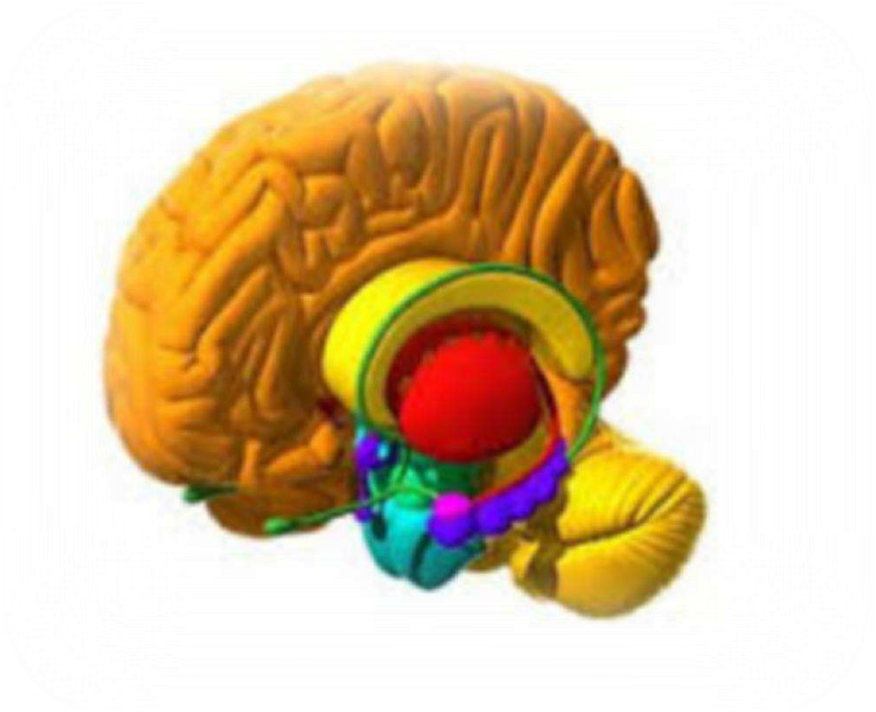
NEUROPSYCHIATRIC RELEVANCE OF BASAL GANGLIA



OVERVIEW

- HISTORICAL HIGHLIGHTS
- ANATOMY- STRUCTURAL AND FUNCTIONAL ANATOMY OF BASAL GANGLIA AND INDIVIDUAL STRUCTURES
- PHYSIOLOGY OF BASAL GANGLIA- AFFERENT CONNECTIONS, INTERNAL PROCESSING AND OUTPUT
- FUNCTIONS OF BASAL GANGLIA
- ROLE OF BASAL GANGLIA IN PSYCHIATRIC DISORDERS
- NEUROPSYCHIATRIC MANIFESTATIONS OF BASAL GANGLIA DISORDERS

HISTORICAL HIGHLIGHTS

- 1664- first clear identification of distinct subcortical structures was published by the English anatomist THOMAS WILLIS.
- CECILE & OSKAR VOGT coined the term “corpus striatum”.
- CAJAL AND SAMUEL WILSON gave detailed anatomical descriptions of corpus striatum
- VON SOMMERING described the Substantia nigra.
- JULES BERNARD LUYS described the Subthalamic nucleus.
- 1950’S- Pallidotomy for treatment of Parkinson’s Disease
- 1968- Advent of Levodopa

STRUCTURAL ANATOMY

- Large grey masses situated within white core of each cerebral hemisphere subcortically in telencephalon, diencephalon and midbrain

- Basal- most elements in basal part of brain
- Ganglia- misnomer
- Basal ganglia now recognized as basal nuclei

- Anatomically the term ‘basal ganglia’ includes:
- Corpus striatum
- Claustrum
- Amygdaloid body

CORPUS- BODY
+
STRIATUM- STRIPED

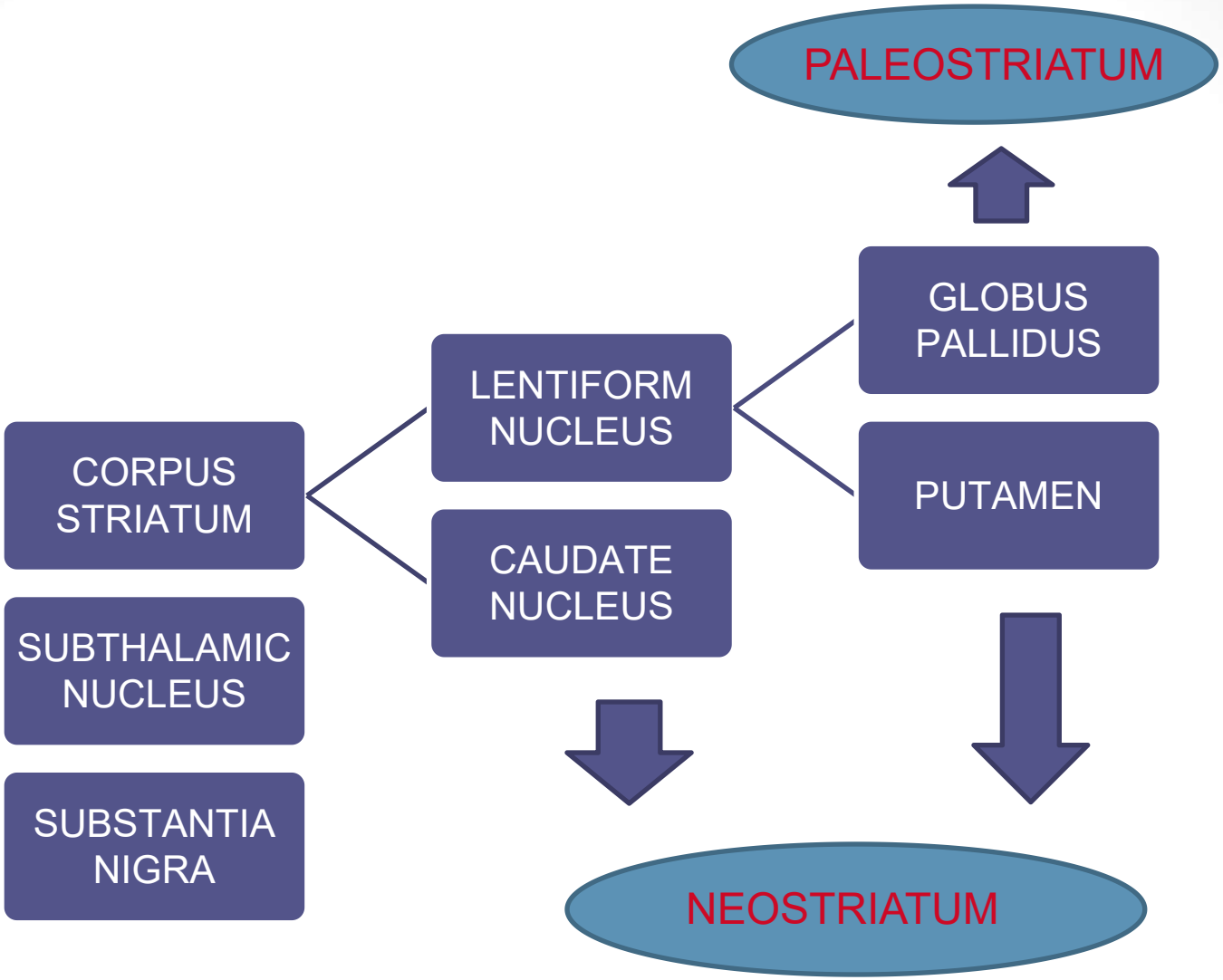
FUNCTIONAL ANATOMY

- Functionally basal nuclei include:

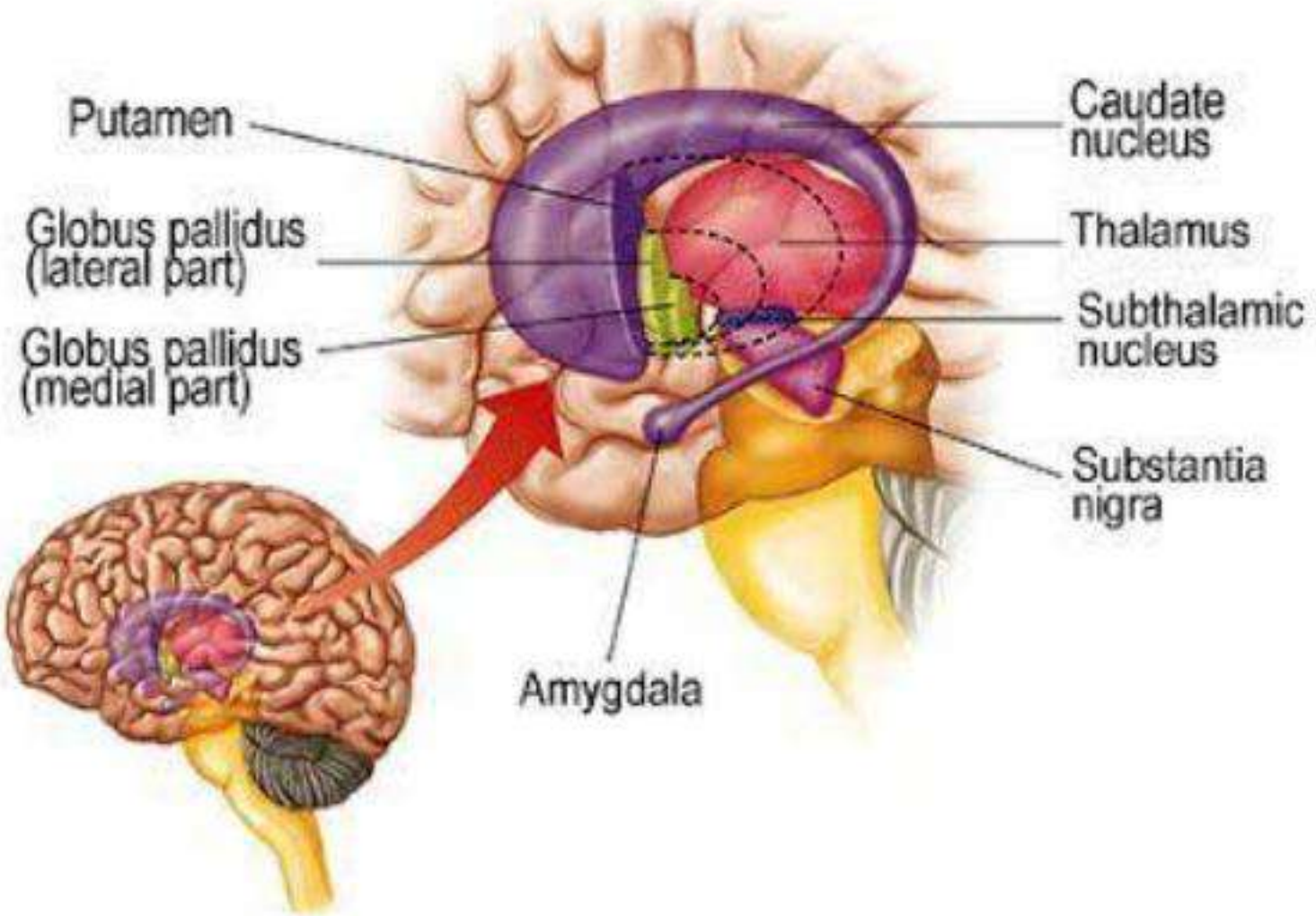
1. Corpus striatum
2. Substantia nigra
3. Subthalamic nuclei

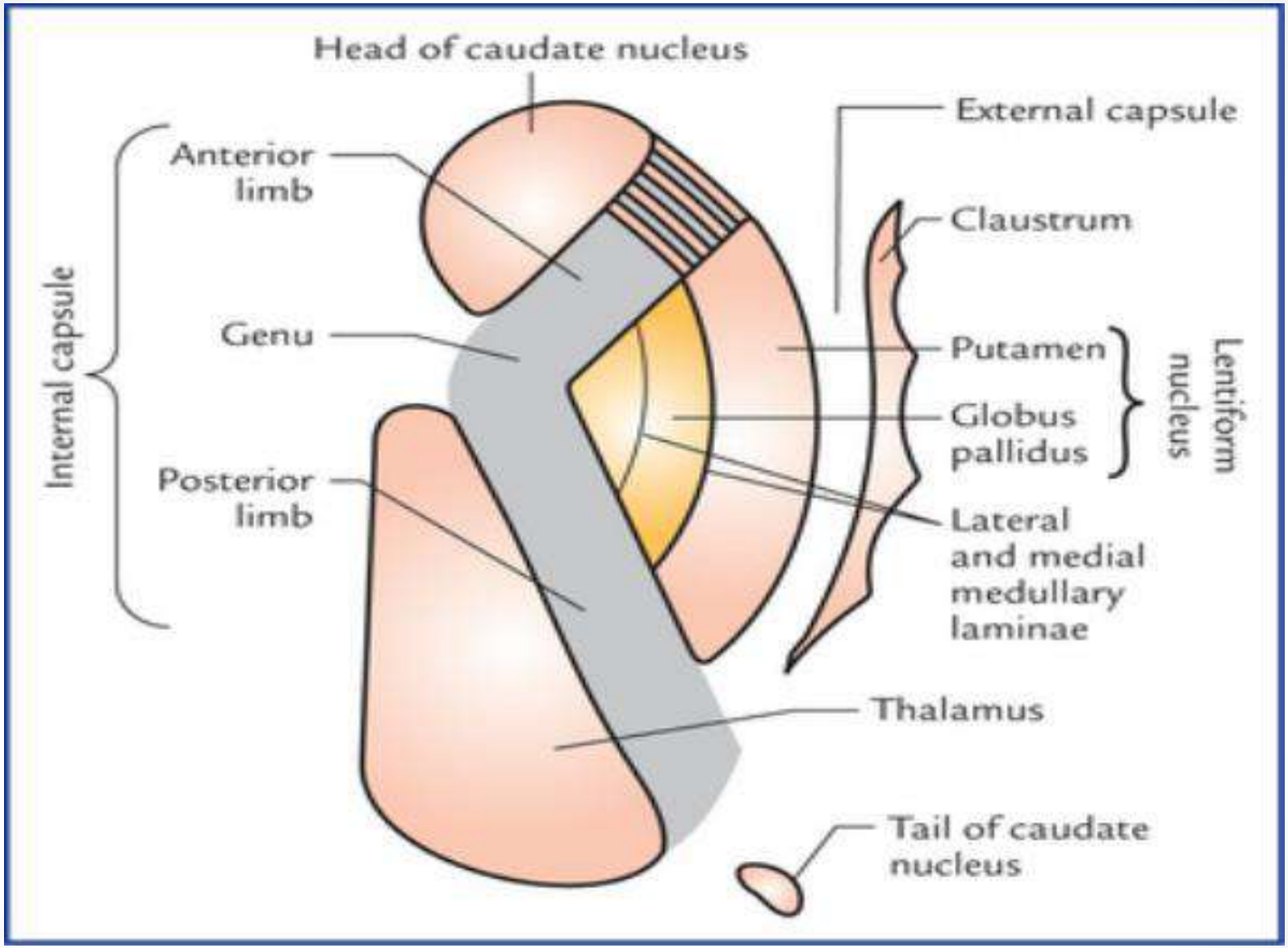
- Controversial inclusion of:

4. Ventral striatum (nucleus accumbens)
5. Ventral pallidum (substantia inominata)

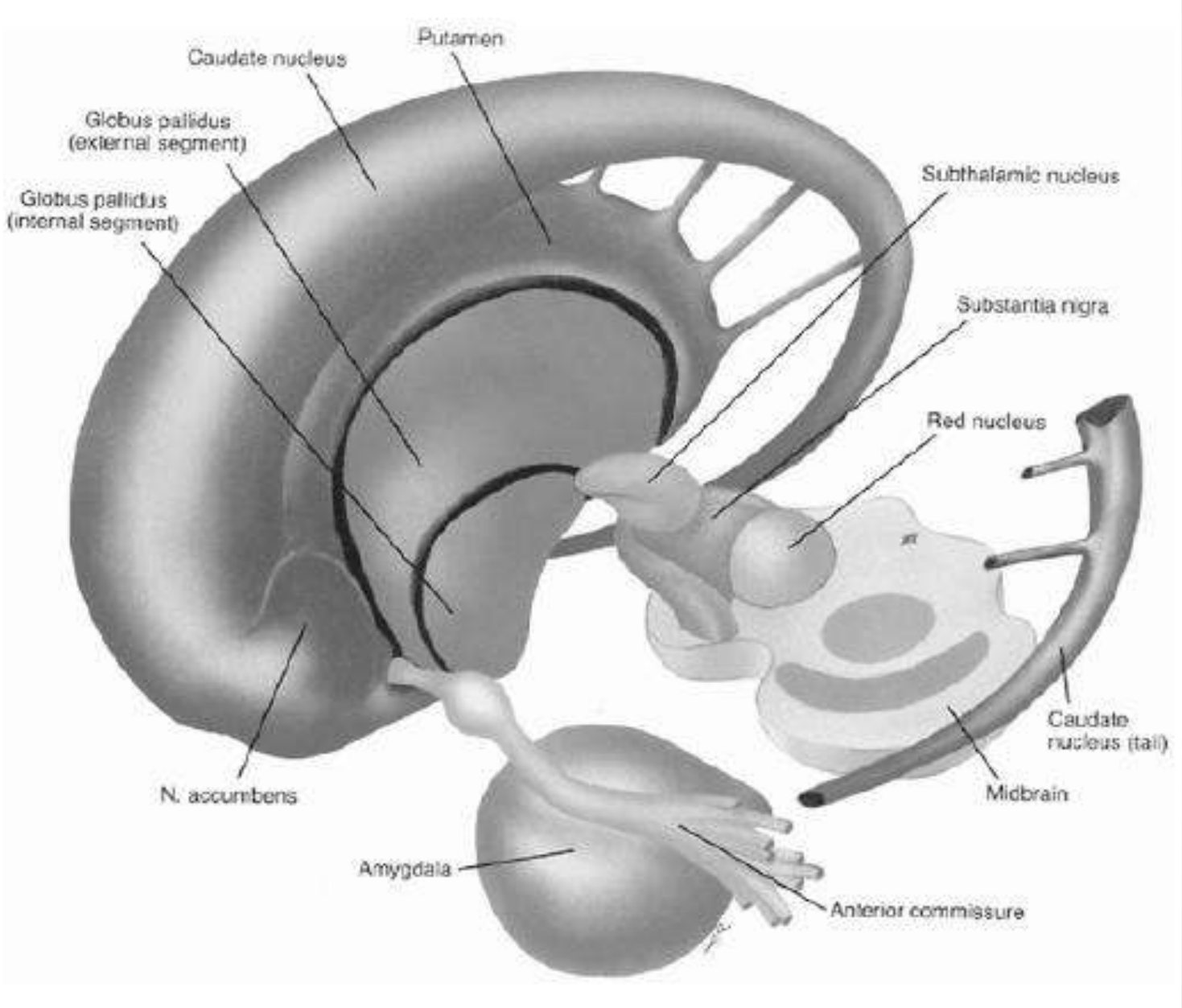

PALEOSTRIATUM
GLOBUS PALLIDUS
LENTIFORM NUCLEUS
PUTAMEN
CORPUS STRIATUM
CAUDATE NUCLEUS
SUBTHALAMIC NUCLEUS
SUBSTANTIA NIGRA
NEOSTRIATUM

The Human Basal Ganglia





HORIZONTAL SECTION OF CEREBRAL HEMISPHERE

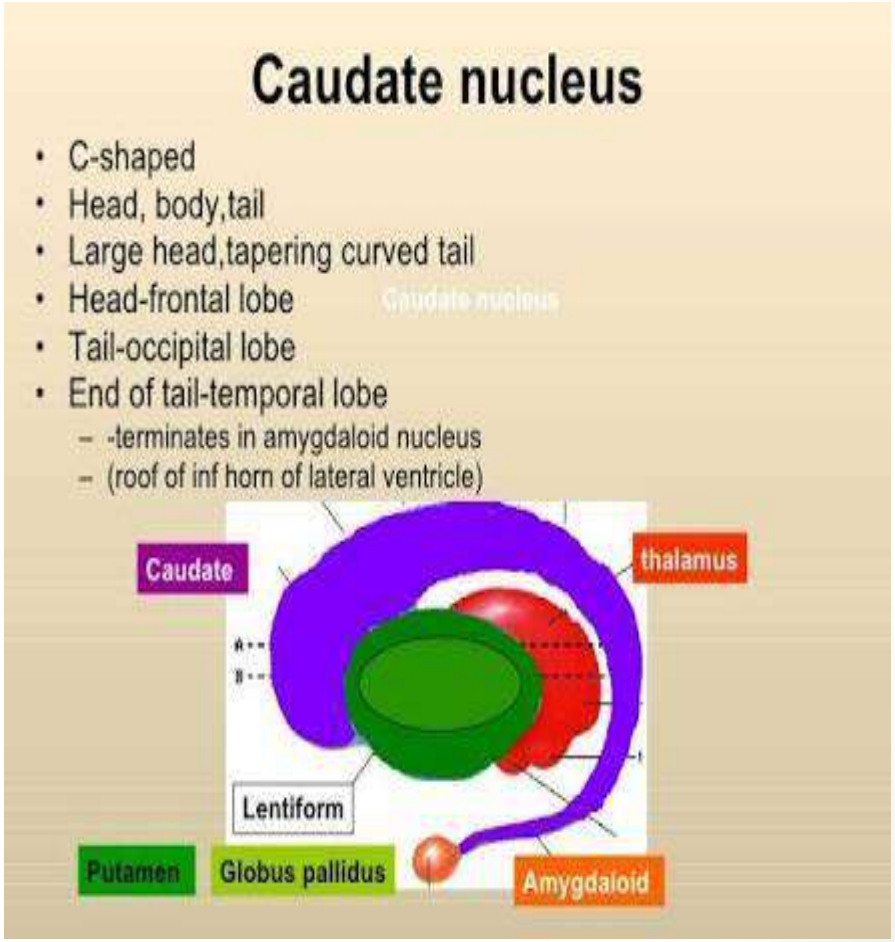

Caudate nucleus
Putamen
Globus pallidus (external segment)
Globus pallidus (internal segment)
Subthalamic nucleus
Substantia nigra
Red nucleus
Caudate nucleus (tail)
Midbrain
N. accumbens
Amygdala
Anterior commissure

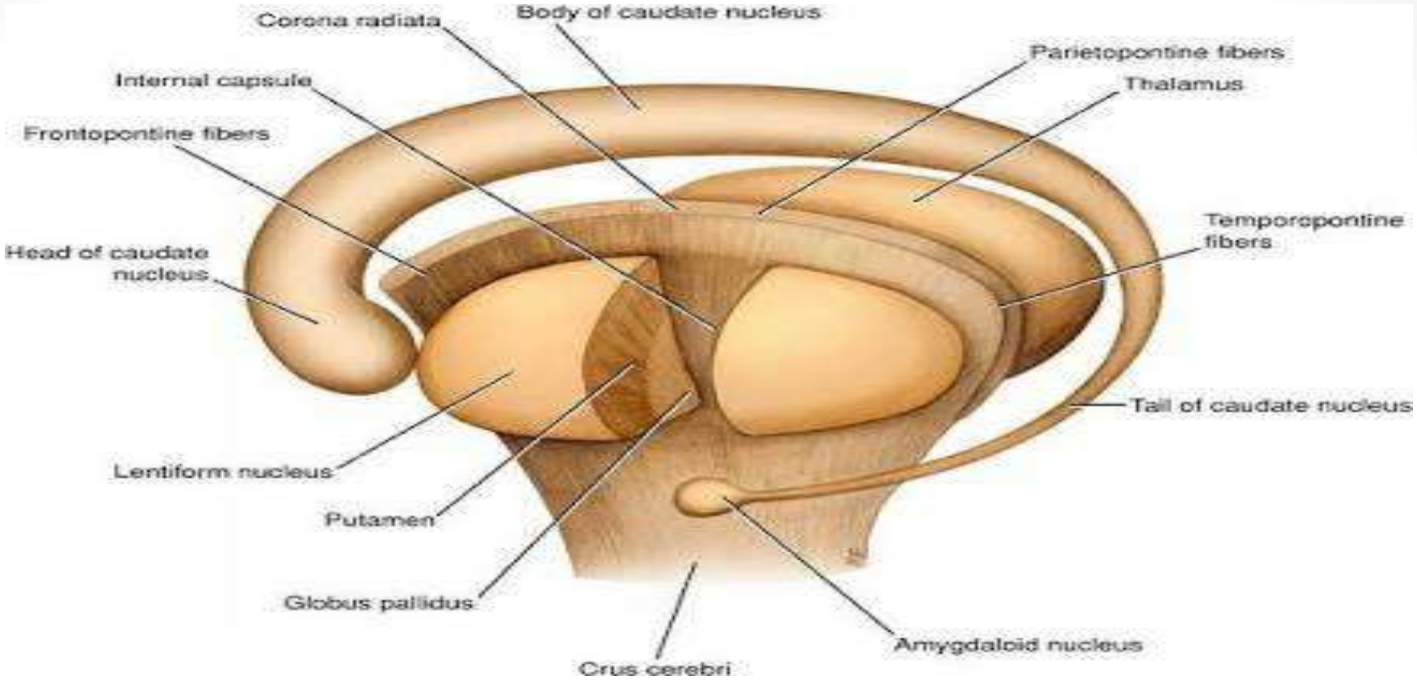
MEDIAL VIEW

ANATOMY OF INDIVIDUAL STRUCTURES

Caudate nucleus

- Telencephalic origin
- Comma shaped with head body and tail
- Convexity projects into cavity of lateral ventricle
- Tail terminates in amydaloid body
- Head connected to putamen by bands of grey matter





Lentiform nucleus

- Biconvex mass of grey matter
- Three surfaces-

1. Lateral- external capsule
2. Medial – internal capsule,
3. Inferior – sublentiform part of internal capsule

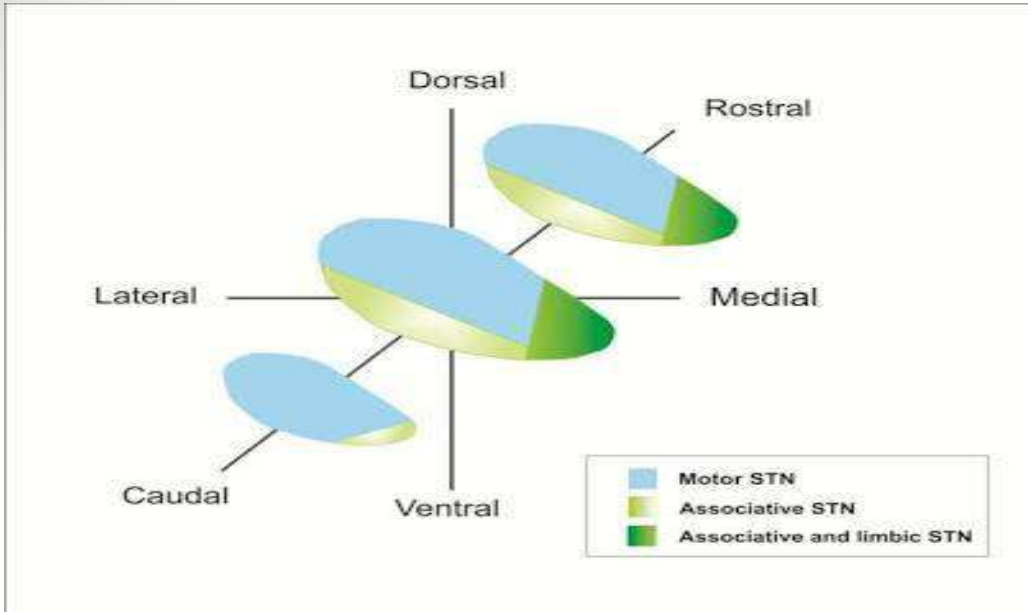
- Two parts- putamen and globus pallidus divide by external medullary lamina

Putamen

- Telencephalic origin
- Larger lateral part
- Separated from caudate by anterior limb of internal capsule

Globus pallidus

- Diencephalic origin
- Smaller medial part
- Subdivided into outer and inner segments by internal medullary lamina

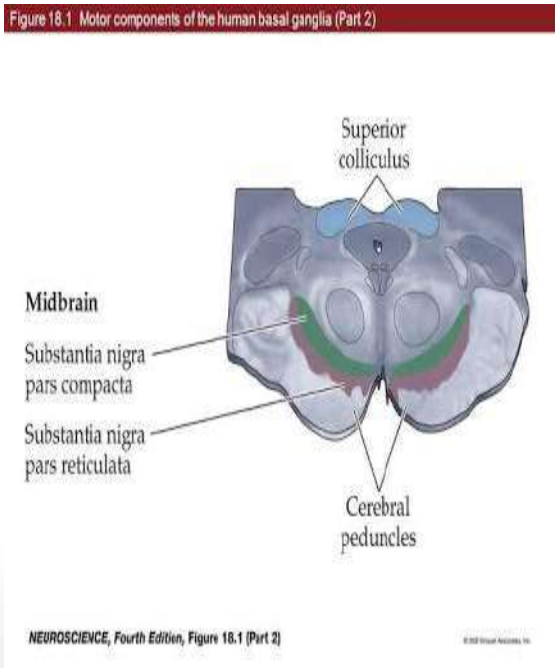


Subthalamic nucleus (of luys)

- Diencephalic origin
- Caudal to lateral half of thalamus; seperated from thalamus by zona inserta
- Inferomedial to globus pallidus; connected to it subthalamic fasciculus
- Dorasal to substantia nigra

SUBSTANTIA NIGRA (SN)

- Large nucleus extending through length of midbrain
- Crescent shaped band of grey matter
- Between crus cerebri and tegmentum



SUBSTANTIA NIGRA

PARS COMPACTA SNC	PARS RETICULATA SNR
• Dorsal • Cell rich • Neuromelanin • Dopamine • Main dopamine source	• Ventral • Cell sparse • No pigment • GABA • Main output nuclei

DOPAMINE NEURONS

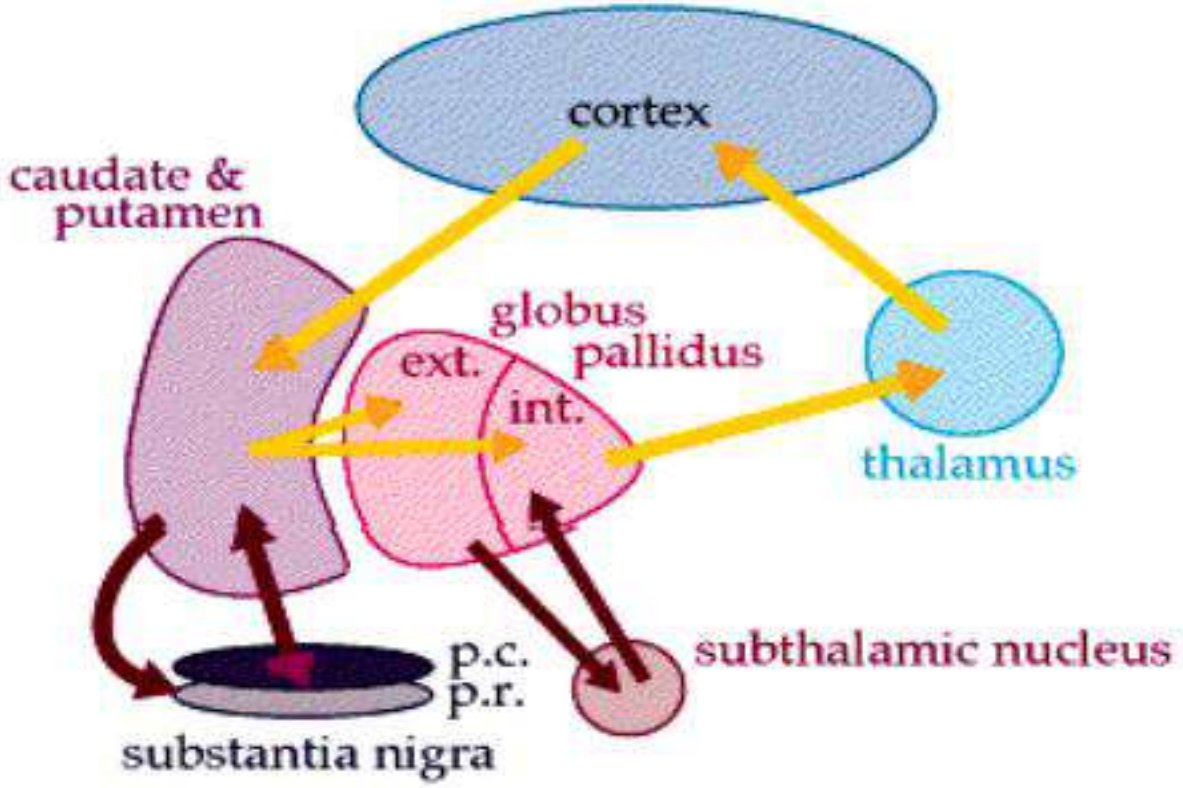
VENTRAL TIER

- SUBSTANTIA NIGRA (SN)
- ↑ LEVELS OF m-RNA FOR DOPAMINE TRANSPORTER & D2 RECEPTOR
- ↓ CALBINDIN
- PROJECT INTO AREAS OF STRIATUM FOR LIMBIC AND ASSCOCIATION AREAS
- PARKINSONISM

DORSAL TIER

- MEDIAL VENTRAL MESENCEPHALON, DORSAL TO SNc & CAUDAL TO RED NUCLEUS
- ↓ LEVELS OF m-RNA FOR DOPAMINE TRANSPORTER & D2 RECEPTOR
- ↑ CALBINDIN
- PROJECT INTO SENSORIMOTOR AREAS
- SCHIZOPHRENIA

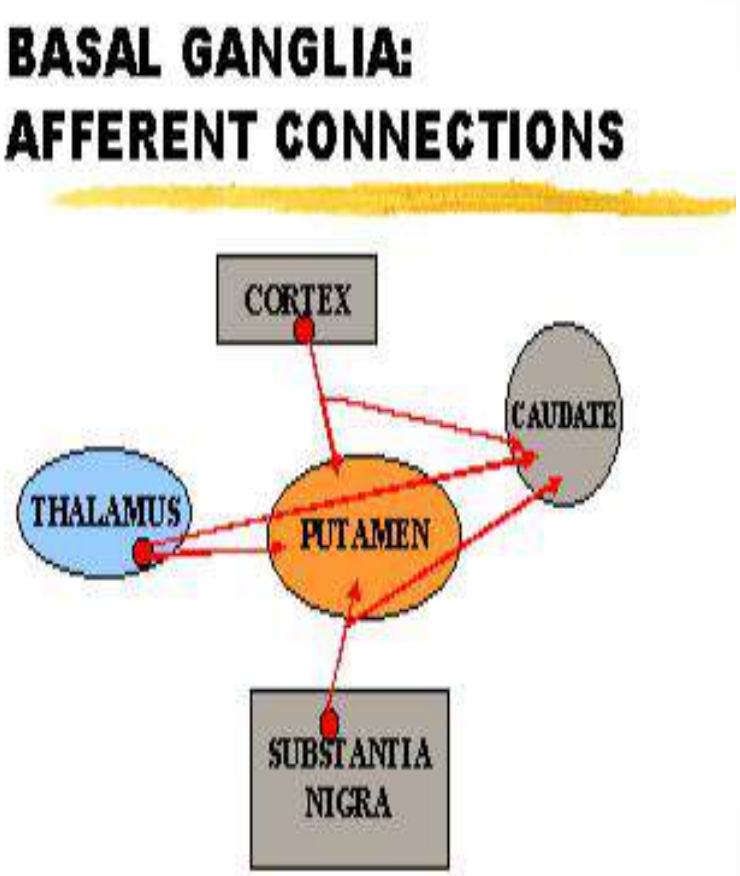
BASAL GANGLIA PHYSIOLOGY



NEURAL CIRCUITRY

Afferent connections

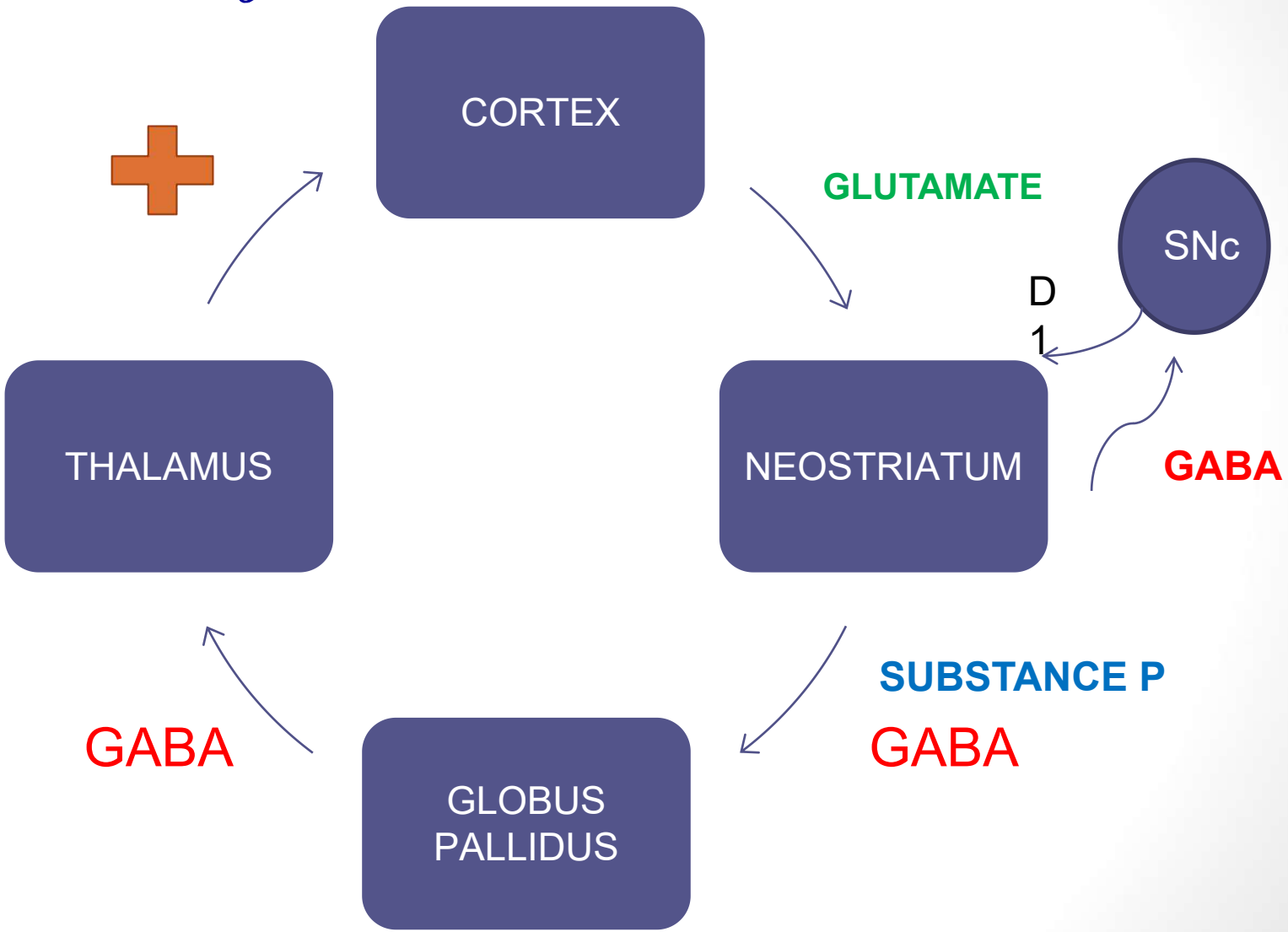
- Corticostriatal
  (glutamate)
- Thalamostriatal
- Nigrostriatal
  (dopamine)



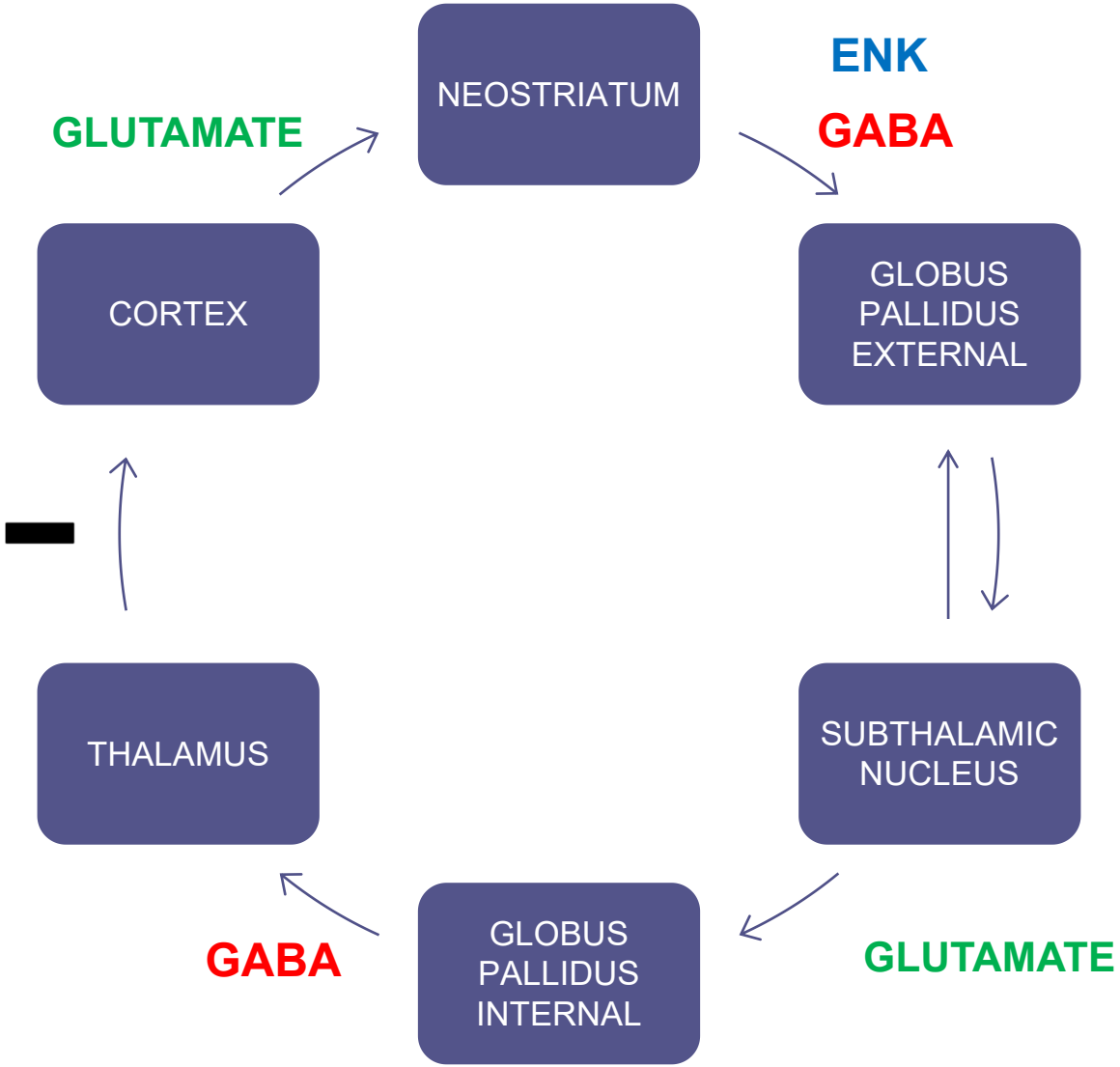
PATHWAYS

DIRECT	INDIRECT	HYPERDIRECT
• Direct loop from striatum to GPi • Inhibit pallidothalamic pathway • Net cortical excitation • Promote movement	• STN facilitates pallidothalamic pathway • Decrease thalamocortical activity • Net cortical inhibition • Inhibit movement	• Avoids striatum • Motor cortex, STN, Gpi • Inhibit initiated actions • Disturbance-impulsive behaviours

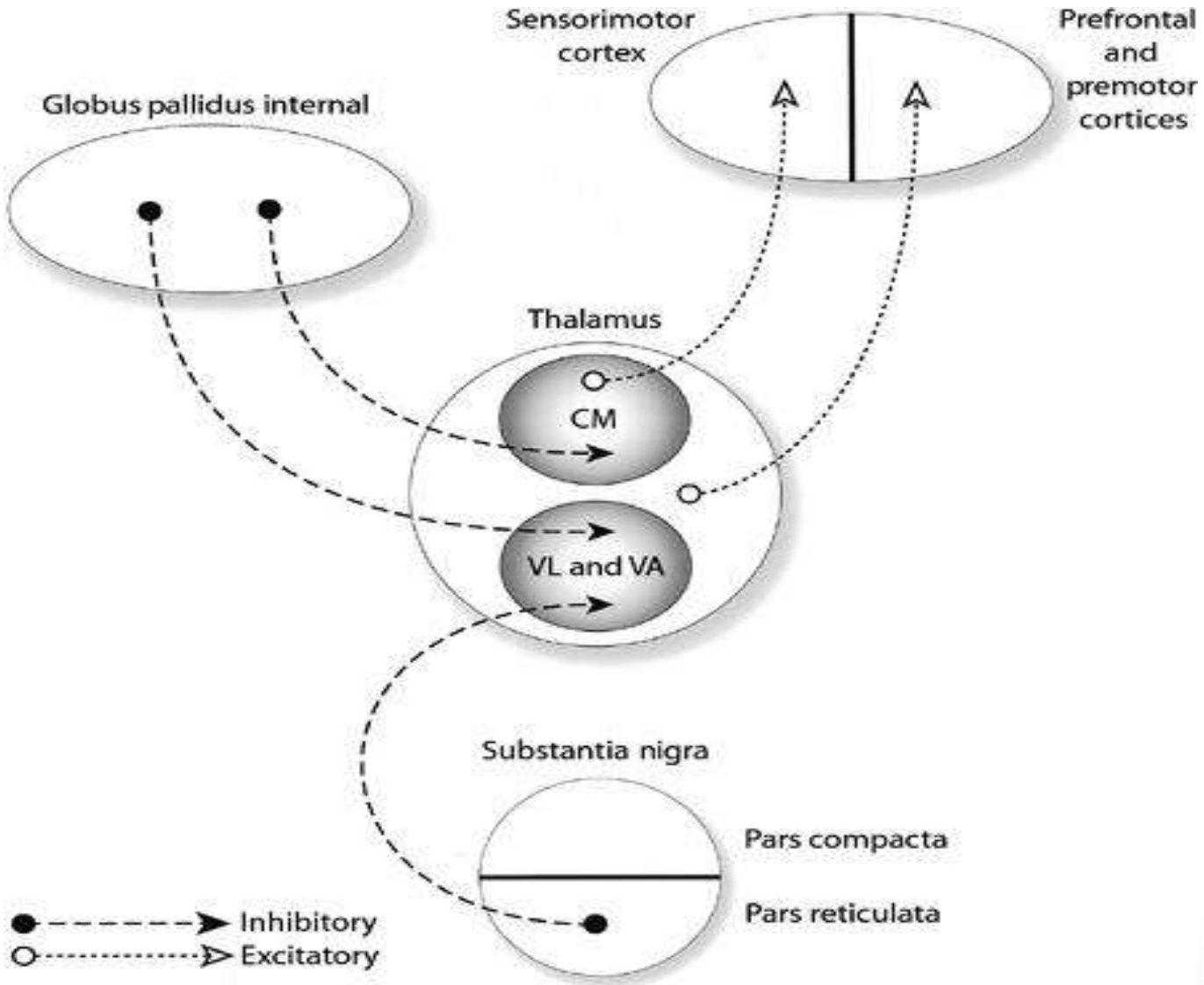
DIRECT PATHWAY



INDIRECT PATHWAY



BASAL GANGLIA OUTPUT



FUNCTIONS OF BASAL GANGLIA

- Planning and programming of voluntary movements (motor learning & sequencing)
- Execution of specific movement
- Regulation of muscle tone
- Control automatic associated movements like swinging of arms during walking
- Control reflex muscular activity

- Attention allocation and filtering
- Working memory, implicit learning and memory
- Reward processes reinforcement

ROLE OF BASAL GANGLIA IN PSYCHIATRIC DISORDER

1. OCD
2. Autism
3. ADHD
4. Schizophrenia
5. Depression
6. Addiction

Obsessive-compulsive disorder (OCD)

- There is evidence of basal ganglia dysfunction from imaging studies of OCD
- Both reduced and increased volumes of caudate nuclei are reported
- Increased caudate metabolism has been found to reduce after effective treatment of the OCD
- Patients with OCD have shown **increased caudate blood flow**

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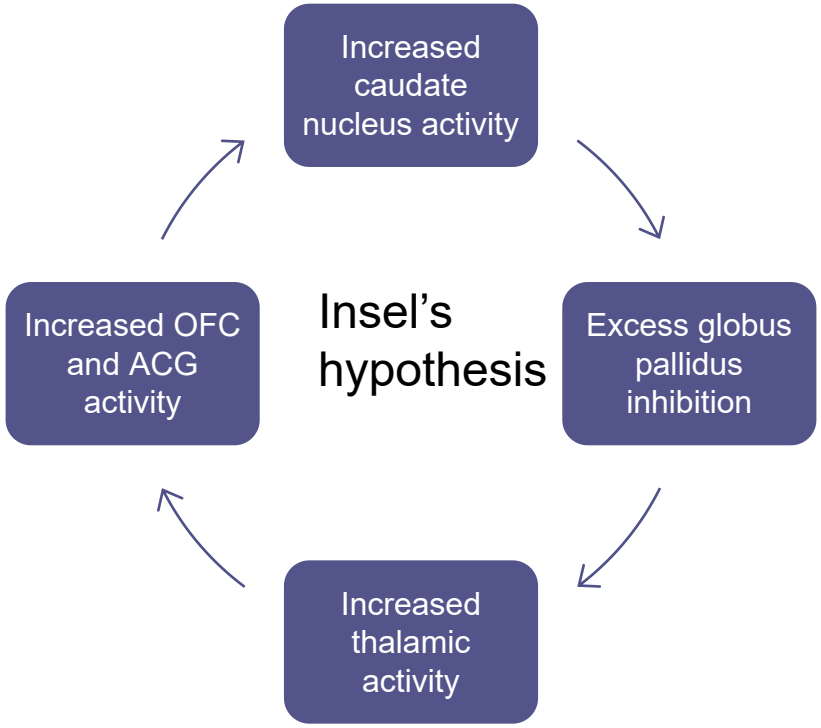
- Imagining studies point to the importance of **limbic-orbitofrontal-basal ganglia-thalamocortical** circuits in the pathogenesis of OCD



AUTISM

- Significant enlargement of the total **caudate volume** in the order of 8% was found in the subjects with autism

- This **greater caudate volume** was proportional to the increased total brain volume

- Motor, social, and communicative impairments in boys with autism are associated with **shape abnormalities in the basal ganglia**
- Studies suggest abnormalities within **frontal-subcortical circuits**
- **Glutamate** dysfunction in the **basal ganglia** may be associated with Autism

ADHD

- This condition linked clinically and genetically to GTS and OCD
- There is evidence from Neuroimaging studies of **striatal dysfunction** in patients with ADHD

- Teicher and colleagues concluded that ADHD may be related to **functional abnormalities in the putamen**
- Boys with ADHD showed significantly **smaller basal ganglia** volumes compared with typically developing boys
- They concluded that in ADHD there is atypical brain development involving multiple **frontal-subcortical control loops**

Schizophrenia

- Basal ganglia disturbance has a role in causation of Schizophrenia
- In the striatum, anomalies of dopamine synthesis, storage and release have been reported
- Striatal dopaminergic system is overactive
- The striatum of schizophrenia patients displays augmentation of presynaptic dopamine function indicating an increase in dopamine synthesis capacity

continued..

- Schizophrenia subjects show elevations in **striatal D_2 receptors**
- **Enhanced striatal dopamine** levels, synthesis and release are present in drug free schizophrenia subjects
- Antipsychotics- dopamine receptor antagonism- drug-induced EPS

Depression

- Nucleus accumbens important focus of pathological change in affective disorders
- Imaging studies- pathological interactions between amygdala, parts of ventral striatum and prefrontal cortex in genesis of major depression
- Cerebrovascular insufficiency in subcortical and basal ganglia may precipitate some cases of late-onset affective disturbances

Addiction

- It has been hypothesised that the **amygdala** is a critical structure in which neuroadaptations lead to positive effects of many drugs of misuse
- **Amygdala** has a role in abstinence or withdrawal of the drugs of misuse
- The **nucleus accumbens** has been described as a limbic-motor interface and receives innervation from amygdala

- Connections of the **orbitofrontal cortex-ventral tegmental area-nucleus accumbens-thalamus** are important for **drug reinforcement and addiction**

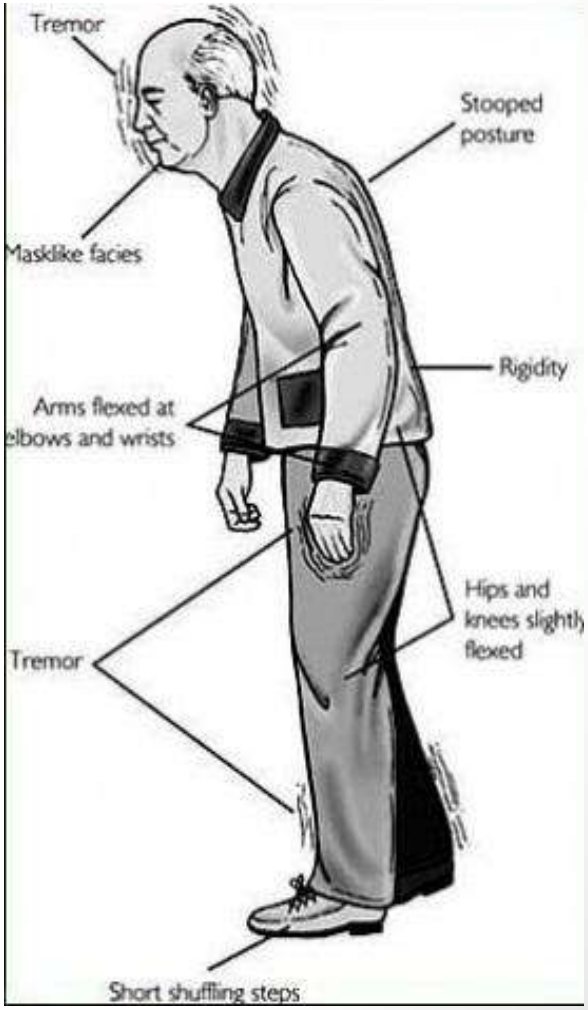
- This circuit is important in the compulsive aspect of drug taking behaviour

NEUROPSYCHIATRIC MANIFESTATIONS OF BASAL GANGLIA DISORDERS

PARKINSON'S DISEASE

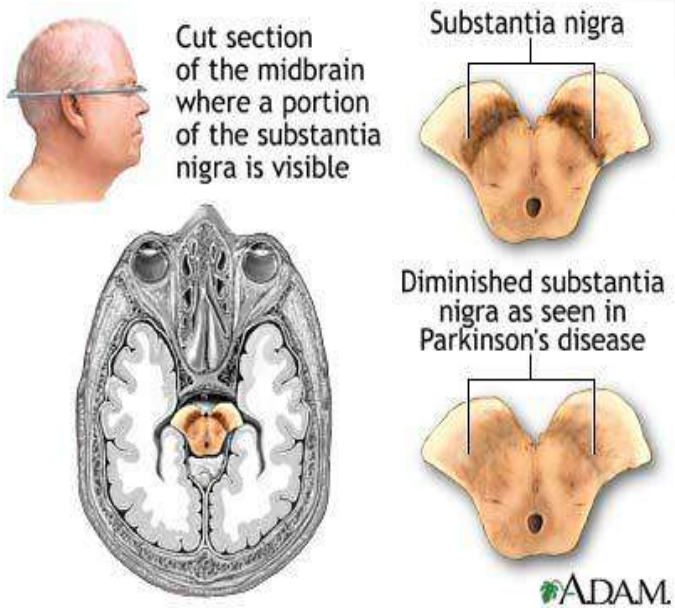
The cardinal manifestations of Parkinson's disease (PD) are

1. Tremor
2. Rigidity
3. Bradykinesia
4. Postural instability



Pathologically PD is characterized by

- Degeneration of the dopamine neurons in the **substantia nigra pars compacta** accompanied by a loss of dopamine terminals in the **striatum**
- Presence of **Lewy bodies** in the **substantia nigra**, locus coeruleus, nucleus basalis, raphe and ventral tegmental area



PSYCHIATRIC MANIFESTATIONS IN PARKINSON'S DISEASE

- DEPRESSION– 50% patients afflicted of which 20% are mdd
  Biological hypothesis- deficit in nor adrenaline, serotonin, dopamine
- ANXIETY- GAD, panic and phobic disorders in 40% patients
  Deficit in noradrenaline, serotonin as well as psychosocial factors
- APATHY- associated with cognitive dysfunction
- SLEEP DISORDERS- REM behaviour disorders, sleep attacks
- VISUAL HALLUCINATIONS- anticholinergic and other antiparkinsonian drug – induced.
- DELUSIONS – 3 % to 30 %
  Generally seen after > 2 years after initiating levodopa
- HEDONISTIC HOMEOSTATIC DYSREGULATION
- COGNITIVE IMPAIRMENT AND DEMENTIA

Extra-pyramidal movement disorders

- Akinetic- rigid syndromes
- Dystonia
- Tremors
- Myoclonus
- Chorea
- Athetosis
- Ballismus
- Tics
- Akithisia
- Others

Extrapyramidal or basal ganglia diseases do not produce weakness but cause abnormalities in the initiation of movement (hypokinetic parkinsonian disorders) or exhibit abnormal activation of muscle programs and plans leading to hyperkinetic disorders

- **Akinetic rigid syndromes** are parkinsonian disorders characterized by reduced initiation of movement (akinesia), a slowed execution of movement (bradykinesia), and plastic or lead pipe rigidity

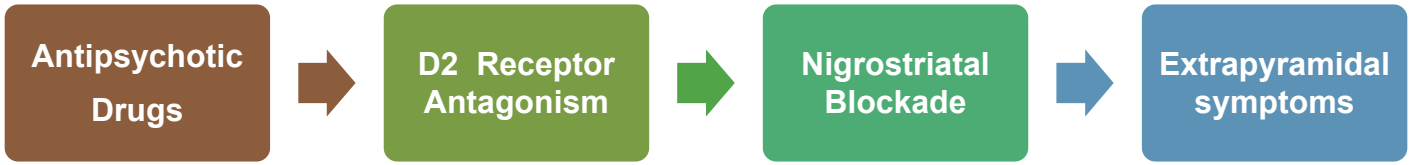
- **Dystonia** refers to a movement disorder caused by sustained muscle contractions causing twisting and repetitive movement or abnormal postures

- **Tremor** results from involuntary oscillations of a body part produced by alternating or synchronous contractions of reciprocally enervated muscles

- **Myoclonus** refers to sudden shock-like muscle contractions that may be focal, multifocal, or generalized. It is typically random and irregular

- **Chorea** consists of arrhythmic, rapid, and often jerky movements that may be simple or complex and involve one body part or another in a continuous random sequence
- **Athetosis** refers to slow, sinuous, writhing movements of the distal parts of limbs
- **Ballism or ballismus** describes wild flinging or throwing
- **Tics** are repetitive, irregular, stereotyped movements or vocalizations that are subject to partial voluntary control
- **Akathisia** is a subjective sensation of restlessness associated with an inability to remain still.
- **Tardive dyskinesia** is a special case of a choreaform disorder following exposure to dopamine blocking agents.

DRUG INDUCED EXTRAPYRAMIDAL SYMPTOMS



1. Acute Dystonias- muscle spasms like oculogyric crisis, trismus, larygospasm, ante/retro/torti-collis, opisthotonus, blepharospasm

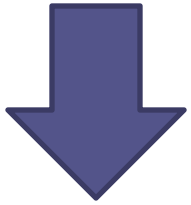
2. Acute akathisia- Motor restlessness, fidgeting, inability to be still, pacing, rocking

3. Secondary Parkinsonism

4. Pisa syndrome- leaning to one side

5. Rabbit syndrome- fine tremor of lower lip

- Long term antipsychotic use- Supersensitivity of post-synaptic dopamine receptors due long term blockade



TARDIVE SYNDROMES

6. Tardive Dyskinesia- involuntary choreo-athetoid movement of face, tongue and/or limbs like tongue protusion, grimacing, tics, twitching, irreversible

7. Neuroleptic Malignant Syndrome- extreme muscle rigidity, high fever, coma and even death

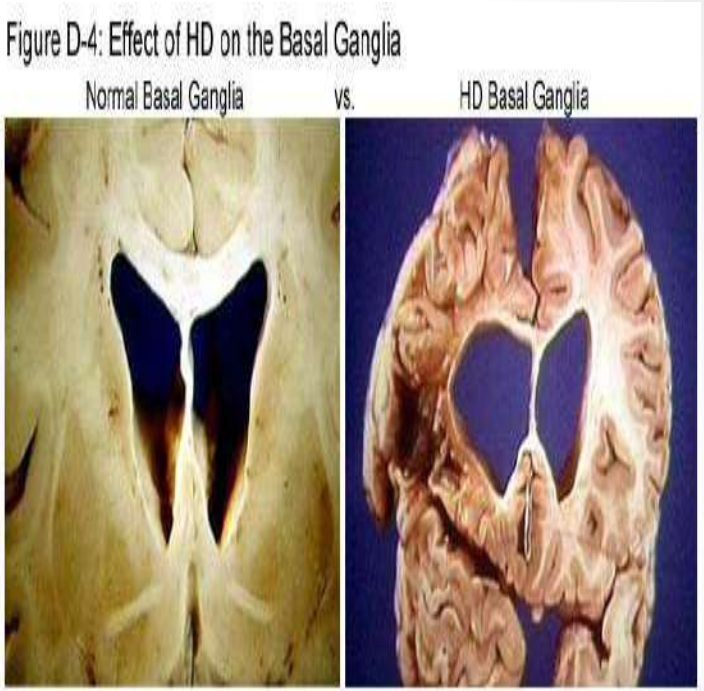
Huntington's disease

- Huntington's disease (HD) is an autosomal dominant disorder with a 100% penetrance caused by an unstable nucleotide repeat (CAG) in the IT15 gene on chromosome 4

- Main clinical features are :

- Movement disorders
- Personality change
- Psychiatric disorder
- Cognitive impairment

- In Huntington disease (HD) there is loss of neurons in the striatum which project primarily to Gpe
- Loss of these neurons removes inhibition from GPe which leads to **inhibition of STN**
- **Excitation of thalamus** leading to increased thalamocortical activity and hyperkinesis



The basal ganglia of the human brain, showing the impact of HD on brain structure in this region. Note especially that the brain of a person with HD has bigger openings due to the death of nerve cells in that region.

Source: Singer, Jonathan. Huntington's Disease. Online. Available at: http://ist-socrates.berkeley.edu/~jmp/HD.html

Progressive supranuclear palsy (Steele-Richardson-Olszweski's disease)

- Pathologically PSP is considered a "tauopathy" and the main neurochemical deficits found relate to dopamine in the nigrostriatal pathway and acetylcholine
- Cognitive impairment is very common in PSP **affecting 80%** of patients
- The pattern of deficits is characteristic of **"subcortical dementia**
- Apathy, depression, anxiety and disinhibition

Wilson's disease (WD)/ hepatolenticular degeneration

- Autosomal recessive disorder of copper metabolism
- The cerebral pathology of WD mainly affects the lenticular nuclei (pallidus and putamen)
- Abnormalities can also be found in the caudate, thalamus, cerebellar nuclei and white matter

Psychiatric manifestations of WD

- Psychiatric presentation of WD occurs in up to a third of cases
- Depression occurs in 30% of cases of WD
- Suicidal behaviour may occur in between 4% and 16%
- Mania can occur but is less frequent than depression

Psychiatric manifestations of WD

- **Psychosis** may be the initial presentation but its frequency is very low at about 2%
- Cognitive impairment has frontosubcortical pattern.

Fahr's disease (idiopathic clacification of the basal ganglia)

- Characterised by progressive calcium deposition in the basal ganglia
- Tissue damage by free radicals or by abnormal iron transport triggers calcification

Pathophysiology of FD

- The pallidus is most affected

- The pattern of cognitive impairment found in FD is of the **frontosubcortical** type

Gilles de la Tourette's syndrome (GTS) (Tourette's disorder)

- Characterized by a combination of both **multiple motor and one or more vocal (phonic) tics** which wax and wane and occur many times a day in bouts with varying intensity and complexity
- Its onset occurs **before** the age of **18 years**

Pathophysiology of GTS

- There is evidence of involvement of the **dopaminergic system**

- **Caudate nucleus** volumes were significantly **smaller** in children and adults with GTS

- **Lenticular nucleus** volumes were **smaller** in adults with GTS and in children with GTS with **comorbid OCD**

- **Smaller lenticular nucleus** volumes serves as additional **marker** for the presence of **comorbid OCD** and for the persistence of **tic** symptoms into adulthood

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Thankyou