THE EXTRAPYRAMIDAL SYSTEM

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ABSTRACT

The extrapyramidal system (EPS) is a crucial neural network within the central nervous system (CNS) that controls posture, muscle tone, involuntary movement, and motor coordination. Unlike the pyramidal system, which directly controls voluntary movement, the EPS operates through a network of interconnected subcortical structures including the basal ganglia, cerebellum, thalamus and brainstem nuclei, to refine and modulate motor activity. This intricate system ensures smooth, automatic motor control, refining movement precision and suppressing unwanted motion (Lee and Muzio, 2020). The EPS operates through multiple pathways, including the reticulospinal, vestibulospinal, rubrospinal, and tectospinal tracts, which transmit signals from the brain to the spinal cord, influencing motor responses. Neurotransmitters such as dopamine, gamma-aminobutyric acid, glutamate, and acetylcholine play key roles in regulating these pathways, facilitating movement modulation and habit formation. Dysfunction within the EPS contributes to debilitating movement disorders like Parkinson's disease, Huntington's disease, and tardive dyskinesia, each characterized by impaired motor regulation. These conditions manifest through tremors, rigidity, involuntary movements, and postural instability, profoundly affecting daily life. Advances in neuroimaging, including MRI and PET scans, have enhanced diagnostic precision, while electrophysiological assessments like EMG and EEG provide further insight into EPS activity. Treatment strategies range from pharmacological interventions and deep brain stimulation (DBS) to emerging therapies such as gene therapy and stem cell transplantation (Saeed *et al.*, 2020; Pitton-Rissado and Caprara, 2023). By orchestrating involuntary and automatic movements, the EPS plays a fundamental role in motor function. Understanding its mechanisms is vital for developing innovative treatments and improving outcomes for individuals affected by movement disorders.

CHAPTER 1

INTRODUCTION

1.0 INTRODUCTION TO THE EXTRAPYRAMIDAL TRACT

The Central Nervous System is a complex network of components that enable an organism to interact with its surroundings. It is composed of several distinct parts, each of which has a distinct function. The CNS is primarily made up of upper motor neurons, which transmit movement signals to lower motor neurons, which then instruct muscles to contract or relax. The upper motor neurons further subdivide into multiple tracts, each of which has a specific function within the body; specifically, the Pyramidal tract is the primary pathway that transmits signals for voluntary movement, while the Extrapyramidal tract is the primary pathway that transmits signals for involuntary movement (Lohia and McKenzie, 2019).

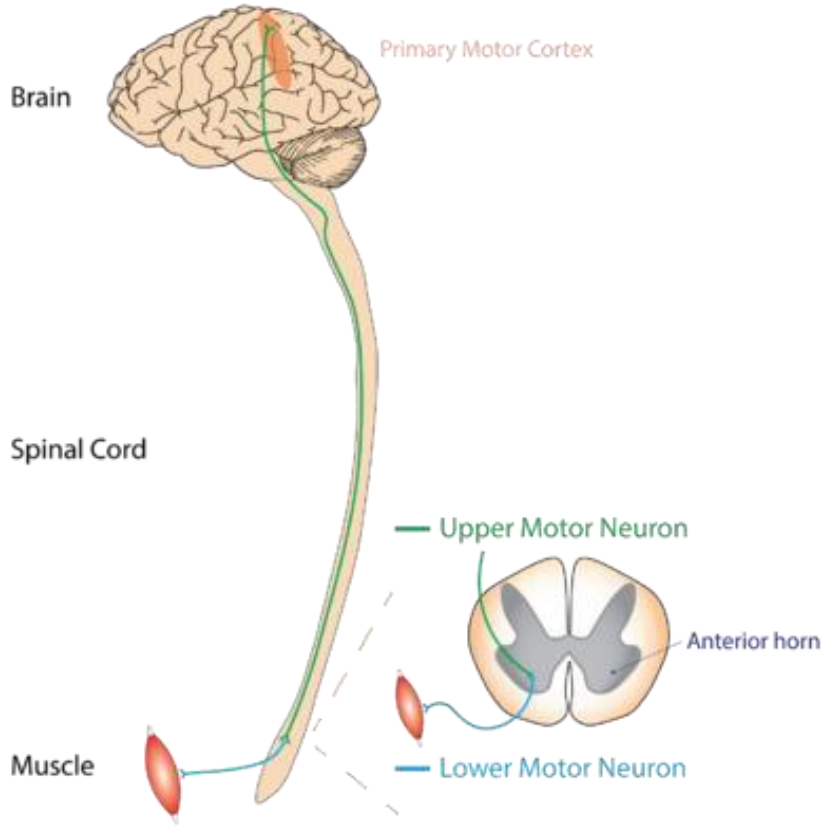


Fig 1.1: Diagram of the Central Nervous System (CNS) (Physiopedia, 2024)

The Extrapyramidal Tract is polysynaptic in nature and composed of several tracts and nuclei. All descending upper motor neuron tracts, with the exception of the corticospinal and corticobulbar tracts, are part of the extrapyramidal system (Lee and Muzio, 2020).

The Extrapyramidal Tracts can be separated into four functional categories:
The Reticulospinal and Vestibulospinal pathways which provide ipsilateral innervation and do not decussate; and the Tectospinal and Rubrospinal pathways which supply contralateral innervation and decussate. Through a tonic function, the EPS affects voluntary motility and regulates automatic actions. The processing centres situated in many brain regions, such as the reticular formation, the cerebellum, the thalamus, portions of the cerebral cortex, and the basal ganglia (a collection of subcortical nuclei), is a part of these control processes (Lee and Muzio, 2020). Maintaining posture and controlling involuntary motor processes depend on the EPS.
Specifically, the EPS offers:

i. Adjustment of postural tone. ii. Preparation of predisposing tonic attitudes for involuntary movements. iii. Performing actions that improve the naturalness and accuracy of voluntary motions. iv. Control over automatic tone and movement changes v. Control over reflexes that go along with affective and attentive responses (reactions) vi. Control over voluntary movements that eventually become automatic via practice and education (e.g. in writing) (Lee and Muzio, 2020).

My goal in writing about this system is to provide additional insight into a topic that is rarely discussed yet is extremely significant, and doing so in words that can be easily understood. When the extrapyramidal system is being talked about, more often than not, it is in the context of extrapyramidal syndromes, extrapyramidal side effects, extrapyramidal lesions or extrapyramidal dysfunction but in this paper, I will be talking about the extrapyramidal system

as a whole. Understanding the role of this pathway could lead to new insights into the mechanisms of motor control and the development of novel treatments for movement disorders.

1.1 DISCOVERY OF THE EXTRAPYRAMIDAL SYSTEM

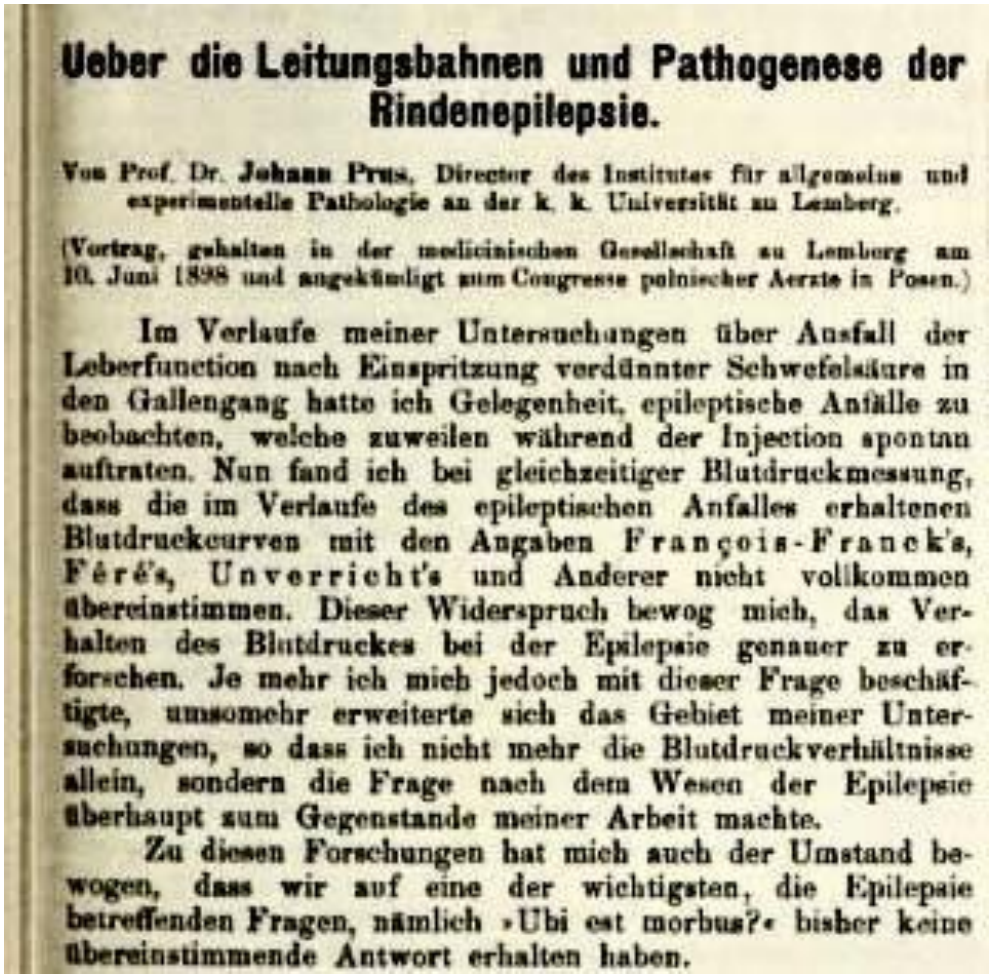
The existence of an extrapyramidal system and the motor function of the corticospinal pyramidal tract were unknown prior to 1870. The brain was merely the organ responsible for intelligence, memory, and consciousness. Because the anatomy and physiology of the various descending routes had not been well defined by anatomists, it was unknown whether the cortex initiated or controlled motor function (Pearce, 2021).

In terms of electrophysiology, the pyramidal system—that is, the motor cortex and its efferent tracts—was first demonstrated in 1870 by Gustav Fritsch and Eduard Hitzig. Fritsch and Hitzig's findings were expanded upon by David Ferrier's traditional ablation/stimulation research. He defined cerebral localisation by demonstrating that Faradic stimulation of the cerebral cortex could result in movements and fits and that cerebral functions were confined in distinct, measurable regions, which he mapped as sensory and motor across multiple species. Ferrier's cerebral localisation was considered "among the greatest advances in the physiology of the nervous system made in the last 50 years" by Carpenter in 1874 (Ferrier, 1886; Carpenter, 1874).

Johann Prus first proposed the anatomical idea of the Extrapyramidal System (EPS) in 1898 when he found that generated cortical epilepsy was not controlled by experimental lesions in the pyramidal tracts. Prus proposed that there must be other channels, referred to as "extrapyramidal tracts," that "delivered epileptic activity" from the cerebral cortex to the spinal cord in addition to pyramidal tracts. Therefore, the word "extrapyramidal" was used in clinical settings to differentiate between the effects of damage to the traditional "pyramidal" route and

those caused by injury involving the basal ganglia. The two systems do, however, have significant anatomical and functional connections in spite of this difference (Lee and Muzio, 2022).

In his experiment, Prus cut through a dog's pyramidal tract at the medulla, pons, midbrain, and internal capsule levels and noted that when the cerebral cortex was stimulated, both the side opposite the operation and the same side experienced bilateral epileptic seizures. He made the following assumptions to explain the results of his experiments: either the dog has bilateral innervation in the cortex, and when the pyramidal tract is cut, excitation travels to the other hemisphere via the commissure fibres, or in this instance, conduction of cortical epilepsy occurs via an unidentified centrifugal, or motor pathway.



Ueber die Leitungsbahnen und Pathogenese der Rindenepilepsie.

Von Prof. Dr. **Johann Prus**, Director des Institutes für allgemeine und experimentelle Pathologie an der k. k. Universität zu Lemberg.

(Vortrag, gehalten in der medicinischen Gesellschaft zu Lemberg am 10. Juni 1898 und angekündigt zum Congresse polnischer Aerzte in Posen.)

Im Verlaufe meiner Untersuchungen über Ausfall der Leberfunction nach Einspritzung verdünnter Schwefelsäure in den Gallengang hatte ich Gelegenheit, epileptische Anfälle zu beobachten, welche zuweilen während der Injection spontan auftraten. Nun fand ich bei gleichzeitiger Blutdruckmessung, dass die im Verlaufe des epileptischen Anfalles erhaltenen Blutdruckcurven mit den Angaben François-Franck's, Féré's, Unverricht's und Anderer nicht vollkommen übereinstimmen. Dieser Widerspruch bewog mich, das Verhalten des Blutdruckes bei der Epilepsie genauer zu erforschen. Je mehr ich mich jedoch mit dieser Frage beschäftigte, umsomehr erweiterte sich das Gebiet meiner Untersuchungen, so dass ich nicht mehr die Blutdruckverhältnisse allein, sondern die Frage nach dem Wesen der Epilepsie überhaupt zum Gegenstande meiner Arbeit machte.

Zu diesen Forschungen hat mich auch der Umstand bewogen, dass wir auf eine der wichtigsten, die Epilepsie betreffenden Fragen, nämlich »Ubi est morbus?« bisher keine übereinstimmende Antwort erhalten haben.

Fig 1.2: Prus' 1898 publication in the Wiener klinische Wochenschrift (Pearce, 2021)

Prus concluded that an unidentified centrifugal motor pathway was present. However, the term "extrapyramidal" in its contemporary usage was originally used by Samuel Kinnier Alexander Wilson. To differentiate between the clinical consequences resulting from damage to the conventional pyramidal route and those resulting from injury to the basal nuclear tracts, he coined the term "extrapyramidal." In his seminal work, Progressive Lenticular Degeneration (Wilson's illness), from 1912, he detailed the autopsy of three people with the condition, identifying extrapyramidal tracts as pathology beyond the pyramidal system (Wilson, 1912).

Despite his inability to provide an anatomical definition for specific tracts, this was the first time the term "extrapyramidal" was used in neurology literature. During this time, a number of

other people deduced that regions outside the pyramidal tract had a motor function. The Austrian neuropsychiatrist Baron Constantin von Economo suggested that the substantia nigra was involved in the motor control of chewing and swallowing, while the Swiss neurologist Constantin von Monakow outlined a rubrospinal tract. In cats and monkeys, lesions of the substantia nigra and red nucleus resulted in choreoathetosis. After stimulating the substantia nigra in dogs, Russian neurologist Vladimir Bechterew observed alterations in breathing, swallowing, pupillary and ocular abnormalities, and contraction of the neck muscles (von Monacow, 1909; von Economo, 1910)

James Parkinson's description of the condition he discovered in 1817, in which he incorrectly assumed it started in the "medulla spinalis," demonstrates the uncertainty regarding the origins of pathology in the various extrapyramidal disorders prior to Wilson's study. Although the pathology was unknown at the time, Hermann Oppenheim, a leading clinical neurologist in Berlin, established the duality of motor control and inferred the involvement of both pyramidal and extrapyramidal tracts in motor function in 1894 while researching paralysis agitans (Oppenheim, 1894).

Wilson’s long classic paper11 pointed out that the EPS (extrapyramidal system) had a “steadying” influence on the anterior horn cells: “the relation of the corpus striatum (basal ganglia) to the rest of the motor system is one of tone control, and of steadiness of innervation… Remove its influence by disease, [then] tonic postures become overemphasized”, his view of dual motor function, pyramidal and extrapyramidal, was quickly and widely accepted.(Wilson, 1912; Pearce, 2021).

CHAPTER 2

LITERATURE REVIEW

2.0 ANATOMICAL COMPONENTS OF THE EXTRAPYRAMIDAL SYSTEM

The extrapyramidal system is a vital network of neuronal channels and structures that are within the central nervous system and they regulate involuntary motor control, including posture, balance, muscle tone, and movement coordination. The extrapyramidal system functions more indirectly than the pyramidal system, which is directly involved in the execution of voluntary motor activities through the corticospinal and corticobulbar tracts. By affecting motor neurones in the brainstem and spinal cord through a network of interrelated subcortical nuclei and pathways, it regulates motor activity.

To understand the extrapyramidal system's function in motor regulation and its relevance in neurological disorders, we must first know and understand its anatomical components.

This system involves several key structures, including the basal ganglia, the subthalamic nucleus, the substantial nigra, the red nucleus, the anterio-vascular nucleus of the thalamus, the reticular formation, the cerebellum, the vestibular nucleus and the olivary nucleus (Konstantopoulos and Giakoumettis, 2023).

1. THE BASAL GANGLIA

The basal ganglia are a group of nuclei located deep within the cerebral hemispheres, that play an important role in regulating voluntary motor control, procedural learning, and a number of other cognitive and emotional processes. The basal ganglia play a central role in the extrapyramidal system by serving as a mediator between the thalamus and the cortex, thus the basal ganglia refine motor impulses and inhibit unnecessary movement (Young *et al.*, 2023; Yoshida *et al*., 2022).

Anatomical components

The basal ganglia is comprised of several key structures including the striatum, the globus pallidus, the subthalamic nucleus and the substantial nigra (Young *et al.*, 2023).

a. Striatum: This consists of the caudate nucleus and putamen which together make up the dorsal striatum; and the nucleus accumbens and olfactory tubercle which make up the ventral striatum (Young *et al.*, 2023).
b. Globus pallidus: This is divided into the globus pallidus internus (GPi) and the globus pallidus externus (GPe) and its main function is to regulate proprioceptive and conscious motions (Javed and Cascella, 2020).
c. Subthalamic nucleus: This is not an anatomical part of the basal ganglia, rather it is a functional part playing a functional role in the circuitry of the basal ganglia.
d. Substantial nigra: The substantial nigra is anatomically and functionally divided into 2 parts which are the pars compacta (SNpc) that contains dopaminergic neurones and the pars reticulata (SNpr) that contains inhibitor gamma-aminobutyric acid-containing (or GABAergic) neurones. It is an essential component of the circuitry of the basal ganglia that regulates reward and motor activity (Sonne et al., 2022).

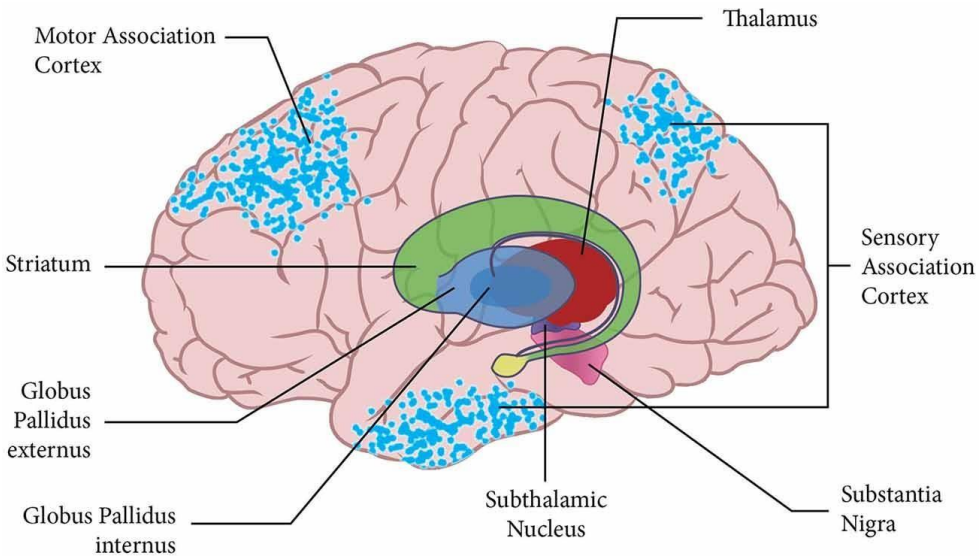


Fig 2.1: Diagram of the brain showing some of the components of the EPS (Colder, 2015)

Functional Pathways of the Basal Ganglia

The basal ganglia communicate with the thalamus through three pathways which are the direct, indirect and hyperdirect pathways. While the direct pathway is excitatory and plays a significant role in starting a voluntary movement, the indirect pathway is inhibitory and stops involuntary movements and the hyperdirect pathway is the fastest way to suppress all involuntary movement and inhibit all motor activities (Vasković. 2023).

a. Direct pathway: The direct pathway is excitatory and plays a significant role in starting a voluntary movement. It does this by releasing or disinhibiting motor movement by disinhibiting the globus pallidus internus or the pars reticulata of the substantia nigra (Young *et al.*, 2023).

   Let me explain this in simple terms; the direct pathway is a coach (the striatum) who is clearing the tract for his sprinter (the movement you want to carry out) at the start of the race, but there is a referee that has strict instructions not to let anyone run (the globus pallidus internus). The coach (the striatum), then tells the referee (the GPi) to relax and

allow the sprinter run since they have permission. The referee (the GPi) then relaxes and allows the sprinter (movement) to pass through. In all of this, there is the tract official (the thalamus), who now blows the whistle to signal the sprinter to run to the finish line (the motor cortex). Basically, what this pathway does is to remove barriers to movement and allow your intended movement happen smoothly and efficiently.

b. Indirect pathway: Again, I'll explain in simple terms; the indirect pathway is like a coach (the striatum) who see's unprepared or unnecessary players (unwanted movements) running onto the tract and stops them, ensuring only the right and prepared players run the race. When the coach (striatum) see's the unnecessary players (unwanted movements), he tells his assistant (the globus pallidus externus), whose job is to keep everything in check and has been shielding all the players from all the officials, to let the enforcer (the subthalamic nucleus), whose job is to maintain tight control of the tract and to inform the referee of where tight control is needed, to do his job. Since the assistant (GPe) is now out of his way, the enforcer (the subthalamic nucleus) can now work properly and starts tightening control. He informs the referee (GPi) who then firmly keeps the unwanted players out by making sure the gatekeeper (the thalamus) keeps the gate to the tract firmly shut thereby keeping the unwanted players out of the tract and preventing them from running the race to the finish line (motor cortex). Basically, the indirect pathway inhibits unnecessary motor activity, keeping movement precise and under control (Young *et al.*, 2023).

c. Hyperdirect pathway: The hyperdirect pathway is like when the enforcer (the subthalamic nucleus) immediately stops the game the moment something unexpected happens. He doesn't wait to inform anyone; he immediately blows the whistle to stop

everyone. The referee (GPi) gets the message and makes sure the gatekeeper (thalamus) doesn't allow any sprinter (movement), wanted or unwanted to run the race i.e. it stops relaying any signals to the motor cortex. Basically, the hyperdirect pathway provides immediate inhibition to suppress motor action (Chen *et al.*, 2020).

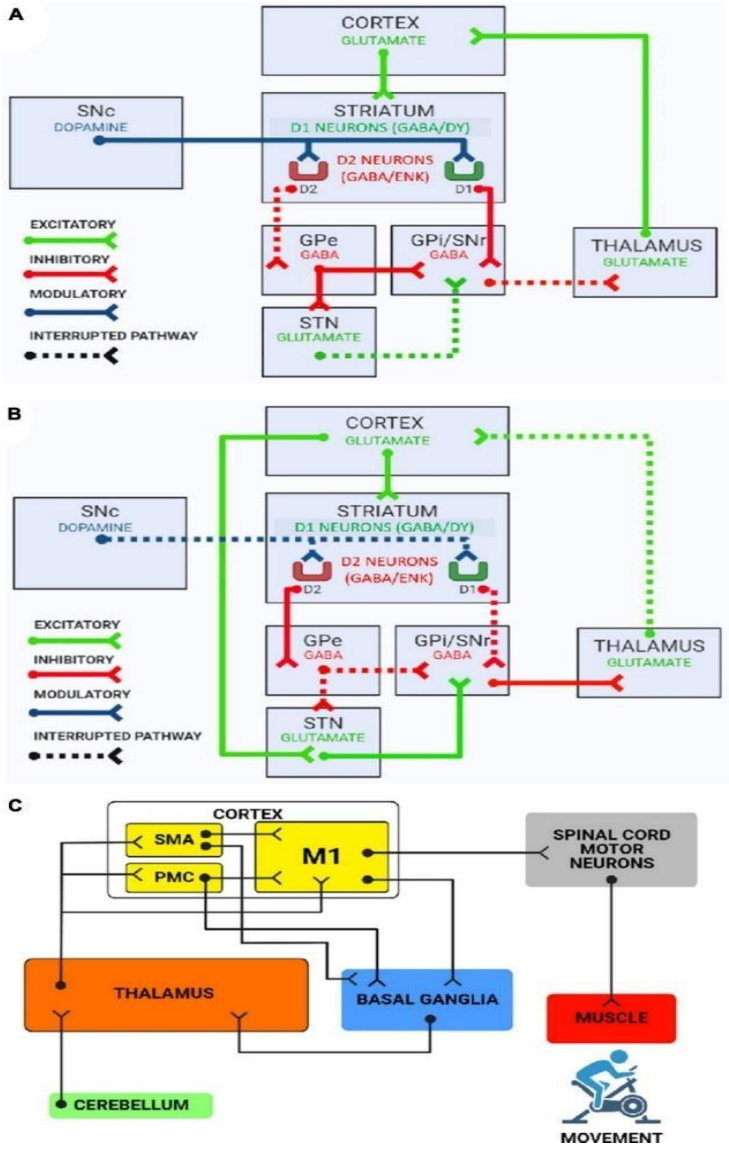


Fig 2.2: The direct, indirect and hyper-direct pathways of the basal ganglia

(A) The direct pathway of the basal ganglia motor circuit. Globus pallidus externus (GPe), globus pallidus internus (GPi), substantia nigra pars compacta (SNc), substantia nigra pars reticulata (SNr), and subthalamic nucleus (STN). The direct pathway results in tonic disinhibition of the VL nucleus of the thalamus, which in turn sends excitatory

projections to the motor cortex, causing the activation of voluntary movement. **(B)** The indirect pathway of the basal ganglia motor circuit. The indirect pathway results in inhibition of the VL nucleus of the thalamus by GPe and SNr. This way VL nucleus of thalamus is not able to send excitatory projections to the motor cortex, causing the inhibition of undesired movements. **(C)** Overall circuit of voluntary movement. SMA, supplementary motor area; PMC, premotor cortex; M1, primary motor area. This scheme shows how the motor cortex, basal ganglia, thalamus, and cerebellum interact to promote precise voluntary movement. After the adjustment circuits involving these subcortical nuclei, neurons in the motor cortex excite α motor neurons in the spinal cord. Finally, α motor neurons stimulate muscle contraction, producing movement. (Rocha *et al.*, 2023)

2. THE CEREBELLUM

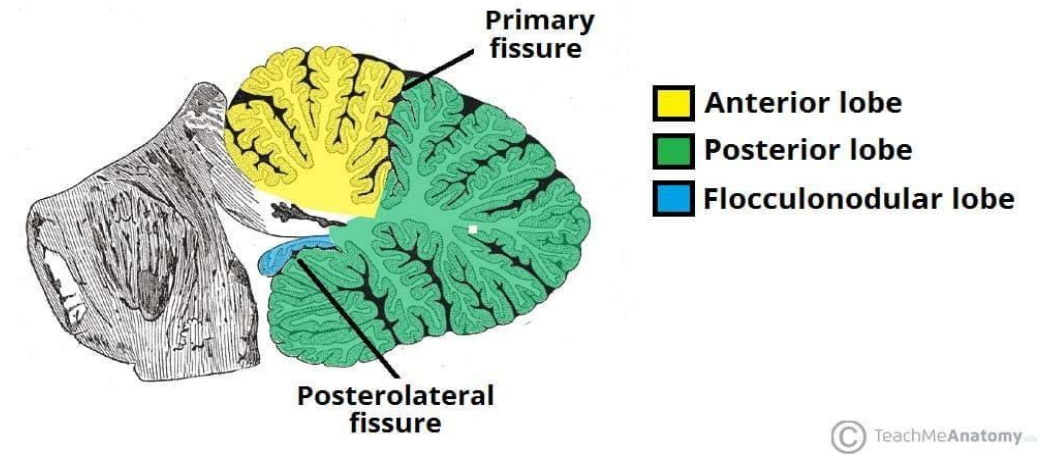
The cerebellum is the encephalic region where the movement planned is compared with the one executed, thus providing feedback so that the individual can succeed in his future motor actions if the previous movement has not been correct (Bear *et al.*, 2020). The cerebellum plays a crucial role in coordinating movement, motor learning, maintaining posture and balance, and cognition (ten Donkelaar, 2011; Błaszczyk *et al.*, 2024).

The cerebellum receives input from the spinal cord, brainstem, and cerebral cortex, providing information about body position and movement. Outputs from the cerebellum influence motor control by modulating activity in the red nucleus, reticular formation, and vestibular nuclei, which are components of the EPS.

Anatomically, the cerebellum can be divided into 3 lobes (Jimsheleishvili and Dididze, 2019):

a. Anterior lobe: This lobe is located superiorly and is separated from the posterior lobe by the primary fissure. It plays a critical function in controlling muscle tone and coordinating skilful voluntary movements.
b. Posterior lobe: this lobe is located below the primary fissure and is the largest of the three lobes. It has a role in both the storage of procedural memories and the planning and regulation of voluntary action.
c. Flocculonodular lobe: The flocculonodular lobe is the earliest section of the cerebellum in terms of evolution. It is located inferiorly and is divided from the corpus cerebelli by the posterolateral fissure. Receiving sensory information from the vestibular system, it is principally in charge of preserving equilibrium and regulating eye movements.

Additionally, the cerebellum is separated into three sagittally aligned zones that extend from medial to lateral. The cerebellum's midsagittal plane contains the vermis, which is derived from the Latin word for worm. The intermediate zone is directly lateral to the vermis. Last but not least, the lateral hemispheres are situated lateral to the intermediate zone; from a gross specimen, it is impossible to discern distinct morphological boundaries between the two (Knierim, 2020).



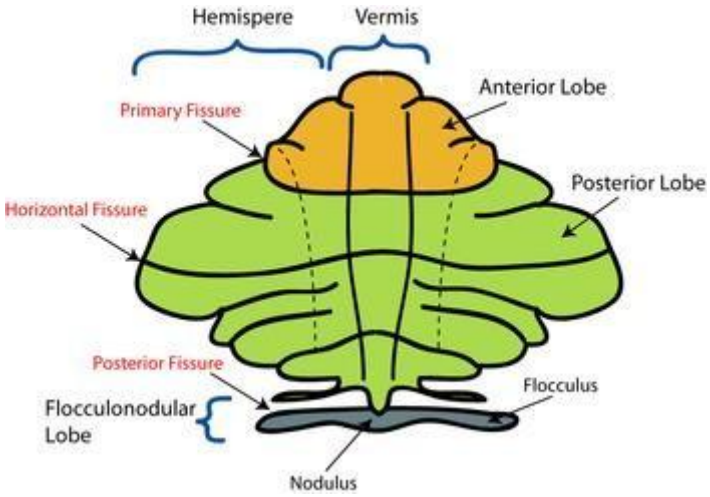


Fig 2.3: Diagram of the cerebellum showing its anatomical divisions (Venturini, 2022) The cerebellum can be divided into 3 functional areas thus:

1. Cerebrocerebellum: Comprising the lateral parts of the cerebellar hemispheres, this is the largest functional area. The dentate nuclei are connected to it. It has a role in motor learning and movement planning. The pontine nuclei in the cerebrocerebellar loop carry information from the cerebral cortex to the cerebellum. This information is processed by the cerebellum and transmitted to the thalamus and red nucleus (Xuan, 2024). It is concerned with smooth performance of skilled voluntary movements (Singh, 2020).

2. Spinocerebellum: It is in charge of tone, posture, and rudimentary limb motions and is involved with spinocerebellar connections (Singh, 2020). It is made up of the anterior lobe, vermis and the fastigial and interposed nuclei. It is involved in integrating sensory inputs and motor commands to coordinate truncal and limb movements. In the spinocerebellar loop, the cerebellum receives proprioceptive information from the dorsal column of the spinal cord. The cerebellum processes this information and sends it to the spinal cord and cortex to adjust and fine-tune movements (Xuan, 2024).

3. Vestibulocerebellum: It keeps the trunk muscles balanced, toned, and erect (Singh, 2020). It is made up of the flocculonodular lobe and paravermis, and has connections to the lateral vestibular nuclei. It helps to control balance and the ocular reflexes, including fixation on targets. In the vestibulocerebellar loop, the cerebellum receives information about balance from the vestibular system. It then sends information to the vestibular nuclei and spinal cord to ensure trunk stability and balance are maintained (Xuan, 2024).

The function of the cerebellum in the EPS is highlighted by the fact that damage to it can result in ataxia, dysmetria, and other problems with motor coordination.
It is essential to comprehend how the cerebellum functions inside the EPS in order to diagnose and treat a variety of movement problems.

3. THE THALAMUS

The thalamus plays a crucial role in the extrapyramidal system by acting as a relay and integration centre for motor signals. It conveys processed motor information to the cerebral cortex after receiving input from the cerebellum and basal ganglia, among other extrapyramidal

system components. The modulation and coordination of motor processes depend on this thalamocortical transmission, which affects posture, muscle tone, and involuntary movements.

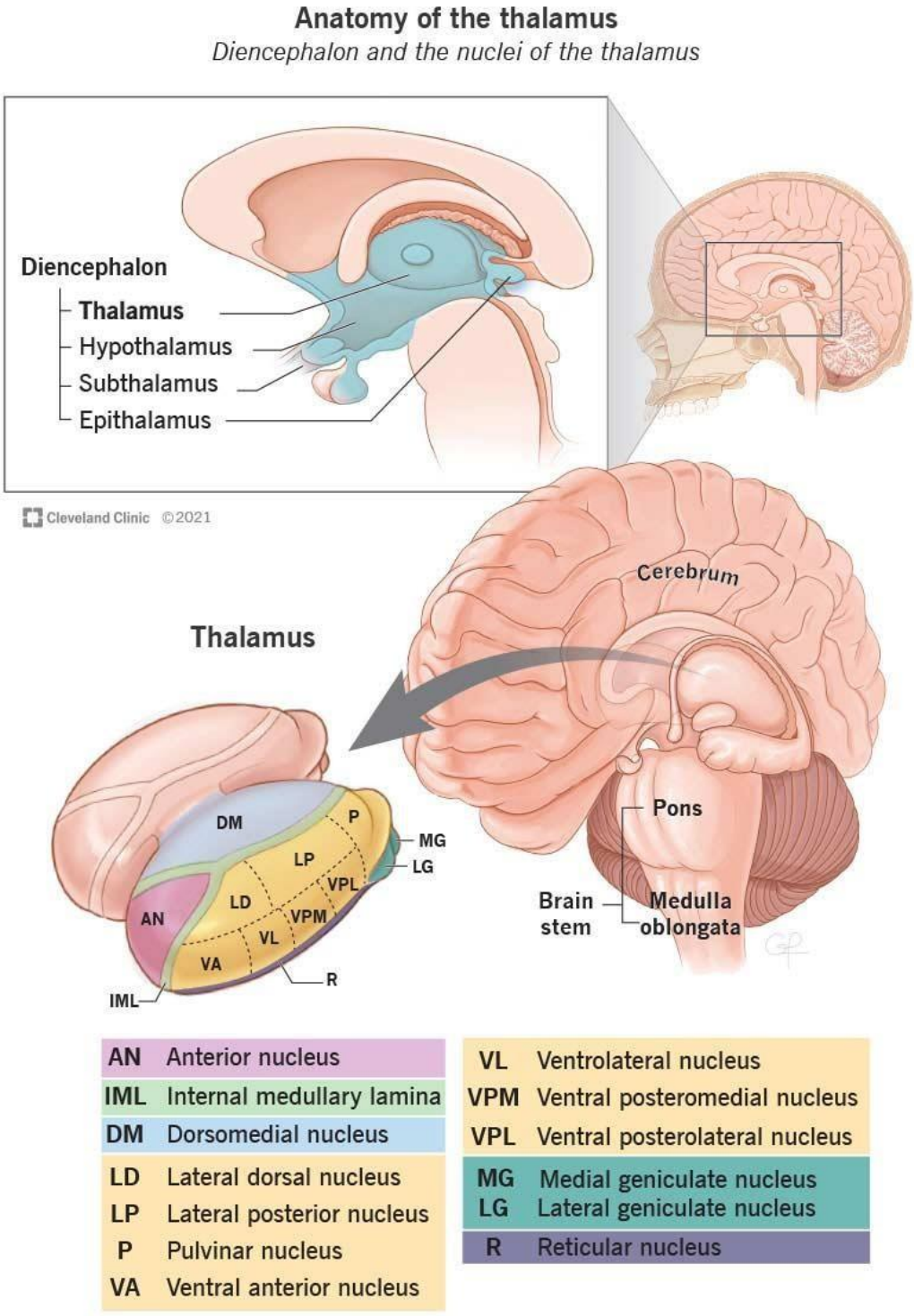


Fig 2.4: Diagram of the thalamus showing its anatomical divisions (Cleaveland clinic, 2021)
The thalamus is divided into five main functional components, which are as follows:

1. Reticular and Intralaminar nuclei regulate pain and arousal
2. Sensory nuclei regulate all the sensory domains except smell
3. Effector nuclei regulate motor language function
4. Associative nuclei connote cognitive process
5. Limbic nuclei involve mood and motivation (Torrico and Munakomi, 2019).

The thalamus has a role in consciousness, thinking (cognitive), memory, prioritising attention, relaying sensory information, and relaying motor information (Blumenfeld and Gummadavelli, 2025).

2.1 NOTABLE RESEARCH ON THE EXTRAPYRAMIDAL SYSTEM

Research on the extrapyramidal system (EPS) is crucial for understanding motor physiology because it plays a vital role in regulating involuntary movements, maintaining posture, and modulating muscle tone, which are essential components of smooth and coordinated movement, and disruptions in its function directly lead to a range of motor disorders like Parkinson's disease and other movement abnormalities**.** Some key reasons why research is being made into the extrapyramidal system include;

i. **Its fundamental role in motor control**: The EPS plays a key role in controlling posture, muscular tone, and involuntary movements. Through its interactions with the cerebellum, basal ganglia, and other motor pathways, it is essential for fine-tuning motor control. By knowing how these elements work together, researchers can gain a greater understanding of the mechanisms governing coordinated and fluid movement. ii. **It gives us a better understanding of neurological disorders**: Disorders such as Parkinson’s disease, Huntington's disease, and dystonia’s arise from dysfunctions

within the EPS. Parkinson's disease, for instance, is linked to the loss of dopamineproducing neurons in the substantia nigra, which are part of the EPS. Research helps pinpoint the specific mechanisms and genetic factors contributing to these conditions, leading to better diagnostic tools and treatment options (Pearce, 2021).

iii. **Development of innovative therapies**: Treatment breakthroughs like deep brain stimulation (DBS) and medications that target EPS pathways (like dopamine agonists for Parkinson's disease) are the result of advances in research. Researchers hope to improve patient outcomes and quality of life by developing more effective therapies through further study of the EPS.

iv. **Understanding the broader clinical implications of the EPS**: The EPS is implicated in both motor and non-motor functions, including cognition and behaviour. Research into its broader role helps in understanding how motor disorders intersect with psychiatric symptoms or cognitive decline. This knowledge has a profound impact on the treatment and management of complex, multifactorial diseases (Pearce, 2021; Combs, 2024).

Johann Prus' research into the extrapyramidal system is a notable example of research into the extrapyramidal system. These studies frequently used animal models to examine the effects of lesions in particular extrapyramidal structures on motor function. We will be looking in-depth into some of these research works.

JOHANN PRUS' RESEARCH INTO THE EXTRAPYRAMIDAL SYSTEM

The early work of Johann Prus, who first indirectly conceived the term "extrapyramidal" after he found alternative motor pathways outside the pyramidal tracts and showed that damage to the pyramidal tracts alone did not stop epileptic activity, and subsequent studies that examined

the role of the basal ganglia in movement control, particularly in relation to diseases like Parkinson's and Huntington's (Pearce, 2021; Lee and Muzio, 2020).

He concluded that an unidentified centrifugal motor pathway was present. However, the term "extrapyramidal" in its contemporary usage was originally used by Samuel Kinnier Alexander Wilson (1878–1937). To differentiate between the clinical consequences resulting from damage to the conventional pyramidal route and those resulting from injury to the basal nuclear tracts, he coined the term "extrapyramidal."(Pearce, 2021).

RESEARCH INTO THE BASAL GANGLIA

Thomas Willis is usually credited as the first person to describe the structures that we now know as parts of the basal ganglia, such as the striatum, in his work ‘Cerebri Anatome’. Although the term basal ganglia is not used, he was able to describe it as the part of the brain that is responsible for motor and cognitive functions.

The actual term ‘Basal ganglia’ was introduced by Karl Friedrich Burdach, a German anatomist in the early 19th century. He used the term to describe a group of subcortical structures located at the base of the brain.

Later scientists like Luigi Rolando and Pierre Flourens, contributed to understanding the roles of these structures in motor control. In the 20th century, researchers like Cecile and Oscar Vogt expanded knowledge about the basal ganglia’s connections and their role in motor regulation (Pearce, 2021,).

RESEARCH INTO THE CEREBELLUM

Although clinical and experimental observations of cerebellar involvement in nonmotor processes date back approximately two centuries, their significance has just lately come to light (Schmahmann, 2023).

RESEARCH INTO THE SUBSTANTIA NIGRA

The substantia nigra (Latin for “black substance”) was first described in the 18th century due to its distinct dark pigmentation, which results from high levels of neuromelanin in its dopaminergic neurons.

The French anatomist Félix Vicq d’Azyr is credited with discovering the substantia nigra in 1786, noting its distinct pigmentation during his neuroanatomical studies. He made significant contributions to mapping various brain structures, although he did not identify its specific role in movement (Parent and Parent, 2010). The German anatomist Samuel Thomas von Sömmerring is also credited with one of the earliest anatomical descriptions of the substantia nigra. His work contributed to the broader understanding of brain structures, but at the time, the function of this dark region remained unknown.

While James Parkinson first described the symptoms of Parkinson’s disease in 1817 (An Essay on the Shaking Palsy), it was Konstantin Tretiakoff, a Russian neurologist, who in 1919 identified that degeneration of the substantia nigra is the primary cause of Parkinson’s disease. This was later confirmed by Frederic Lewy, who discovered Lewy bodies, a pathological hallmark of the disease (Parent and Parent, 2010; Mandal, 2023).

Contemporary studies continue to explore the substantia nigra’s role in various neurological disorders, particularly Parkinson’s disease. Advancements in neuroimaging techniques, such as neuromelanin-sensitive MRI, have enhanced visualization of this structure, aiding in early diagnosis and monitoring of disease progression. Understanding the history and function of the substantia nigra remains crucial in developing therapeutic strategies for movement disorders and contributes significantly to the field of neuroscience (Sonne *et al.*, 2022).

2.2 CRITICISM OF THE CONCEPT OF THE EXTRAPYRAMIDAL SYSTEM

According to (Lenka and Jankovic, 2024), the term ‘extrapyramidal’ should be retired. They believe that the EPS lacks clinical, anatomical, and physiological definition and that the pyramidal and extrapyramidal systems are not mutually exclusive. In their paper titled ‘Extrapyramidal System/Symptoms/Signs Should Be Retired’, they proposed and I quote ‘that the term is retired from scientific literature and that clinicians use specific phenomenologic descriptors for the various hypokinetc and hyperkinetic movement disorders’.

However, (de Oliveira-Souza and Tovar-Moll, 2012) in their paper ‘The unbearable lightness of the extrapyramidal system’, believe that as long as the extrapyramidal idea is limited to the group of descending fibres that originate in a small number of distinct brainstem tegmental motor nuclei and project to the spinal cord, we can conclude that it is a legitimate and reliable anatomic concept.

The phrase ‘‘extrapyramidal system’’ has historical significance and has offered a helpful framework for comprehending movement regulation, the current disagreement notwithstanding. Even if contemporary studies emphasize the similarities between pyramidal and extrapyramidal pathways, doing away with the name entirely could lead to more misunderstandings rather than clarifications. It could be more balanced to update its definition to reflect current clinical and neuroanatomical information rather than retire it. In the end, it's not only the terminology that counts; it's about making sure that our classifications and descriptions appropriately capture the intricacies of motor control, supporting clinical practice and research.

CHAPTER 3

EXTRAPYRAMIDAL SYSTEM

3.0 OVERVIEW OF THE EXTRAPYRAMIDAL SYSTEM

Recent studies have significantly reevaluated the extrapyramidal system, which has historically been linked to the regulation of motor control and coordination. A more sophisticated approach that takes into account intricate connections among multiple cerebral pathways has replaced a simplified understanding of this system, especially the function of the basal ganglia (BG).

A significant change in our understanding of the striatum's involvement in the extrapyramidal system is highlighted in "Thinking Outside the Box (and Arrow): Current Themes in Striatal Dysfunction in Movement Disorders," by L. Plotkin and A. Goldberg (2019). They point out that the striatum was hazily classified as a component of this system before the 1970s. The direct vs indirect pathway model, which outlines the antagonistic yet complimentary roles of these pathways in controlling movement, was created as a result of further study. This concept, which frames movement disorders as the result of abnormalities within these pathways, has proven fundamental to our understanding of them.

(Mallet *et al.*, 2019) expand on this basis by exploring the complexities of the basal ganglia, especially in relation to Parkinson's disease (PD). The significance of dopaminergic innervation from the substantia nigra and its impact on both motor and non-motor activities are clarified by them. In addition to motor symptoms, their findings suggest that dopaminergic neurone loss triggers more extensive molecular and synaptic dysfunctions. Furthermore, by providing proof of their coordinated action, they cast doubt on the direct and indirect paths' binary perspective, highlighting the intricacy of BG functions.

By examining the connections between the cortico-basal ganglia and cerebellar network,

(Milardi *et al.*, 2019) broaden the scope of the extrapyramidal system. They contend that the conventional view of these areas as separate entities is inadequate since new research points to a more complex interaction between the cerebellum, basal ganglia, and cerebral cortex. Their review suggests that movement disorders could result from disturbances in this intricate motor and non-motor system, underscoring the need for sophisticated experimental methods to disentangle the anatomical and functional links within this network.

Collectively, these studies show how our understanding of the extrapyramidal system has undergone a dramatic change from a basic model to a comprehensive framework that acknowledges the complexity of neuronal interactions and the multidimensionality of movement disorders.

3.1 FUNCTIONAL ROLES OF THE EXTRAPYRAMIDAL SYSTEM

1. Involuntary motor control: The EPS plays a crucial role in managing involuntary motor activities, such as reflexes, maintaining posture and automatic movements (Lee and Muzio, 2020). The EPS acts below the conscious level, allowing us to stand, walk, and move efficiently. It operates through pathways like the reticulospinal and vestibulospinal tracts, which originate in the brainstem and project to the spinal cord, influencing motor neurons that control involuntary actions. These pathways help maintain muscle tone and posture without conscious effort. For instance, the reticulospinal tract modulates reflexive responses to maintain balance and posture (Mangold and Das, 2023). Damage to components of the EPS can lead to disorders characterized by involuntary movements, such as tremors or rigidity, highlighting its role in involuntary motor control

2. Regulation of muscle tone, posture and balance: The continual, passive partial contraction of muscles is known as muscle tone, and it is regulated by the EPS (Lee and Muzio, 2020). It guarantees that muscles are prepared for action and capable of preserving balance and posture. Information from the vestibular system is transmitted to the spinal cord via the vestibulospinal tract, a part of the EPS, which enables muscle tone modifications for posture and balance maintenance (Casale *et al.*, 2018). Furthermore, the reticulospinal tract affects muscle tone by regulating motor neurone activity, which helps maintain balance and posture across a variety of activities. These pathways are crucial for these processes because disruptions in them can cause abnormal muscle tone and postural instability (Mangold and Das, 2023).

3. Coordination of complex movement: By working closely with the pyramidal system, the EPS refines motions to provide fluid, well-coordinated activities. This collaboration is necessary for tasks requiring accuracy, like writing or sports. The EPS combines impulses from several parts of the brain, such as the cerebellum and basal ganglia, thereby helping to coordinate intricate movements (Singh, 2020).

   By affecting motor neurones in the spinal cord, the rubrospinal tract, which is a component of the EPS, contributes to fine motor control, especially of the upper limbs. The EPS facilitates coordinated and fluid movements by modifying the timing and force of muscle contractions through its connections. Its importance in movement coordination is demonstrated by the fact that disturbances in EPS function can result in movement disorders marked by jerky or disorganised movements (Mangold and Das, 2023).

4. Role in motor learning: EPS function is firmly ingrained with motor habits and procedural memory, such as walking, typing or riding a bike. Over time, the EPS adjusts and strengthens repetitive motions, enabling us to complete tasks with ease. Gaining and honing new motor skills by experience and practice is known as motor learning. This mechanism depends on the EPS, especially the basal ganglia. It facilitates learning new motions by aiding in the selection and reinforcement of motor patterns that produce favourable results. The EPS promotes movement adaptation and optimisation by interacting with the motor cortex and cerebellum to modify motor outputs in response to feedback. Research has demonstrated that EPS dysfunction can impede motor learning, as evidenced by Parkinson's disease patients' difficulties picking up new motor skills (Bear *et al*., 2020; Lee and Muzio, 2020).

5. Role in habit formation: By preserving learnt motor patterns, this system helps create habitual movements, such as the automaticity observed in tasks like walking or typing. Automatic actions carried out with little conscious thought are called habits, and they are formed through repetition. Habit formation and maintenance depend heavily on the EPS, particularly the basal ganglia. It contains motor skills that can be performed automatically without conscious planning once they are learnt. Because of its effectiveness, the brain can assign repetitive duties to the EPS, freeing up cognitive resources for other pursuits. Disturbances in the EPS have been shown to impact habit formation, making it more difficult to form or repress ingrained behaviours (Singh, 2020; ten Donkelaar, 2011; Błaszczyk *et al.*, 2024).

6. Coordination of reflexes: To make sure reflexive motor responses are appropriate for the situation and do not obstruct voluntary motions, the EPS adjusts them. The EPS

modifies the sensitivity and strength of reflexes by influencing spinal reflex arcs through routes such as the reticulospinal tract. This modulation contributes to fluid and adaptable movements by enabling the integration of reflexive and voluntary motions. For instance, in order to keep specific reflexes from interfering with the intended action during voluntary movements, the EPS can suppress them. The EPS plays a crucial function in reflex coordination; damage to it can cause excessive reflexes or the inability to control reflexive responses (Bear *et al*., 2020; Young *et al*., 2023).

7. Inhibition of unwanted movements: The EPS is in charge of preventing undesired or involuntary motions, guaranteeing that motor actions are controlled and intentional. By blocking motor programs unrelated to the desired action, it accomplishes this. This inhibitory regulation is mostly dependent on the indirect pathway of the basal ganglia, which is a component of the EPS. Hyperkinetic disorders, which are typified by excessive and uncontrollable movements, like chorea or tics, can result from dysfunction in this system, highlighting the significance of the EPS in movement inhibition (Young *et al*., 2023; Chen *et al*., 2020).

8. Modulation of motor neuron activity: Both voluntary and involuntary movements are influenced by the EPS's modulation of motor neurone activity in the spinal cord. The EPS regulates muscle tone and reflex responsiveness by modifying the excitability of motor neurones via descending routes such as the vestibulospinal and reticulospinal tracts. Motor outputs are suitably scaled and adjusted to the requirements of the task or environment thanks to this modulation (Bear *et al*., 2020).

3.2 PATHWAYS AND CIRCUITS OF THE EXTRAPYRAMIDAL SYSTEM

The EPS is polysynaptic in nature and includes several tracts including the reticulospinal, vestibulospinal, rubrospinal, and tectospinal tracts (Lee and Muzio, 2020).

1. THE RETICULOSPINAL TRACT

Just like the name implies, this tract originates in the reticular formation and terminates in the spinal cord connecting the two to each other. This tract is further divided in 2 tracts: the medial (pontine) reticulospinal tract and the lateral (medullary) reticulospinal tract. The medial (pontine) reticulospinal tract projects downwards from the pontine reticular formation on the same side (ipsilaterally) and terminates in the ventromedial spinal cord (ventral funiculus), synapsing with the alpha and gamma neurons present there. The alpha and gamma motor neurones found in this area of the spinal cord innervate the trunk and upper limb extensors. However, by forming synapses with the alpha motor neurones that innervate these muscles, the activity of the medial (pontine) reticulospinal tract fine-tunes their voluntary motions.

Additionally, it affects their reflexes and muscle tone by regulating the gamma motor neurones. The lateral (medullary) reticulospinal tract projects downwards from the medullary reticular formation with some of its fibres decussating and projecting downward on the opposite side from which it originated (contralaterally) and terminating in the ventral funiculus and ventral portion of the lateral funiculus. It synapses with the internerons located here. Note that the interneurons oppose the actions of the alpha and gamma neurons, therefore this tract innervate the trunk and upper limbs flexors (Mangold and Das, 2023).

Through its actions on extension and flexion of muscles, the reticulospinal tract has effect on locomotion, posture, muscle tone. It is involved in complex movements like grasping and manipulation of objects. This tract also affects reflexes.

Damage to the reticulospinal tract will lead to postural instability and ataxia (Mangold and Das, 2023).

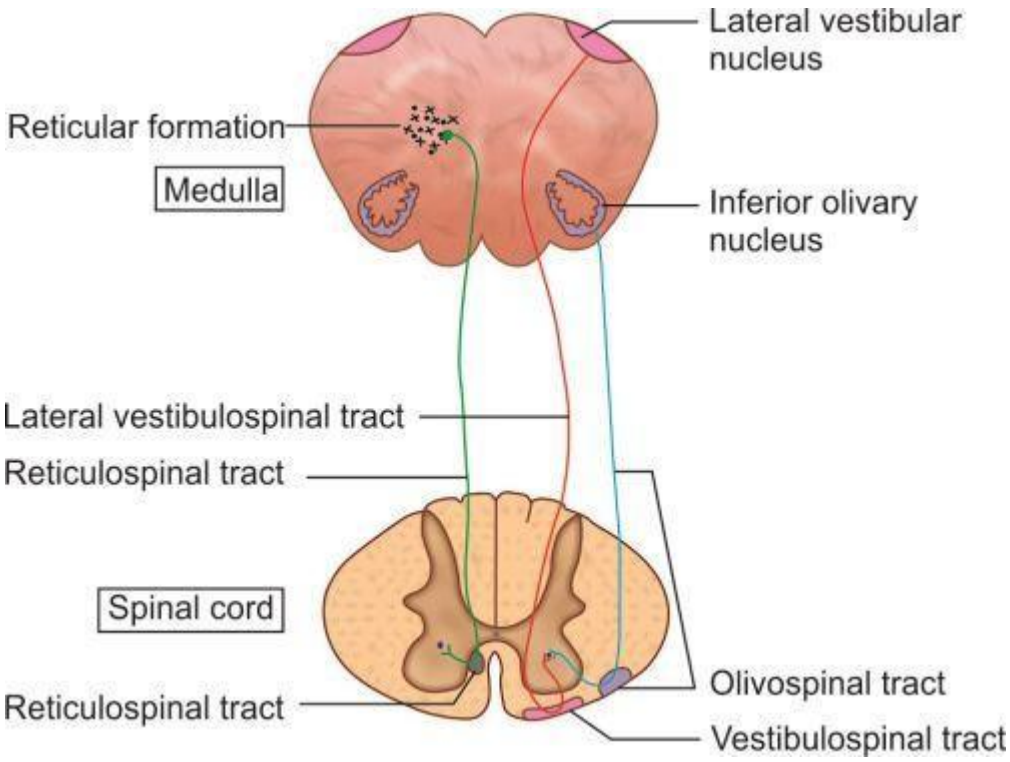


Fig 3.1: Diagram showing the reticulospinal and vestibulospinal tracts (Seshayyan, 2016).

2. THE VESTIBULOSPINAL TRACT

As indicated by the name, this tract originates in the vestibular nuclei and terminates in the spinal cord thereby connecting the two to each other. The vestibular nuclei receive input from the vestibular apparatus of the inner ear. The vestibulospinal tract further divides into 2 tracts: the medial vestibulospinal tract that originates in the medial vestibular nuclei and the lateral vestibulospinal tract that originates in the lateral vestibular nuclei (Boyle, 2025).

The vestibular nuclei play an important role in proprioception and equilibrium. The sense of orientation and acceleration of the head in any direction, along with the corresponding adjustment in eye movement and posture, are among these functions. The vestibulospinal tract is responsible for the latter (Casale *et al.*, 2018).

The function of this tract is to maintain posture and balance especially while we prepare for movement. This tract also helps stabilize the head during movement (Tanaka *et al.*, 2021).

3. THE RUBROSPINAL TRACT

This tract originates in the red nucleus and terminates in the spinal cord. Its fibres decussate and then projects downwards on the contralateral side from where it originates. This tract functions in maintaining muscle tone of muscles and impacts rudimentary motor skills including grasping, especially in babies. While its role in adult humans is not prominent, damage to this tract can still affect movement and fine motor skills (Vadhan and Das, 2023).

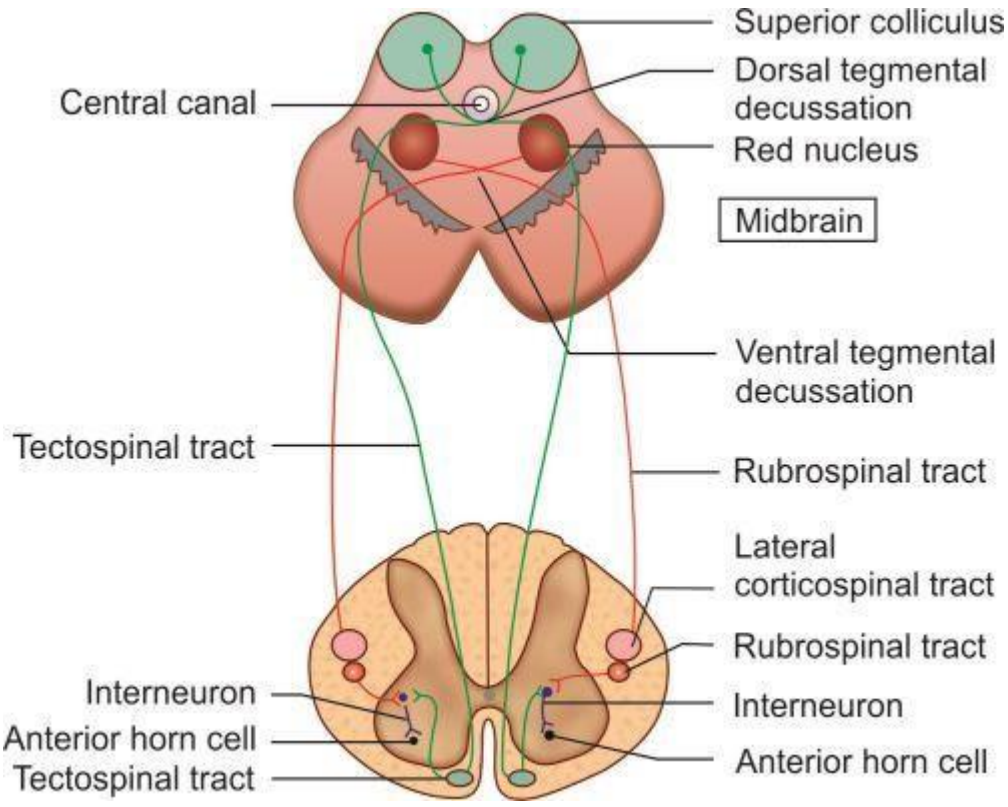


Fig 3.2: Diagram showing the Rubrospinal and Tectospinal tracts (Seshayyan, 2016).

4. THE TECTOSPINAL TRACT

This tract runs from the tectum to the spinal cord. It descends to the cervical and upper thoracic region of the spinal cord and terminate in the contralateral anterior grey horn.

It originates in the superior colliculus in the midbrain and this area is involved in visual and audio stimuli. Therefore, it is involved in orienting the eyes and the head towards sounds and this is typically triggered by abrupt loud noises, motions, or bright lights that enter the field of vision. This tract serves as a link between visual and auditory stimuli and muscle movement (Reynolds and Al Khalili, 2019). We can also say that the tectospinal tract is involved in reflex because in a situation where one hears a sudden sound the tectospinal tract is responsible for the knee jerk reaction of turning you head towards the sound. Damage to the tectospinal tract leads to difficulty coordinating head and eye movement in response to audio and visual stimuli (Reynolds and Al Khalili, 2019).

3.2 NEUROTRANSMITTERS INVOLVED IN THE EXTRAPYRAMIDAL SYSTEM

1. DOPAMINE

The dopaminergic neurones in the substantia nigra are responsible for producing dopamine. Other areas of the brain like the hypothalamus and the ventral tegmental area also produce it. Dopamine is necessary for controlling movement (Latif *et al.*, 2021). It preserves fluid motor control by regulating excitatory and inhibitory impulses in the basal ganglia. The main receptors for dopamine in the basal ganglia are the D1 and D2 receptors which have excitatory and inhibitory effects respectively (Young *et al.*, 2023). Motor planning and the start of movement are significantly influenced by the nigrostriatal pathway, which carries dopamine from the substantia nigra to the striatum (Blaess *et al.*, 2020). Parkinson's disease is caused by degeneration of the dopaminergic neurons that produce dopamine and its symptoms manifest as bradykinesia, tremor, rigidity and impaired posture control (Meder *et al.*, 2019).

2. GABA (Gamma-Aminobutyric Acid)

The extrapyramidal system, especially the basal ganglia, depends heavily on GABA, the main inhibitory neurotransmitter in the central nervous system. The EPS's nuclei contain high levels of GABA and glutamic acid decarboxylase, the enzyme that synthesises it, suggesting that it plays a crucial role in motor regulation. The major GABA receptors in the basal ganglia are GABA-A receptors (inhibitory receptor) and GABA-B receptors (metobotropic receptors) (Chen and Sharma, 2025). The striatonigral pathway, which is crucial for controlling motor activity, is formed by GABAergic neurones, particularly those in the striatum, projecting to the substantia nigra. A number of movement diseases are linked to GABAergic neurone dysfunction in the EPS. For example, Huntington's chorea is characterised by involuntary movements that are caused by a loss of both GABA neurones and GABA receptors in the striatum. Therefore, the EPS's GABA inhibitory function is essential for preserving motor control and preventing excessive or unwanted movements (Bear *et al*., 2020; Fibiger, 2015).

3. GLUTAMATE

Glutamate is the main excitatory neurotransmitter in the central nervous system, it modulates motor control and is essential to the extrapyramidal system (EPS). Glutamatergic pathways within the basal ganglia, a central part of the EPS, are essential for motor planning and execution. Glutamate is released onto striatal neurones by corticostriatal projections, affecting both direct and indirect pathways that control the initiation and inhibition of movement. Movement disorders like tardive dyskinesia, which is characterised by repeated, involuntary movements, might result from disruptions in glutamatergic signalling within the EPS. As a result, maintaining balanced glutamatergic activity is crucial for both preventing

extrapyramidal symptoms and ensuring appropriate motor performance (Fedorenko *et al.*, 2022; Bear *et al*., 2020)

4. ACETYLCHOLINE

Acetylcholine (ACh) is an important neurotransmitter in the central nervous system, regulating the extrapyramidal system (EPS), especially in the basal ganglia. Cholinergic interneurons in the striatum, a significant part of the EPS, release ACh, which interacts with other neurotransmitter systems to affect motor function. ACh is essential for maintaining focus, improving alertness after waking up, and supporting memory and learning. Movement disorders can result from disturbances in the striatal balance between dopamine and ACh, which is necessary for healthy motor function. For example, in Parkinson's disease, a relative increase in cholinergic activity due to decreasing dopamine levels causes motor symptoms including rigidity and tremors. Anticholinergic drugs are therefore occasionally employed to re-establish the equilibrium between ACh and dopamine, thereby alleviating these symptoms (D'Souza and Hooten, 2018; Lenka and Jankovic, 2024; Pearce, 2021).

CHAPTER 4

PATHOPHYSIOLOGY

4.0 EXTRAPYRAMIDAL DISORDERS

Extrapyramidal disorders or extrapyramidal symptoms are movement disorders involving dysfunction of the extrapyramidal system.

Clinically, one or more of the following symptoms can be found in extrapyramidal disorders:

1. Unusual involuntary motions
2. Alterations in skeletal muscle tone accompanied by a rise or fall in passive motion resistance
3. Poverty or excess of movement
4. Modification of automatic movements. (Pearce, 2021)

Some of the most common extrapyramidal disorders include:

1. Parkinson’s disease
2. Huntington’s disease
3. Tardive dyskinesia (Lee and Muzio, 2020)

1. PARKINSON’S DISEASE

Parkinson's disease is a common neurologic condition that progresses over time and is characterised by bradykinesia, stiffness and rest tremor (Bloem *et al.*, 2021; Hayes, 2019). It is caused by degeneration of the dopaminergic nerve cells that produce dopamine leading to an inability to produce it (Meder *et al.*, 2019). Dopamine is necessary for controlling movement and its loss causes movement dysfunction hence, Parkinson’s diseases’ characteristic symptoms

(Latif *et al.*, 2021). Walking, writing, speaking, and carrying out other daily duties might all be severely hampered by these motor symptoms (NNlo, 2022).

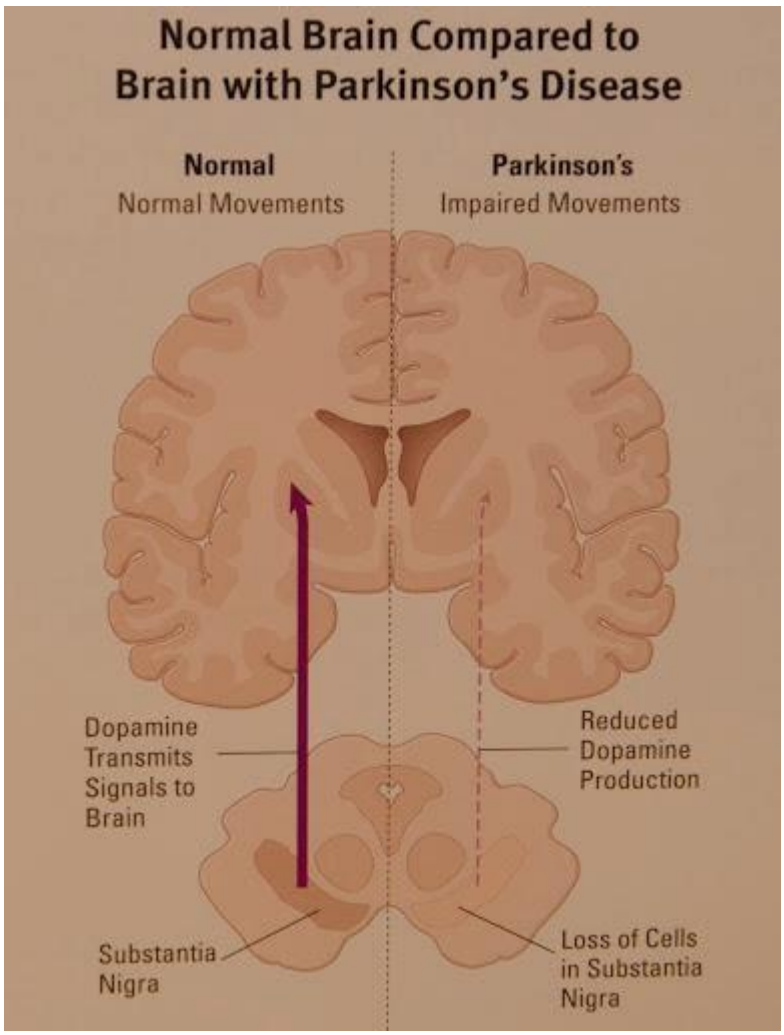


Fig 4.1: Image showing a comparison between a normal brain and a brain of a person with Parkinson's disease (Alvarez, 2022).

While Parkinson's disease does not have a cure yet, it can be managed using medication that stimulate the remaining dopaminergic neurons in the substantial nigra to produce more dopamine (dopamine agonists) or medication that inhibits acetylcholine since it contributes to the symptoms of tremor and muscle rigidity (anticholinergic medication) and therefore alleviate the symptoms (Hayes, 2019; NNlo, 2022).

2. HUNTINGTON'S DISEASE

Huntington's disease is a neurodegenerative disease caused by a mutation in the HTT gene, leading to an abnormal protein that damages neurons, particularly in the striatum of the basal ganglia, a key component of the extrapyramidal system. It has motor, cognitive and psychiatric effect and its motor system symptoms include motor incoordination, motor impersistence, chorea, and dystonia (Barron *et al.*, 2021). Eating, dressing, and walking can become difficult due to these motor symptoms, which can seriously hinder daily activities.

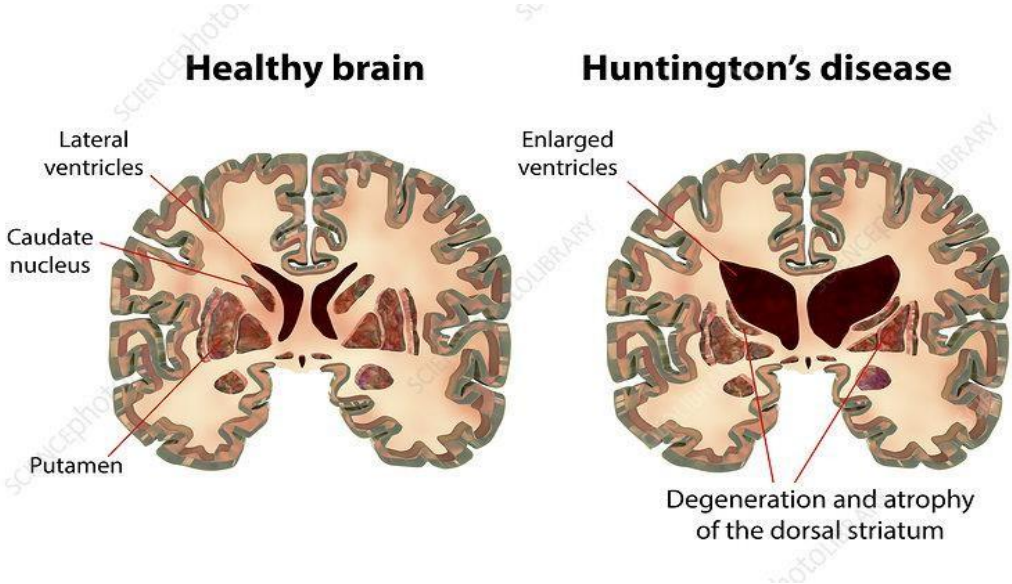


Fig 4.2: Illustration comparing coronal sections of a healthy brain and a brain in Huntington's disease. The brain in Huntington's disease shows enlarged anterior horns of the lateral ventricles, degeneration and atrophy of the dorsal striatum. (Kateryna Kon, 2022).

While Huntington's disease does not have a cure, its symptoms can be managed using drugs like vesicular monoamine transporter 2 (VMAT2) inhibitors: tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) to manage to motor symptoms (Tan *et al.*, 2025). Since it is a genetic disorder, the gene can be targeted by therapies targeting RNA include antisense oligonucleotides (ASOs), RNAi and small molecules, while those targeting

DNA include zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and CRISPR-Cas9 (Barron *et al.*, 2021; Tabrizi *et al.*, 2019).

3. TARDIVE DYSKINESIA

Tardive dyskinesia (TD) is a movement disease marked by recurrent, involuntary motions usually affecting the face and mouth. It is an adverse reaction to long-term usage of some drugs, especially antipsychotics. It has been proposed that TD may occur as a result of dopamine hypersensitivity, damaged gamma-aminobutyric acidergic neurones, and/or increased reactive oxygen species generation (Takeuchi *et al.*, 2022). The dopamine hypersensitivity may lead to an overactivity of dopamine signalling in the extrapyramidal system, resulting in the involuntary movements characteristic of tardive dyskinesia (Chokhawala and Stevens, 2023). Long-term use of antipsychotics can occasionally cause structural alterations in the brain, especially in the basal ganglia, which are an important part of the extrapyramidal system. These modifications could potentially exacerbate tardive dyskinesia (Voineskos *et al.*, 2019). The main line of action in treating tardive dyskinesia is to stop the administration of antipsychotics or at least using the lowest dose of antipsychotic drugs available (Takeuchi *et al.*, 2022).

Fig 4.3: Image showing the symptoms and risk factors of Tardive Dyskinesia (Liang, 2024).

4.1 EXTRAPYRAMIDAL SIDE EFFECTS

Drug-induced movement abnormalities, often known as extrapyramidal side effects (EPS), are among the most frequent negative pharmacological effects that patients encounter when using dopamine-receptor blocking medications (D'souza and Hooten, 2018).

In her paper, A Clinical Case Report on Extrapyramidal Symptom, (Gawai, 2020) wrote, 'Extrapyramidal signs are side effects of antipsychotic medications when the patient is receiving Schizophrenia treatment. Such signs include dystonia (continuous spasms and muscle contractions), akathisia (may manifest as muscular restlessness), Parkinsonism (characteristic signs such as stiffness), bradykinesia (slow motion), tremor, and intermittent dyskinesia (irregular, jerky motion)'.

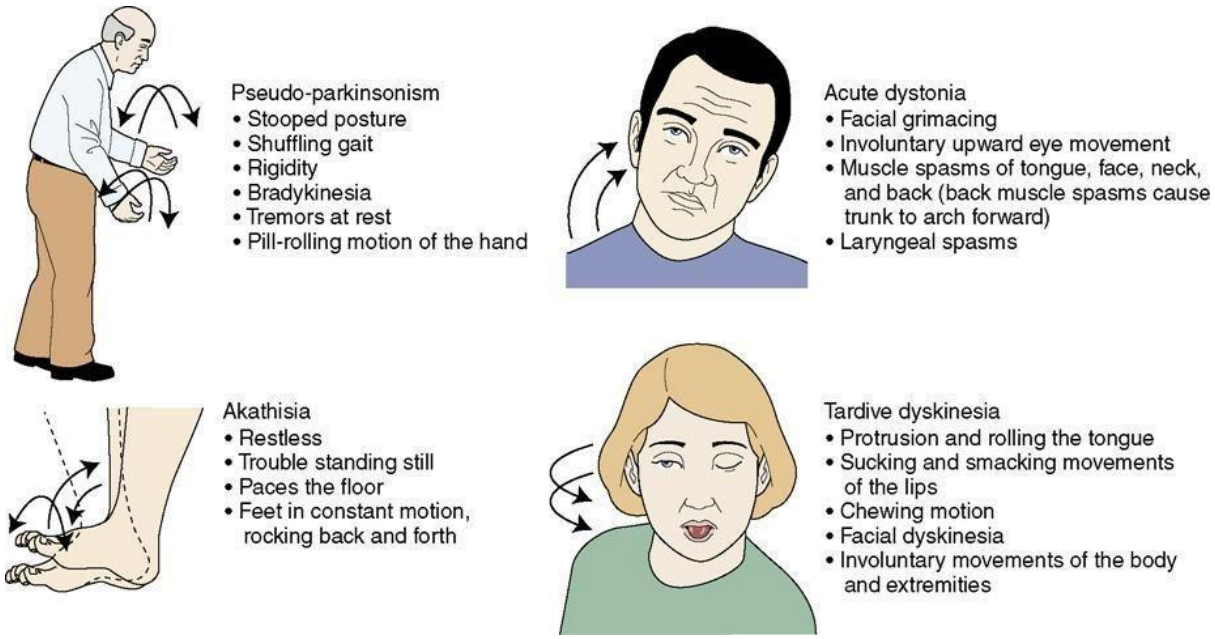


Fig 4.4: Image showing the symptoms of some extrapyramidal side effects (Nursekey, 2017).

The antipsychotics or dopamine-receptor blocking medication block dopamine receptors in the brain, which can disrupt the delicate balance of neurotransmitters in the extrapyramidal system.

Some common extrapyramidal side effects include:

1. Dystonia: Dystonia is a movement disorder marked by sporadic or prolonged muscle spasms that result in aberrant postures, movements, or both (Albanese *et al.*, 2019). Dystonia can affect any part of the body, but it is most common in the neck, face, and tongue.
2. Akathisia: Akathisia is an adverse medication effect described as an unpleasant feeling of restlessness and an inability to stay still (Scahill, 2021).
3. Bradykinesia: Bradykinesia refers to a slow pace of movement. Both voluntary and spontaneous/automatic movements are frequently referred to by this term, which is still used interchangeably to denote low amplitude movement (hypokinesia) or no movement (akinesia) (Bologna *et al.*, 2023).

4. Tremor: (Louis, 2019) defines tremor as “an involuntary movement that is rhythmic (i.e. regularly recurrent) and oscillatory (i.e. rotating around a central plane) and may manifest in a variety of ways”
5. Dyskinesia: Dyskinesias are characterised by writhing, unpredictable, and uncontrollable movements of the arms, legs, face, or trunk. In addition to being fluid and dance-like, they can also result in gradual, prolonged muscle spasms or quick jerking.
6. Parkinsonism: This refers to symptoms that mimic Parkinson's disease, such as tremor, rigidity, and bradykinesia (slow movement) (Hayes, 2019)

4.2 DIAGNOSTIC APPROACHES TO EXTRAPYRAMIDAL DISORDERS

Diagnosis of extrapyramidal system dysfunction involves medical history reviews, physical exams, neurological tests, and imaging studies. Imaging and laboratory tests are typically not necessary. An accurate history and physical examination, particularly mentioning a history of medication exposure, clearly show the diagnosis (D’souza and Hooten, 2018).

Since EPS disorders affect movement, neurological tests focus on evaluating motor skills, coordination, and involuntary movements. As demonstrated by James Parkinson's identification of three of his original six cases while passing by on the street, a patient's facies (overall appearance), station and gait may instantly trigger suspicion of a movement problem. Disorders of involuntary movement, including chorea, tremor, or myoclonus, may also be noticeable right away (Larner *et al.*, 2021). There can also be motor skills tests like finger tapping where the patient is asked to tap their finger and thumb together repeatedly (slowness and decreased dexterity can indicate Parkinsonism) and rapid alternating movement tests where the patient can be instructed to tap their feet, quickly pronate and supinate their hands, or engage

in other alternate motions. Improved neuroimaging techniques, such as MRI and PET scans provide high-resolution views of EPS structures. These techniques provide detailed images of EPS structures, allowing us to detect subtle changes that may indicate early stages of neurodegenerative diseases like Parkinson's or Huntington's disease, even before significant symptoms appear. This enables earlier diagnosis and intervention, potentially slowing down disease progression (Saeed, 2020; Pitton, Rissardo and Caprara, 2023). Neuroimaging also allows us to track changes in EPS structures over time, providing valuable information about how the disease is progressing and how well the treatment is working. This helps in adjusting treatment plans and predicting long-term outcomes. By visualizing specific areas of damage or dysfunction within the EPS, we can tailor treatment strategies to the individual patient's needs. For example, deep brain stimulation (DBS) targets specific brain regions involved in movement control, and neuroimaging helps guide the precise placement of electrodes for optimal outcomes (Chang *et al.*, 2024).

In evaluating EPS function, electrophysiological methods such as EMG and EEG are also essential:

Electromyography measures the electrical activity of muscles and aids in locating anomalies in the patterns of muscle activation that could be a factor in movement disorders. It can be helpful in the diagnosis of tremors and other movement-related conditions (Prell and Skinner, 2022).

Electrodes are applied to the scalp in electroencephalography (EEG) to measure electrical activity in the brain. EEG can identify aberrant brainwave patterns linked to specific movement disorders, even though it cannot directly image EPS structures (Zhang, 2023).

4.3 THERAPEUTIC APPROACHES TO EXTRAPYRAMIDAL DISORDERS

Extrapyramidal disorders can be treated using a range of methods that includes medication, surgical intervention, non-pharmacological therapies and emerging therapies like gene therapy and stem cell therapy.

Medication for extrapyramidal disorders are of different forms. We have dopamine-related drugs like Levodopa, dopamine agonists, COMT inhibitors and MAO-B inhibitors. There are also anticholinergic medications to help reduce tremor and rigidity (Höglinger and Trenkwalder, 2024).

Surgical intervention typically involves Deep brain stimulation (DBS) which is a surgical procedure where a device is implanted to deliver electrical stimulation to specific brain regions involved in movement control. DBS is commonly used to treat Parkinson's disease, essential tremor, and dystonia (Senevirathne *et al.*, 2023; Lee and Yankee, 2021).

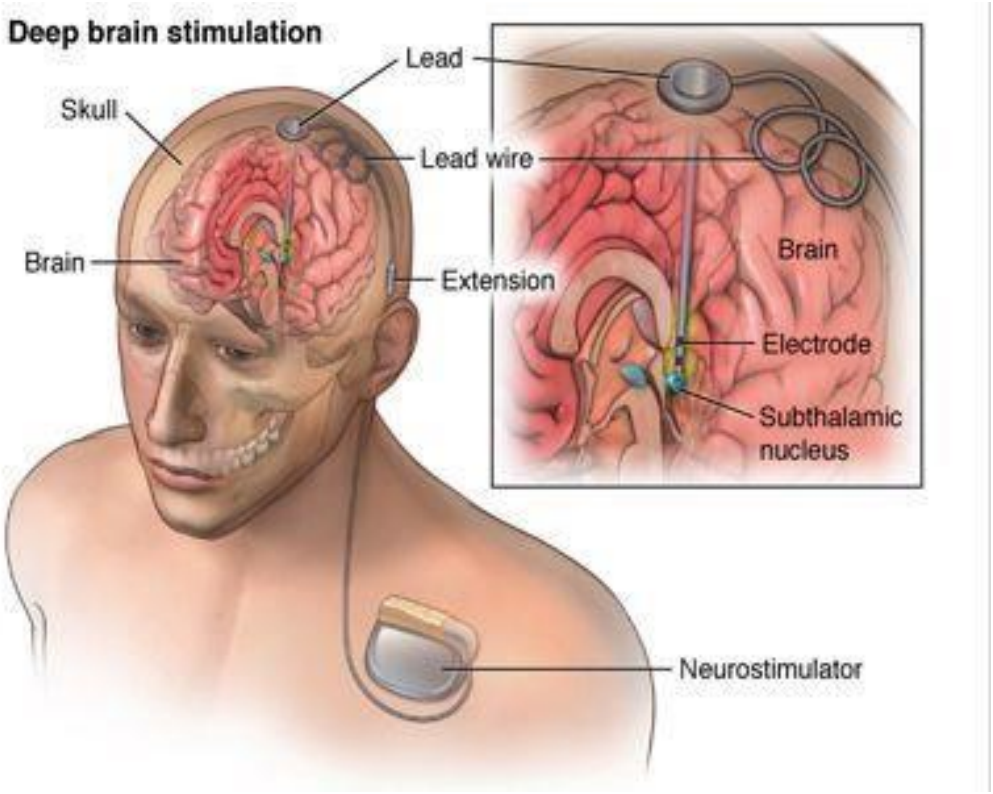


Fig 4.5: Deep Brain Stimulation (DBS) (Nordi *et al.*, 2022).

Non-pharmacological therapies include physical therapy, speech therapy, occupational therapy, cognitive-behavioural therapy and support groups (Zhang *et al.*, 2020; Lee and Yankee, 2021).

Lastly, emerging therapies like gene therapy to correct faulty genes responsible for some EPS disorders, like Huntington's disease and stem cell therapy which holds promise for regenerating

damaged brain cells in neurodegenerative conditions like Parkinson's disease are believed to be the future of extrapyramidal system disorder therapy (Barron *et al.*, 2021; Tabrizi *et al.*, 2019; Morizane, 2023; Rahimi *et al.*, 2024).

CHAPTER 5

SUMMARY AND CONCLUSION

5.0 Summary and conclusion

The extrapyramidal system (EPS) is a vital component of the central nervous system responsible for involuntary motor control, muscle tone regulation, posture, balance, and movement coordination. Unlike the pyramidal system, which directly controls voluntary movements, the EPS functions through a complex network of subcortical structures including the basal ganglia, cerebellum, thalamus, substantia nigra, and various brainstem nuclei. Historically, the EPS was differentiated from the pyramidal system due to its role in refining and modulating movement rather than directly executing it. Early research by figures like Johann Prus and Samuel Wilson helped establish the concept of the EPS, although modern studies suggest a more integrated motor control network involving both systems (Lee and Muzio, 2020).

The anatomical components of the EPS, particularly the basal ganglia, play a crucial role in motor control through three key pathways: the direct, indirect, and hyperdirect pathways. These pathways either facilitate, inhibit, or rapidly suppress movement, ensuring smooth and precise motor execution. The system also operates through major tracts, including the reticulospinal, vestibulospinal, rubrospinal, and tectospinal pathways, each contributing to specific aspects of movement regulation. The EPS also relies on key neurotransmitters such as dopamine, GABA, glutamate, and acetylcholine, which modulate motor activity and contribute to habit formation, reflex control, and motor learning (Konstantopoulos and Giakoumettis, 2023; Lee and Muzio, 2020).

Dysfunction in the EPS results in serious movement disorders, including Parkinson’s disease, Huntington’s disease, and tardive dyskinesia, all of which significantly impair daily activities.

Parkinson’s disease arises from dopaminergic neuron degeneration, leading to tremors, rigidity, and slowed movement, while Huntington’s disease is a genetic disorder that progressively damages the basal ganglia. Tardive dyskinesia, often a side effect of long-term antipsychotic use, results from dopamine receptor hypersensitivity. Diagnosing these conditions requires neurological assessments, imaging techniques like MRI and PET scans, and electrophysiological tests (EMG, EEG). Treatments range from medications (dopamine agonists, VMAT2 inhibitors) to advanced therapies like deep brain stimulation (DBS), gene therapy, and stem cell research. Despite ongoing advancements, further research is necessary to fully understand the interactions between the EPS and pyramidal system, refine therapeutic interventions, and develop more effective treatments for movement disorders (Lee and Muzio, 2020; Lee and Yankee, 2021; D’souza and Hooten, 2018).

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