprising the caudate nucleus and putamen) and the ventral striatum (comprising the nucleus accumbens and olfactory tubercle), along with the globus pallidus, ventral pallidum, substantia nigra, and subthalamic nucleus. Each of these components possesses intricate internal anatomical and neurochemical structures. The largest component, the striatum (both dorsal and ventral), receives input from various brain areas but only transmits output to other segments of the basal ganglia. The globus pallidus receives input from the striatum and issues inhibitory output to numerous motor-related regions. The substantia nigra serves as the source of the striatal input of the neurotransmitter dopamine, which plays a crucial role in basal ganglia function. The subthalamic nucleus predominantly receives input from the striatum and cerebral cortex, projecting to the globus pallidus. The basal ganglia is believed to play a pivotal role in action selection, contributing to the determination of behaviors to be executed. Specifically, it regulates motor and premotor cortical areas, facilitating the smooth execution of voluntary movements. Experimental studies indicate that the basal ganglia exerts an inhibitory influence on various motor systems, and the release of this inhibition allows a motor system to become active. The process of "behavior switching" within the basal ganglia is influenced by signals from various parts of the brain, including the prefrontal cortex, which plays a central role in executive functions. Furthermore, there is a hypothesis suggesting that the basal ganglia are not solely responsible for motor action selection but also for the selection of more cognitive actions. Computational models of action selection in the basal ganglia incorporate this concept.

Methods and materials: Information on the history, development, structure and functions of the basal ganglia was analyzed from various literatures.

History

The study of the basal ganglia has a rich history that spans centuries, marked by significant contributions from anatomists, physiologists, and neuroscientists. Initial observations of structures that would be identified as part of the basal ganglia date back to the 17th and 18th centuries. Thomas Willis as Anatomist, in the 17th century, made first descriptions of structures like the corpus striatum. In 19th Century, researchers like Félix Vicq d'Azyr and Charles-Édouard Brown-Séquard made important contributions, identifying structures like the substantia nigra and globus pallidus. Paul Broca, a French physician and anatomist, provided detailed descriptions of the basal ganglia and their connections in the mid-19th century. He emphasized the role of the basal ganglia in motor functions. Carl Wernicke, a German neurologist, expanded on Broca's work and proposed that damage to the basal ganglia could result in movement disorders.

In 20th Century, advances in neuroscience techniques, including the advent of neuroimaging and electrophysiology, allowed for more detailed investigations into the functions of the basal ganglia. Sir Charles Sherrington's work on reflexes and the concept of inhibition contributed to our understanding of the role of the basal ganglia in motor control. David Marsden, a British neurologist, made significant

Vol. 2 No. 1 (2023)
ISSN: 2995-5483

contributions to the understanding of movement disorders associated with basal ganglia dysfunction. His research helped delineate the clinical features of disorders like Parkinson's disease. The identification of dopamine as a neurotransmitter in the basal ganglia, particularly the substantia nigra, was a crucial breakthrough. The loss of dopamine-producing neurons in the substantia nigra is a key factor in Parkinson's disease. Research continues to uncover the complexities of the basal ganglia circuitry and its involvement in various neurological and psychiatric disorders.

Development

Precursor cells that will give rise to the basal ganglia originate from the telencephalon. These cells migrate to their designated locations within the developing brain. The migration of cells that form the basal ganglia is guided by structures known as ganglionic eminences, including the lateral and medial ganglionic eminences. As cells migrate and organize, the anatomic structures of the basal ganglia, such as the striatum, globus pallidus, substantia nigra, and subthalamic nucleus, begin to take shape. Developing neurons within the basal ganglia establish complex connections with other brain regions, including the cortex, thalamus, and brainstem. This connectivity forms the intricate circuitry of the basal ganglia. Over time, the basal ganglia undergoes maturation and refinement of its circuitry, continuing postnatally and into early childhood. The fully developed basal ganglia becomes functionally integrated into the broader neural networks of the brain, contributing to motor control, learning, and cognitive processes.

Structure

The basal ganglia represent a fundamental component of the cerebrum. In contrast to the cortical layer lining the surface of the forebrain, the basal ganglia are discrete masses of gray matter located deep in the brain, in close proximity to the junction of the thalamus. They encircle the thalamus and are positioned to its side. Similar to most parts of the brain, the basal ganglia are composed of left and right sides that mirror each other virtually. In terms of anatomy, the basal ganglia are categorized into four distinct structures based on their superior or rostral position (i.e., their proximity to the top of the head). Two of these structures, the striatum and the pallidum, are relatively large, while the other two, the substantia nigra and the subthalamic nucleus, are smaller. It is important to note that the subthalamic nucleus and substantia nigra are situated more posteriorly in the brain compared to the striatum and pallidum.

Striatum: The striatum, typically divided into the dorsal striatum and ventral striatum, is a subcortical structure. A medial-lateral classification, deemed more behaviorally relevant, is increasingly utilized. Comprising mainly medium spiny neurons, which are GABAergic, the striatum projects to the external (lateral) globus pallidus, internal (medial) globus pallidus, and substantia nigra pars reticulata. The dorsal striatum, associated with sensorimotor activities, receives substantial glutamatergic inputs from the cortex and dopaminergic inputs from the substantia nigra pars compacta. The ventral striatum, believed to play a role in reward and other limbic functions, receives glutamatergic inputs from limbic areas and dopaminergic inputs from the ventral tegmental area via the mesolimbic pathway. Specific regions within the striatum, including the caudate, putamen, nucleus accumbens, and olfactory tubercle, exhibit distinct connectivity patterns. Striatopallidal fibers establish connections from the striatum to the pallidum.

Pallidum: The pallidum comprises the globus pallidus, characterized as a "pale globe," and the ventral pallidum. The globus pallidus is functionally divided into internal (medial) and external (lateral)

Vol. 2 No. 1 (2023)
ISSN: 2995-5483

segments, abbreviated as GPi and GPe. Both segments predominantly contain GABAergic neurons with inhibitory effects on their targets. The GPe, receiving input mainly from the striatum, projects to the subthalamic nucleus. The GPi receives signals from the striatum via the "direct" and "indirect" pathways. Pallidal neurons operate on a disinhibition principle, where striatal input diminishes the tonic inhibition exerted by pallidal cells on their targets, resulting in increased target firing. The ventral pallidum represents a smaller extension. The overall effect of the pallidal circuitry is described in terms of disinhibition, leading to heightened target firing due to reduced pallidal inhibition.

Substantia Nigra: The substantia nigra, a midbrain gray matter portion of the basal ganglia, consists of two parts – the pars compacta (SNc) and the pars reticulata (SNr). The SNr often collaborates with the GPi, inhibiting the thalamus. The SNc produces the neurotransmitter dopamine, critical for maintaining balance in the striatal pathway. The circuit section below elucidates the roles and circuit connections of each component of the basal ganglia.

Subthalamic Nucleus: The subthalamic nucleus, a diencephalic gray matter portion of the basal ganglia, is the only portion that produces an excitatory neurotransmitter, glutamate. Its role is to stimulate the SNr-GPi complex, and it is part of the indirect pathway. The subthalamic nucleus receives inhibitory input from the external part of the globus pallidus and sends excitatory input to the GPi.

Function

The basal ganglia is involved in the coordination of voluntary movements and is interconnected with other regions of the brain. The basal ganglia is primarily associated with the regulation of voluntary motor movements. It helps to initiate, modulate, and terminate movements to achieve smooth and coordinated actions.The basal ganglia is involved in procedural memory, which is the memory for skills and habits. It plays a role in learning and automating motor tasks through repetition and practice. This function is crucial for acquiring and performing routine activities. The basal ganglia contributes to the formation and execution of habits. It is involved in the process of transitioning from goal-directed actions to automatic, habitual behaviors. Habits are actions performed without conscious thought, and the basal ganglia helps in their establishment.The basal ganglia is implicated in conditional learning, where behaviors are modified based on the context or specific conditions. It helps in adjusting motor responses to different environmental cues. The basal ganglia is involved in controlling eye movements. It contributes to the coordination and regulation of gaze, particularly in activities such as tracking moving objects. Beyond its role in motor control, the basal ganglia has connections with the prefrontal cortex and is implicated in various cognitive functions. These include aspects of executive functions, such as decision-making, working memory, and attention. The basal ganglia is associated with emotional processing. It plays a role in regulating emotional responses and is connected with limbic structures involved in the emotional circuitry of the brain. The basal ganglia is thought to play a key role in action selection, aiding in the choice of behaviors to execute. It helps in determining which actions to initiate and which to inhibit based on the context and goals. Experimental studies suggest that the basal ganglia exerts an inhibitory influence on various motor systems. The release of this inhibition permits the activation of motor systems, allowing for the execution of specific actions.

Results: We analyzed the above methods and materials. And as a result, we tabulated the structures of the basal ganglia, their locations and functions.

Analysis of basal ganglia structures

Vol. 2 No. 1 (2023)
ISSN: 2995-5483

Structure	Location	Function
Striatum	Subcortical structure in forebrain	Motor and cognitive functions,
Pallidum	Telencephalon	Regulation of voluntary movements.
Substantia nigra	Mesencephalon	Produces the neurotransmitter dopamine
Subthalamic Nucleus	Diencephalon	Produces the excitatory neurotransmitter glutamate.

Also, as results, we placed the neurotransmitters produced in the basal ganglia structures and their function in the table.

Analysis neurotransmitters of basal ganglia

Neurotransmitter	Production structure	Function
Dopamine (DA)	Substantia nigra	Plays a crucial role in regulating movement, mood, and reward pathways
Gamma-Aminobutyric Acid (GABA)	Pallidum	Acts as the primary inhibitory neurotransmitter, regulating neuronal excitability and preventing excessive signaling
Acetylcholine (ACh)	Striatum	Involved in motor control, cognitive functions, and memory

Discussion: Based on all our materials and results, we will analyze the mechanism of operation of the basal ganglia. The basal ganglia is a complex network of nuclei (clusters of neurons) interconnected with various regions of the brain. These connections form intricate circuits that play a crucial role in motor control, procedural learning, and other cognitive functions. The major components of the basal ganglia include the striatum, globus pallidus, substantia nigra, and subthalamic nucleus. on the basis of the mechanism of operation of the basal ganglia, circuit connections stand.

1. Cortico-Basal Ganglia-Thalamo-Cortical Loop: The primary circuit involving the basal ganglia is known as the cortico-basal ganglia-thalamo-cortical loop. It consists of connections between the cortex (particularly the motor and prefrontal areas), the basal ganglia, and the thalamus.

2. Direct Pathway:

- The direct pathway facilitates the initiation of voluntary movements. It involves the following sequence of connections:

Vol. 2 No. 1 (2023)
ISSN: 2995-5483

Cortex → Striatum (specifically the caudate and putamen): The cortex sends excitatory signals to the striatum.

Striatum → Globus Pallidus Internal Segment (GPi) and Substantia Nigra Pars Reticulata (SNr), The striatum inhibits these output nuclei, reducing their inhibitory influence on the thalamus.

GPi/SNr → Thalamus: With reduced inhibition from the GPi/SNr, the thalamus becomes more active.

Thalamus → Cortex: The thalamus then sends excitatory signals back to the cortex, completing the loop.

3. Indirect Pathway:

- The indirect pathway exerts inhibitory control over unwanted movements. It involves the following sequence of connections:

Cortex → Striatum:Similar to the direct pathway, the cortex sends excitatory signals to the striatum.

Striatum → Globus Pallidus External Segment (GPe): The striatum inhibits the GPe.

GPe → Subthalamic Nucleus (STN): With reduced inhibition from the GPe, the STN becomes more active.

STN → GPi/SNr: The STN sends excitatory signals to the GPi/SNr, increasing their inhibitory influence on the thalamus.

GPi/SNr → Thalamus: With increased inhibition from the GPi/SNr, the thalamus becomes less active.

Thalamus → Cortex: Reduced thalamic activity leads to decreased excitatory signals to the cortex.

4. Modulation by Dopamine:Dopaminergic projections from the substantia nigra pars compacta (SNc) to the striatum modulate the activity of both the direct and indirect pathways. Dopamine helps fine-tune the balance between these pathways, influencing the selection and initiation of movements.

5. Loop Completion: The loops involving the direct and indirect pathways are interconnected, allowing for dynamic modulation and coordination of motor outputs.

These circuits are highly interconnected and work together to regulate the initiation, modulation, and inhibition of voluntary movements. Dysfunction in these circuits can lead to movement disorders, such as Parkinson's disease or Huntington's disease, highlighting the importance of understanding basal ganglia circuitry in both health and disease.

Parkinsonism is a term that encompasses a group of neurological disorders sharing common symptoms with Parkinson's disease. The primary features of parkinsonism include tremors, bradykinesia (slowness of movement), rigidity, and postural instability. These symptoms can be caused by various underlying conditions, making parkinsonism a broader category.In Parkinsonism, particularly in Parkinson's disease, there is a disruption in the normal circuit connections within the basal ganglia. The key circuitry involves the cortico-basal ganglia-thalamo-cortical loop. Here's how the circuit connections are affected:

Loss of Dopaminergic Neurons:In Parkinson's disease, there is a significant loss of dopamine-producing neurons in the substantia nigra pars compacta (SNc), a key structure in the basal ganglia.

Vol. 2 No. 1 (2023)
ISSN: 2995-5483

Direct Pathway Dysfunction: Reduced dopamine levels lead to decreased activation of the direct pathway, where the striatum (specifically the caudate and putamen) sends inhibitory signals to the globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNr).With less inhibition, the GPi/SNr overly inhibits the thalamus, resulting in decreased thalamic activity.

Indirect Pathway Dysfunction: Reduced dopamine levels also impact the indirect pathway, where the striatum inhibits the globus pallidus external segment (GPe).This leads to decreased inhibition of the subthalamic nucleus (STN) by the GPe, causing increased activity in the STN.The overactive STN sends excitatory signals to the GPi/SNr, further contributing to increased inhibition of the thalamus.

Thalamic Inhibition and Cortical Output: With both pathways affected, there is an imbalance in thalamic activity, disrupting the normal regulation of cortical output.The overall result is a reduction in the facilitation of voluntary movements, contributing to the characteristic motor symptoms of parkinsonism.

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and psychiatric symptoms. It is caused by a mutation in the HTT gene, leading to the production of a mutated form of the huntingtin protein. The hallmark of HD is the degeneration of neurons in specific brain regions, primarily the striatum. In HD, the mutated huntingtin protein leads to neuronal dysfunction and degeneration, particularly affecting the medium spiny neurons (MSNs) in the striatum. The degeneration of MSNs contributes to the characteristic motor and cognitive symptoms observed in individuals with Huntington's disease. How Disorder Circuit Connections in Huntington's Disease:In HD, the degeneration of MSNs disrupts both pathways.

In the direct pathway, the loss of inhibitory signals from the striatum (caudate and putamen) to the globus pallidus internal segment (GPi) leads to increased inhibitory output from the GPi to the thalamus.

In the indirect pathway, the loss of inhibitory signals from the striatum to the globus pallidus external segment (GPe) results in reduced inhibitory output to the subthalamic nucleus (STN).

These changes in both pathways contribute to abnormal thalamic activity and altered cortical output, impacting motor function. The imbalances in basal ganglia circuitry have downstream effects on cortical areas, leading to cognitive decline and psychiatric symptoms.

Conclusion: In conclusion, the basal ganglia stands as a pivotal and intricate structure within the brain, orchestrating a symphony of functions essential for motor control, procedural learning, habit formation, conditional learning, eye movements, cognition, and emotion. This cluster of subcortical nuclei, including the striatum, globus pallidus, substantia nigra, and subthalamic nucleus, operates in concert with various brain regions, forming complex circuits crucial for the execution of voluntary movements and cognitive processes. Developmentally, the basal ganglia emerges from precursor cells originating in the telencephalon, guided by ganglionic eminences, and matures through intricate connectivity with other brain regions. Structurally, the basal ganglia's discreet masses of gray matter, positioned deep in the brain, mirror each other bilaterally, forming a fundamental component of the cerebrum. Functionally, the basal ganglia participates in action selection, contributing to the regulation of motor and premotor cortical areas. It is integral to the initiation, modulation, and inhibition of voluntary movements, procedural memory, habit formation, conditional learning, eye movements, and various cognitive functions. The cortico-basal ganglia-thalamo-cortical loop, direct and indirect pathways,

Vol. 2 No. 1 (2023)
ISSN: 2995-5483

dopamine modulation, and intricate circuit connections delineate the mechanisms underlying its operation.

The journey from historical observations to contemporary neuroscience has positioned the basal ganglia as a key player in the intricate landscape of the human brain, leaving us with a profound appreciation for its role in shaping our actions and cognition.

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