Hyperkinetic and Movement Disorders

Dr. Gary Mumaugh

- Huntington’s Chorea
- Dystonia
- Athetosis
- Ballismus
- Myoclonus
- Wilson’s disease
- Tardive dyskinesia
- Essential Tremor
- Tourette’s Syndrome (tics)

Movement Disorders

- Chorea, athetosis, ballism & dystonia : Non-rhythmic involuntary movements may be combinations of fragments of purposeful movements & abnormal postures.

Movement Disorders

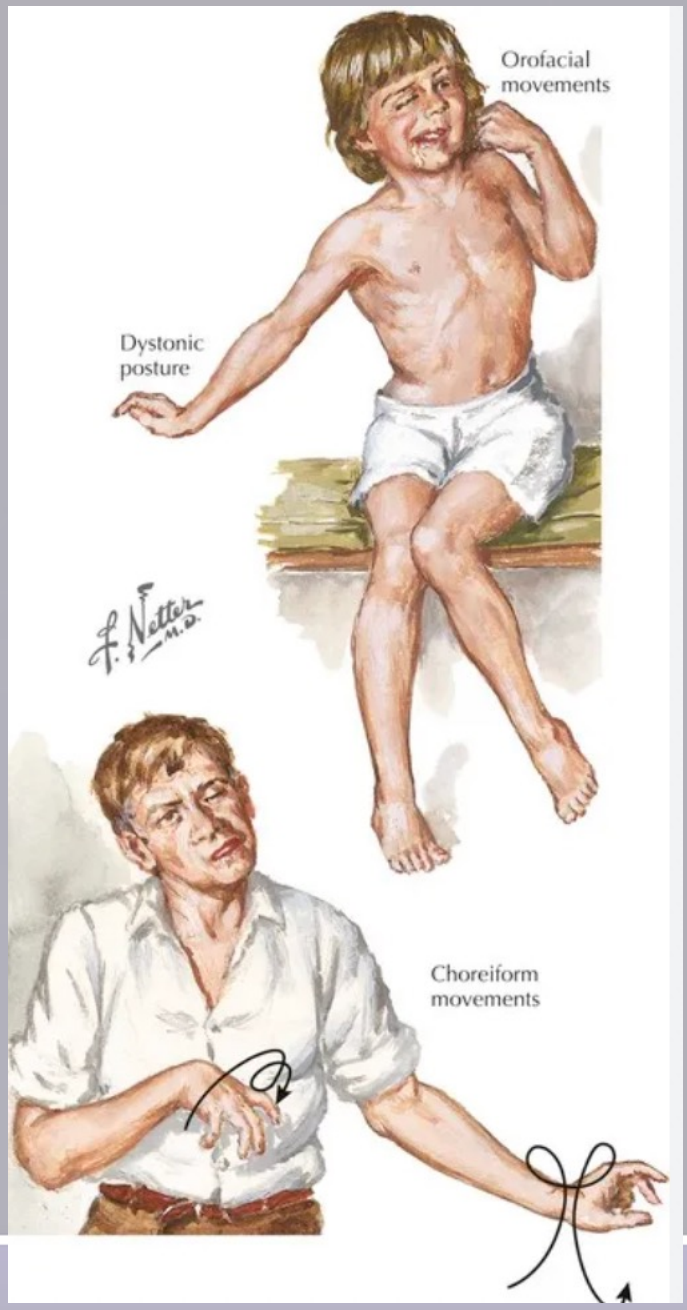
- All due to imbalance of activity in the complex basal ganglia circuits.
- Sometimes also known as “ extrapyramidal disorders ”
- Primarily conditions related to excessive dopaminergic activity in the basal ganglia.

- Chorea - a neurological disorder characterized by jerky involuntary movements affecting especially the shoulders, hips, and face.
- Athetosis - a condition in which abnormal muscle contractions cause involuntary writhing movements.
- Ballismus is a severe movement disorder that is characterized by spontaneous involuntary movements, muscular weakness and incoordination of movements of the proximal extremities.

- Dystonia is a movement disorder that causes the muscles to contract involuntarily
- Chorea, Athetosis, Ballismus and Dystonis should NOT be thought of as separate entities amenable to specific definition but rather as a SPECTRUM of movements that blend into one-another

Why?

They usually co-exist. Neurologists may often not be able to agree as to how a particular movement should be classified!



Movement Spectrum Disorders

Myoclonus Ballismus Chorea Athetosis Dystonia

Movements become
- Less violent / explosive / jerky
- Smoother and more flowing
- More sustained

They differ from tics in that they cannot be suppressed by voluntary control

Chorea(Latin choreus, dance)

- Jerky semi-purposive uncontrollable movements of limbs , face & trunk , increase with anxiety & disappear during sleep.
- In the limbs they resemble fidgety movements, & in the face, grimaces.
- Patients often attempt to conceal involuntary movements by superimposing voluntary movements onto them.
  - Such as an involuntary movement of arm towards face may be adapted to look-like an attempt to look at watch.

- Pathophysiology-Structural lesions putamen, globus pallidus and subthalamic nuclei
- Balance is critical between the direct and indirect motor pathways to produce normal movement patterns.

Chorea Storm

Huntington's Chorea

THE

MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

Original Department.

Communications.

ON CHOREA.

By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic symptoms are manifested in the voluntary muscles. The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

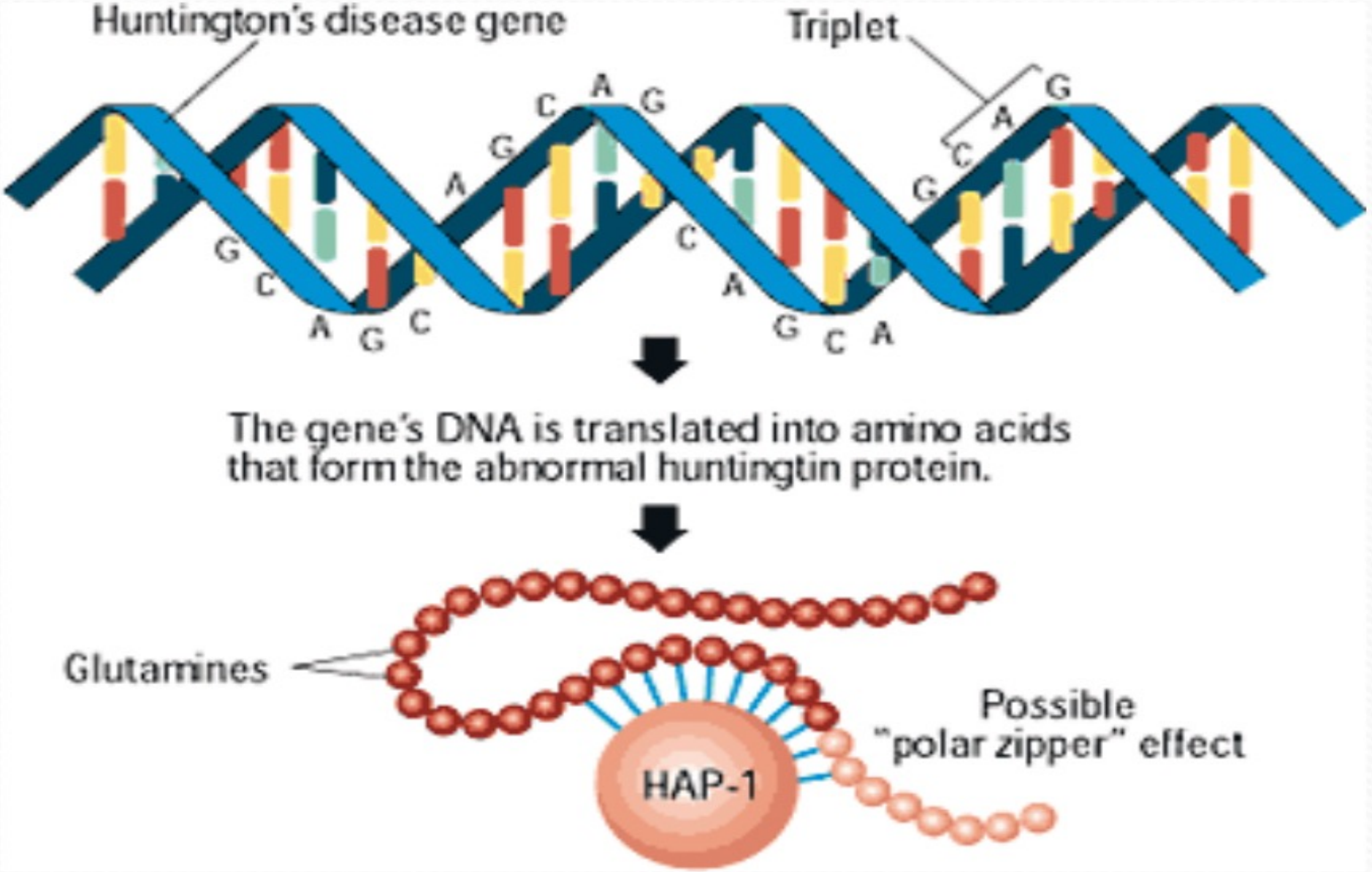
If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of

Huntington's Chorea

- Clinical manifestations:
  - Involuntary choreiform
  - Diminished during sleep
  - Facial tics/grimacing
  - Dementia
  - Paranoia & Hallucinations
  - Ravenous Appetite
  - Labile Emotions

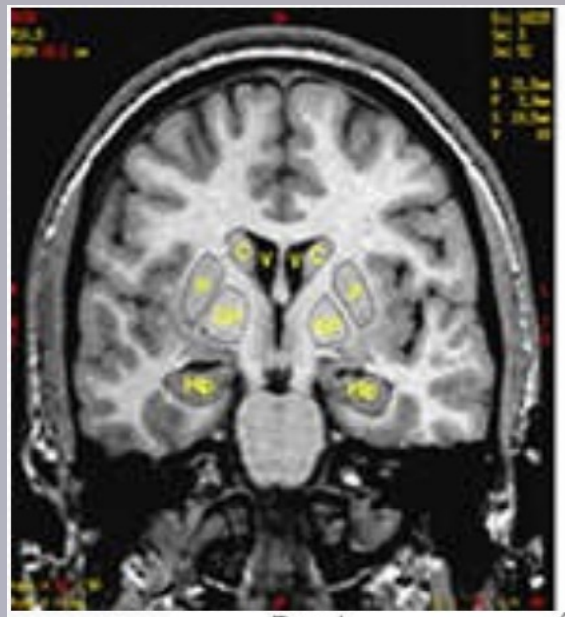
Huntington's Chorea

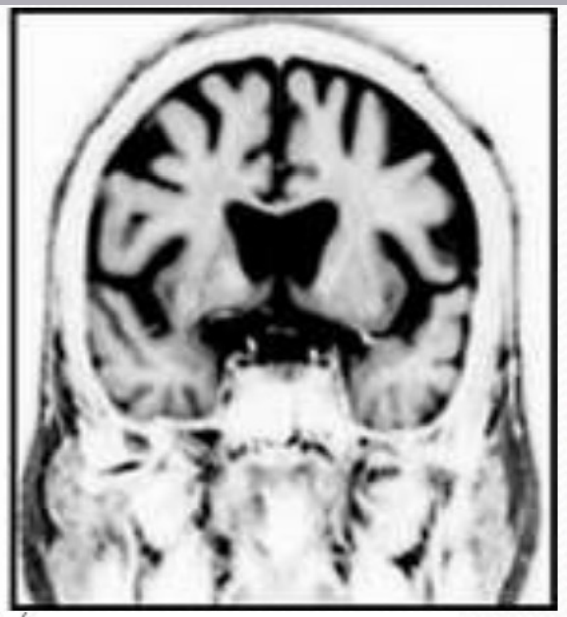
- Prevalence 1 in 10000, average onset 40 and progresses over around 10-15 years.
- Etiology - Autosomal Dominant inherited
  - Gene chromosome 4p. excess number of CAG tri-nucleotide repeats (>35)
- Diagnosis-DNA testing.
  - Mutant protein product called Huntington with 40-150 glutamine residues.
- Usually manifests at middle age – severity related to the number of trinucleotide repeats.

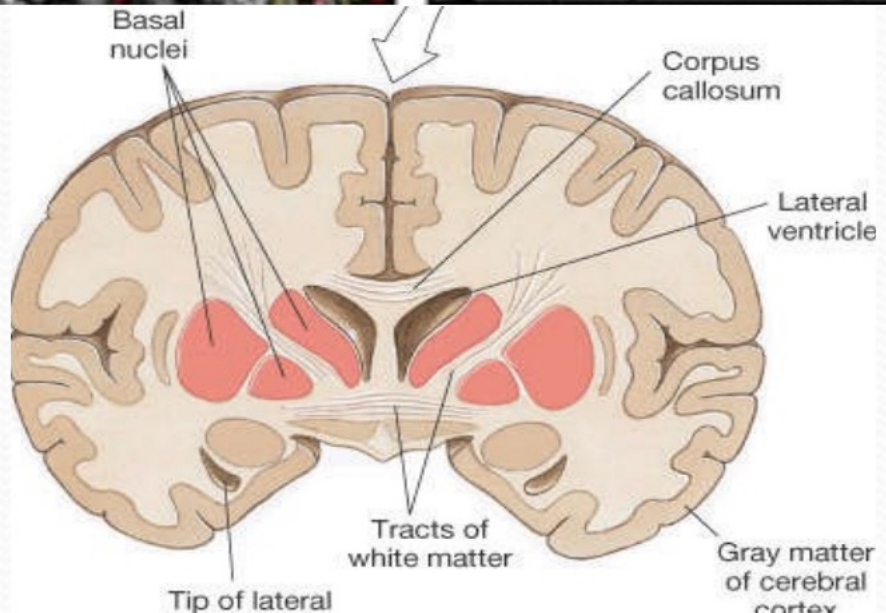

Huntington's disease gene
Triplet
The gene's DNA is translated into amino acids that form the abnormal huntingtin protein.
Glutamines
HAP-1
Possible "polar zipper" effect

Huntington's Chorea Pathology

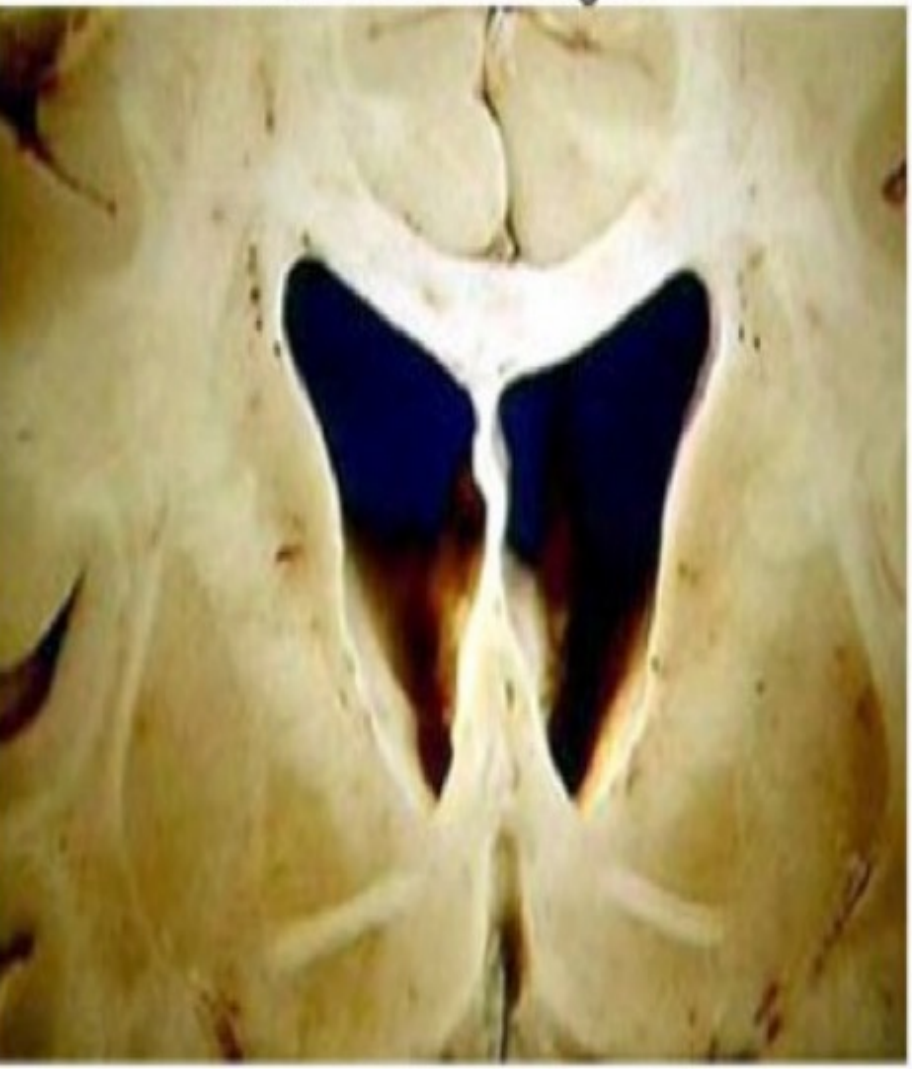
- Grossly characterized as degeneration of the cerebral cortex and the basal ganglia.
- Loss of GABAergic neurons in the striatum.
- Severe striatal atrophy with resulting enlargement of ventricles.

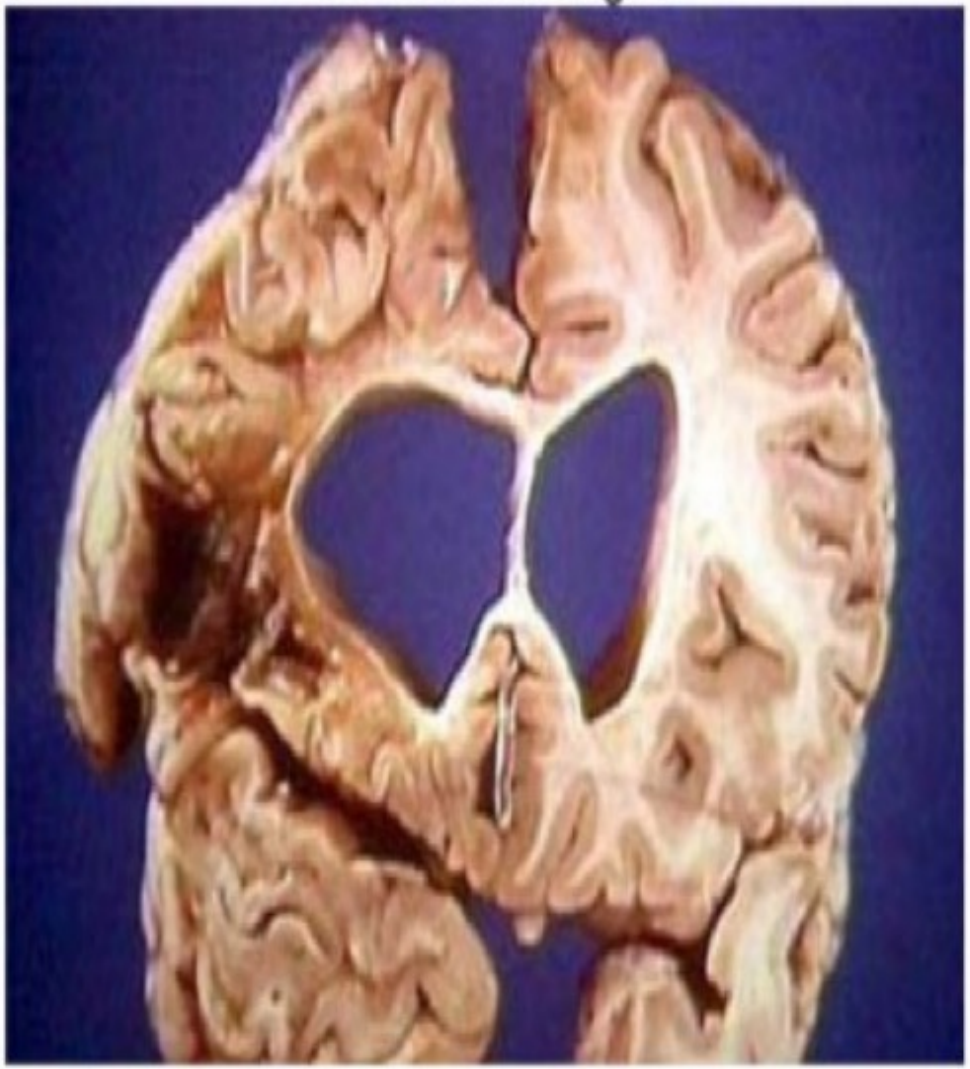




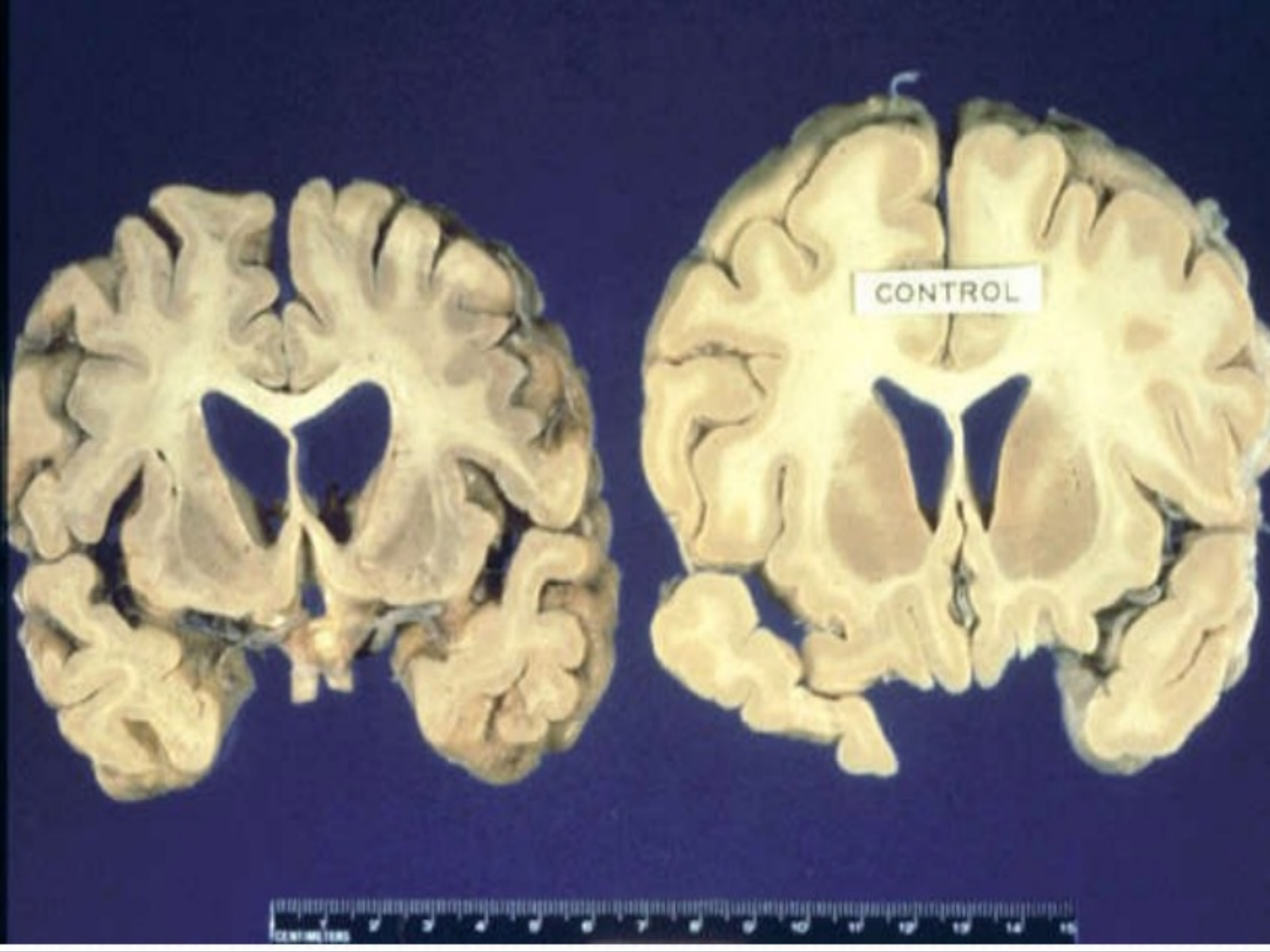


Normal Basal Ganglia vs. HD Basal Ganglia





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.


CONTROL

Huntington's Chorea Treatment

- Loss of GABA mediated inhibition on Substantia Nigra causes hyperactivity of dopaminergic synapses.
- Medical management - No cure
  - Dopamine receptor blocking drugs (antipsychotics)
  - Dopamine depleting drugs
    - Chlorpromazine (Thorazine)
    - Haloperidol (Haldol)

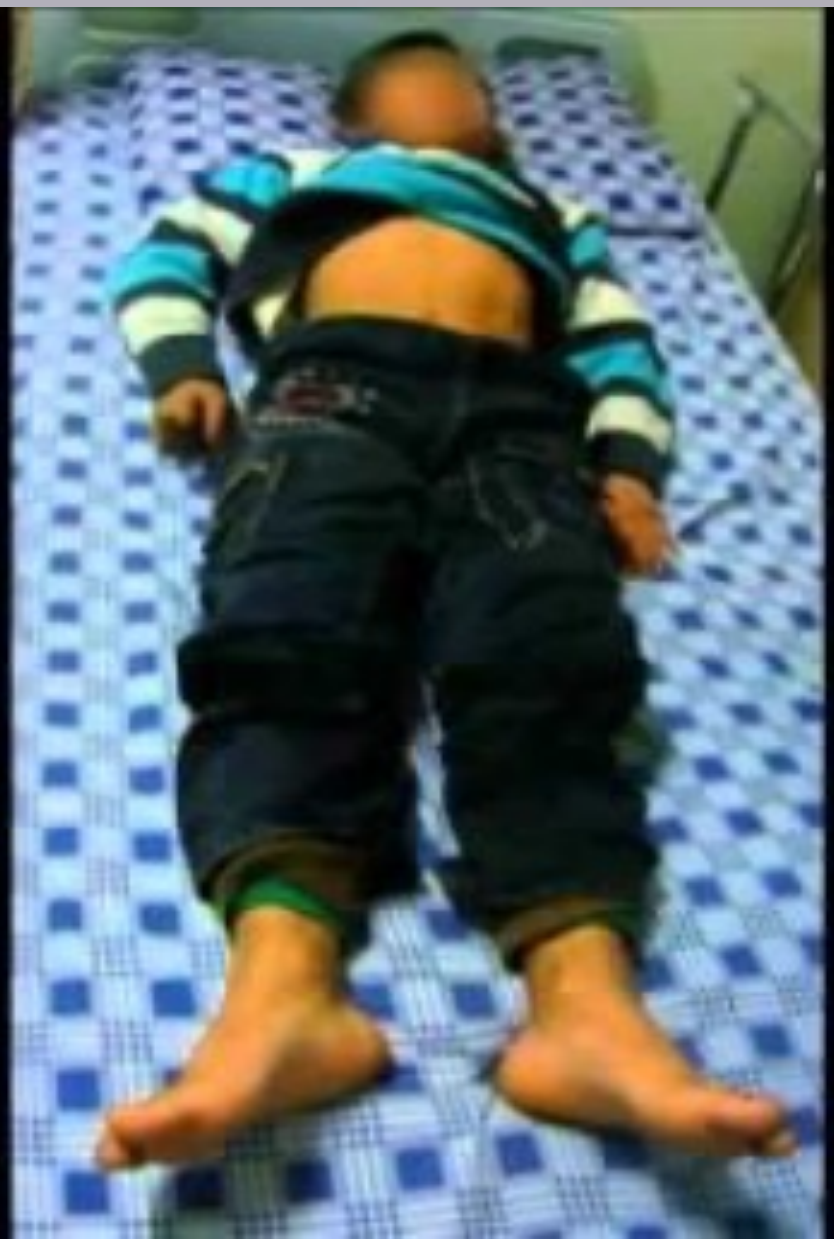
Syndenham's Chorea

- The other most recognized chorea
- Mainly in children & adolescents patients 5-15 years
- Etiology: Autoimmune response following infection with group A βhemolytic Streptococcal infection
- Rare in developed countries - antibiotics!
- Initially characterized by pharyngitis (sore throat) followed within approximately 1 to 5 weeks by the sudden onset of acute rheumatic fever
- Chorea usually only occurs in and usually 1-6 months after the onset of sore throat

- Usually generalized chorea that disappears with sleep
- Usually remits spontaneously within 9 months (on average) to 2 years
- Treatment: Dopamine antagonists, valproic acid
- Severe Cases - Immunosupression, plasmapheresis or immunoglobulin IV

Rheumatic Chorea

Syndenham's Chorea



Dystonia: Clinical Features

- Dystonias are sustained abnormal postures of limbs , neck , trunk, tongue protrusion or fixed upward deviation of the eyes (occulgyric crisis).
- Due to co-contraction of agonist and antagonist muscles in part of body

Classification of Dystonia

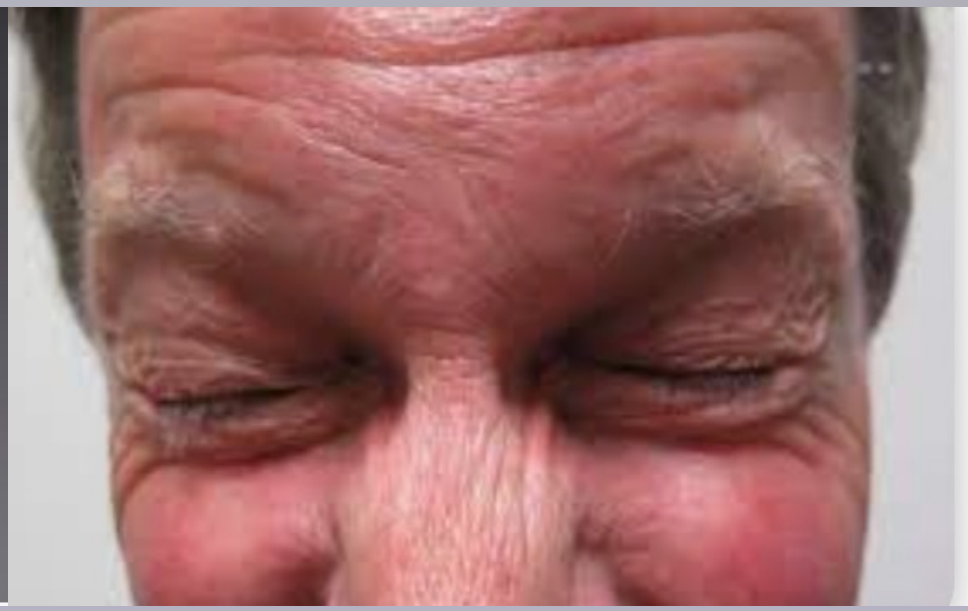
- Most common dystonia are focal (single body part)
  - Affect one part of the body such as eyes, neck, arm or vocal cords
  - Usually idiopathic
- Multifocal dystonia affects many different parts of the body

Classifications of Dystonia

- Segmental dystonias affect two adjoining parts of the body usually symptomatic
- Hemidystonia affects an arm and a leg on one side of the body
- Generalized dystonia affects most of the body, frequently involving the legs and back

Examples of Focal Dystonia

- Blepharospasm means the involuntary contraction of the eyelids, leading to uncontrollable blinking and closure of the eyelids.
  - Affects women more then men



Torticollis

- Torticollis, commonly called wry neck, is the condition of spasm affecting the muscles of the neck, causing the head to assume unnatural postures or turn uncontrollably.
- Spasmodic torticollis, also known as cervical dystonia, is the most common of the focal dystonias.

82% of patients

Torticollis
(rotated)

42% of patients

Laterocollis
(to the side)

25% of patients

Anterocollis
(forward)

29% of patients

Retrocollis
(backward)

Writer’s cramp: - Dystonic posturing of arm when hand used to perform specific tasks e.g. writing, playing piano

Cervical Dystonia

Dystonia Treatment

- Anticholinergics (benzatropine)
- Antihistamines (diphenhydramine)
- Anti-Parkinsons agents (trihexyphenidyl)
- Muscle relaxers (diazepam)
- GABAB receptor agonist (baclofen)
- The drug resistant dystonias can be treated by Botox shots to the responsible muscles, to overcome the abnormal distribution of muscle activity for a period of time.

Dystonia - Drug Induced

- Acute dystonic reaction- occulogyric crisis, sustained upward deviation of the eyes +/- toricollis, jaw opening, tongue protrusion and anxiety.

- Usually a result of administering dopamine receptor blocking drugs, generally metaclopramide (antiemetic and gastroprokinetic agent used to treat nausea and vomiting, and to facilitate gastric emptying) or prochlorperazine (neuroleptic; antiemetic) in young.
- Treatment anticholinergic drugs, usually benztropine 1-2mg IV

Table 1

Signs and Symptoms Associated with Drug-Induced Movement Disorders

Akathisia

- Subjective feeling of restlessness and need to move.
- Objective symptoms of pacing, walking in place, foot or toe tapping, and rocking while seated.
- Distress if restrained or unable to move.
- Symptoms may improve during sleep or in a supine position.

Tardive Dyskinesia

- Abnormal involuntary choreoathetoid movements affecting the orofacial region and tongue.
- Less commonly affected areas include the extremities and trunk.
- Lip smacking, chewing movements, and tongue protrusion are common.
- Symptoms are not painful but may result in embarrassment in social settings and in difficulty with chewing, speech, and swallowing.

Dystonia

- Sustained involuntary muscular contractions or spasms resulting in abnormal postures or twisting and repetitive movements.
- Affected body parts include the back, neck, upper and lower extremities, jaw, and larynx.
- Symptoms are associated with distress.
- Pain may or may not be present.
- Difficulty with ambulation, breathing, head turning, speech, and swallowing may occur.

Parkinsonism

- Tremor, rigidity, and slowness of movement affecting bilateral upper and lower extremities and truncal regions.
- Difficulty arising from a seated position, gait imbalance, masked facies, micrographia, slow shuffling gait, and stooped posture maybe observed.

Table 2

Selected Agents Associated with Drug-Induced Movement Disorders

Acute and Tardive Akathisia

Antiemetics
Droperidol
Metoclopramide
Prochlorperazine
Promethazine
Antiepileptics
Carbamazepine
Psychotropics
Lithium
Neuroleptics
Haloperidol
Molindone
Phenothiazines (e.g., chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine)
Thioxanthenes (e.g., thiothexene)
Reserpine
Selective serotonin-reuptake inhibitors
Tricyclic antidepressants

Acute and Tardive Dyskinesia

Antiemetics
Metoclopramide
Prochlorperazine
Antiepileptics
Phenytoin
Psychotropics
Amoxapine
Haloperidol
Lithium
Molindone
Phenothiazines (e.g., chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine)
Olanzapine (high dosage)
Pimozide
Risperidone (high dosage)
Thioxanthenes (e.g., thiothexene)

Acute and Tardive Dystonia

Antiemetics
Droperidol
Metoclopramide
Prochlorperazine
Promethazine
Psychotropics
Amoxapine
Neuroleptics
Haloperidol
Molindone
Olanzapine (high dosage)
Phenothiazines (e.g., chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine)
Risperidone (high dose)
Thioxanthenes (e.g., thiothexene)

Parkinsonism

Antiemetics
Droperidol
Metoclopramide
Prochlorperazine
Promethazine
Antiepileptics
Valproate
Cardiovascular agents
Alpha-Methyldopa
Reserpine
Psychotropics
Amoxapine
Neuroleptics
Haloperidol
Molindone
Olanzapine (high dosages)
Phenothiazines (e.g., chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine)
Risperidone (high dosages)
Thioxanthenes (e.g., thiothexene)
Vestibular sedatives
Cinnarizine and Flunarizine*
Miscellaneous
Pimozide
Tetrabenazine*

** Not marketed in the U.S.*

Table 3

Risk Factors for Drug-Induced Movement Disorders

Akathisia	Tardive Dyskinesias	Dystonia	Parkinsonism
Advanced age	Advanced age	***Acute Dystonia***	Acquired immune deficiency syndrome
Affective disorder	Affective disorder	High-potency neuroleptics	Advanced age
Cognitive impairment	Alcoholism	History of electroconvulsive therapy	Dementia
Female sex	Diabetes mellitus	Male sex	Female sex
High-potency neuroleptics	Duration of treatment	Mental retardation	
High neuroleptic dosage	Electroconvulsive treatment	Young age	
History of akathisia	Female sex	***Tardive Dystonia***	
Iron deficiency	History of extrapyramidal reaction	Male sex	
Mental retardation	Intermittent neuroleptic treatment	Presence of tardive dyskinesia	
Negative symptoms of schizophrenia	Iron deficiency	Young age	
Rapid neuroleptic dosage escalation	Mental retardation		
	Organic brain disorder		
	Total daily drug dosage		

Table 4

Management of Drug-Induced Movement Disorders

Acute and Tardive Akathisia
Withdrawal or dosage reduction of offending agent If due to neuroleptic, switch to an atypical antipsychotic Trial of antimuscarinic agent or beta-blocker Miscellaneous antidotes (amantadine, amitriptyline, benzodiazepine, clonidine, codeine, cyproheptadine, mianserin, mirtazapine, propoxyphene)
Tardive Dyskinesia
Withdrawal or dosage reduction of offending agent Withdrawal of concurrent antimuscarinic agents If due to neuroleptic, switch to an atypical antipsychotic Management of concurrent anxiety Botulinum toxin (focal dyskinesias) Trial of amantadine, benzodiazepine, levetiracetam, pregabalin, or vitamin E Trial of dopamine-depleting agents (e.g., tetrabenazine) Deep brain stimulation (subthalamic nucleus, globus pallidus)
Acute Dystonia
Discontinue offending agent Administer antimuscarinic agent
Tardive Dystonia
Withdrawal or dosage reduction of offending agent If due to neuroleptic, switch to an atypical antipsychotic Management of concurrent anxiety Botulinum toxin (focal dystonias) Trial of antimuscarinic agent, benzodiazepine, levetiracetam, or pregabalin Trial of muscle relaxant (e.g., baclofen) Trial of dopamine-depleting agents (e.g., tetrabenazine) Deep brain stimulation (globus pallidus) or pallidotomy
Parkinsonism
Withdrawal or dosage reduction of offending agent If due to neuroleptic, switch to an atypical antipsychotic Trial of amantadine, antimuscarinic agent, dopamine agonist, or levodopa

Athetosis

- Athetosis is a slow continuous stream of slow, sinuous, writhing movements, typically of the hands and feet.
- Most commonly seen together with chorea in dyskinetic motor fluctuations in Parkinson.
- Also in athetoid cerebral palsy where damage occurs in the basal ganglia.
- Related to excessive dopaminergic activity.

- If Athetosis becomes faster, it sometimes blends with chorea, ie choreoathetosis/ 'choreo-athetoid' movements.
- Can be thought of as an athetoid movement that “gets stuck” for a period of time; thus, a patient with choreoathetosis may perform an involuntary movement in which his hand and fingers are twisted behind his head.
- He may hold this position for a few moments before his hand moves back in front of his body.
- The part of the movement when the limb was held, unmoving, in an abnormal position would be considered a dystonia (may occur alone).

Athetosis

Ballismus

- Usually in elderly & ceases within few weeks usually self limited, lasting 6 to 8 weeks
- More dramatic ballistic movements of the arms & legs on one side of the body (unilateral) and therefore use term “ Hemiballismus”
- Treatment with antipsychotics is often effective
- Usually due to a CVA in contralateral subthalamic nucleus

Hemiballismus

Myoclonus

- Brief, isolated, random, non-purposeful jerks of muscle groups in the limbs, may occur normally at the onset of sleep (hypnic jerks)
- May be caused by active muscle contraction - positive myoclonus
- May be caused by inhibition of ongoing muscle activity - negative myoclonus (eg. Asterixis)
- Generalized - widespread throughout body
- Focal / segmental – restricted to particular part of body
- Treatment: Valproic acid is drug of choice May respond to benzodiazepines e.g. clonazepam

Etiology of Myoclonus

- Physiologic
  - Nocturnal (usually on falling asleep)
  - Hiccups
- Essential
  - Occurs in the absence of other abnormality
  - Benign and sometimes inherited
- Epileptic
  - Demonstrable cortical source

- Symptomatic - secondary to disease process
  - Neurodegenerative - Wilson's disease
  - Infectious - CJD, Viral encephalitis
  - Toxic - penicillin, antidepressants
  - Metabolic
    - Anoxic brain damage
    - Hypoglycemia
    - Hepatic failure (" asterixis")
    - Renal failure
    - Hyponatremia

Wilson’s Disease

- Wilson's disease is a rare inherited disorder that causes copper to accumulate in your liver, brain and other vital organs.
- Most people with Wilson's disease are diagnosed between the ages of 5 and 35, but it can affect younger and older people, as well.
- Symptoms include swelling, fatigue, abdominal pain, and uncontrolled or poorly coordinated movements.

Tardive Dyskinesia

- Involuntary movements as facial grimacing , chewing movements, tongue movements (oro-bucco-mandibular dyskinesia)
- Appears after weeks, generally years of exposure to dopamine receptor blocking drugs
- Older or classical ‘typical’ antipsychotics e.g. chlorpromazine, haloperidol
- With typical antipsychotics prevalence around 20%

- Treatment is difficult but withdrawal of the causative drug often worsens symptoms
- Tardive dyskinesia disappears with time in 1/3 (generally mild cases)
- Permanent in 2/3s.

TD Commercial

Essential Tremor

- •Probably the most common movement disorder
  •Hallmark - postural and action tremor affecting the hands, head and/or voice
- Presents as a rhythmic tremor (4–12 Hz)
- Typically bilateral, accentuated with goal-directed movement (Action tremor) as opposed to rest tremor (PD)
- Often, it is inherited as an autosomal dominant trait with the tremor becoming apparent by middle age and sometimes as early as childhood

- Diagnosis - Clinical grounds
- No gene or identifiable pathology has been identified for essential tremor
- Abnormalities of the basal ganglia, the cerebellum, the thalamus, the connections between these structures, or a combination of factors may be causative

- Can be confused with
  - Physiologic tremor
    - physical exertion
    - Hyperthyroidism
    - acute hypoglycemia
    - other physical and metabolic stressors
  - Induced tremor from stimulant drugs (including caffeine and the amphetamines), antidepressants, depakote, and β agonist drugs (used to treat asthma)


#peopleshake
"Now to squash a rumor. No, I don't have Parkinson's. I inherited my shaking head from my grandfather Hepburn. I discovered that whiskey helps stop the shaking. Problem is, if you're not careful, it stops the rest of you too. My head just shakes, but I promise you, it ain't gonna fall off!"
- Katharine Hepburn (All About Me, 1993)

Tourette's Syndrome

- Neuropsychiatric condition characterized by the childhood onset of multiple motor and vocal tics
- Repetitive semi-purposeful movements as blinking, winking, grinning or screwing up of the eyes
  - Coprolalia (the inadvertent utterance of obscenities)
  - Cholalia (involuntary repetition of other's phrases)
  - Palilalia (involuntary repetition of one's own utterances)
  - Echopraxia (involuntary mimicking of the action of others)
- Worsen under stress!

- Distinguished from other involuntary movements by the ability of the patient to suppress their occurrence, at least for a short time.
- Often-times, affected individuals have co-existing obsessive-compulsive disorder, learning disabilities, hyperactivity/attention deficit disorder and behavioral problems.

- Although the pathogenic basis is not understood, Tics are believed to result from dysfunction in the thalamus, basal ganglia, and frontal cortex of the brain, involving abnormal activity of the brain chemical, or neurotransmitter, dopamine therefore.
- Tics can be treated with dopamine receptor blocking or dopamine depleting drugs such as neuroleptics.


TOURETTE'S SYNDROME MEETING
NON-SWEAR BOX

Disorders of the Spinal Cord

- **Amyotrophic Lateral Sclerosis (ALS)**

Amyotrophic Lateral Sclerosis (ALS)

- Also called Lou Gerhig's disease and Motor Neuron disease
- Characterized by lower motor neuron lesion and lateral scarring because of upper motor neuron lesion
- Fatal; 80% of people die within 3 years of diagnosis; no effective treatments
- Caused by: Environmental toxins, slow viruses
- Symptom: Excitotoxicity (destructive response of neurons to excessive stimulation)

ALS – Amyotrophic Lateral Sclerosis

- Degenerative disease of UMN & LMN lesions
- Unknown cause autoimmune disorder
- Usually fatal in 1-2 years
- S & S
  - Weakness of hands, loss of grip, tripping, falling
  - Disease begins distally and works proximally
  - No sensation loss, no pain, no mental loss
  - Difficulty speaking and swallowing, drooling
  - Death in 1-3 years from respiratory failure
- Diagnosis
  - History and muscle biopsy

You’re not you

Disorders Arising in the Basal Ganglia

- **Parkinson's Disease**
- **Huntington's Disease**

Parkinson Disease

- Severe degeneration of the basal ganglia (corpus striatum) involving the dopaminergic nigrostriatal pathway
  - Parkinsonian tremor
  - Parkinsonian rigidity
  - Parkinsonian bradykinesia
  - Postural disturbances
  - Autonomic and neuroendocrine symptoms
  - Cognitive-affective symptoms

Parkinson's Disease

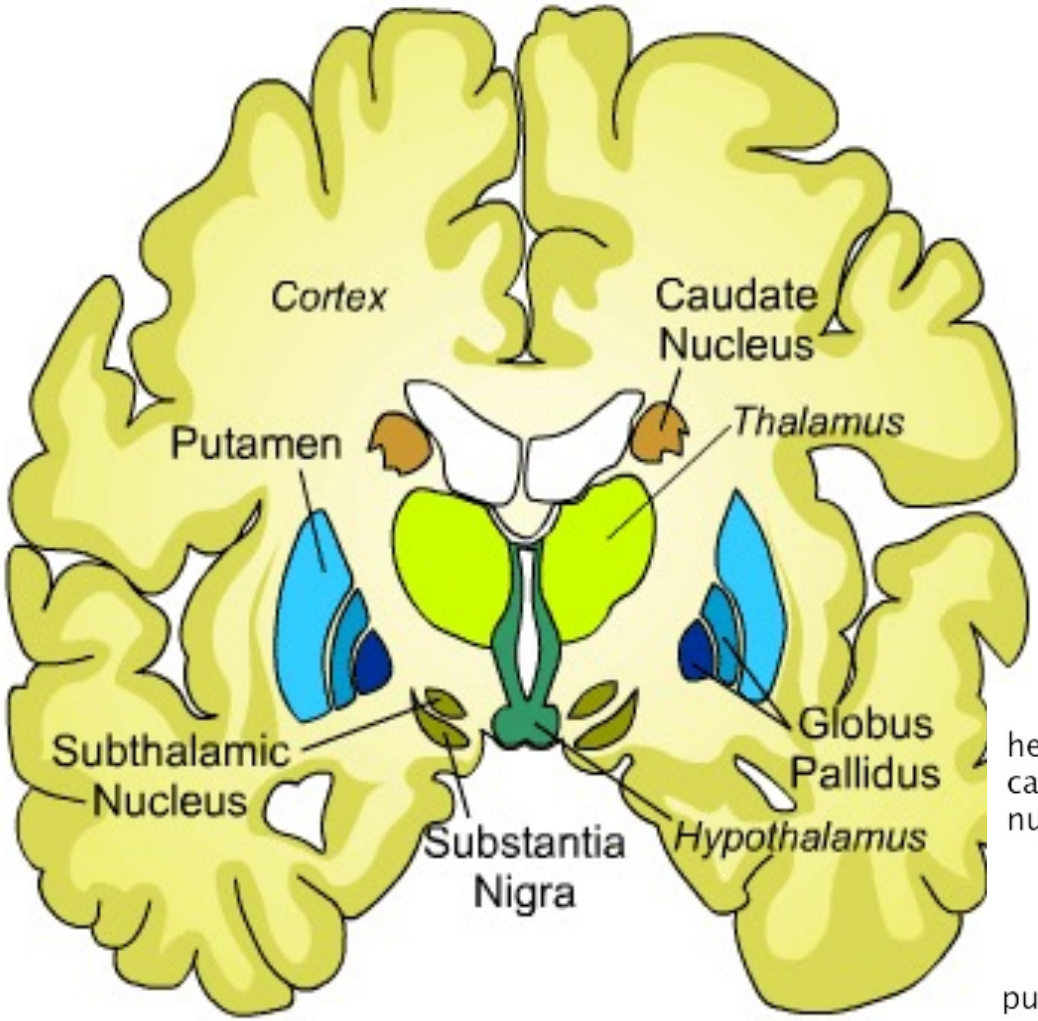
- Slow, degenerative CNS disorder
  - Course of disease lasts 10-20 years
  - Affects twice as many men as women

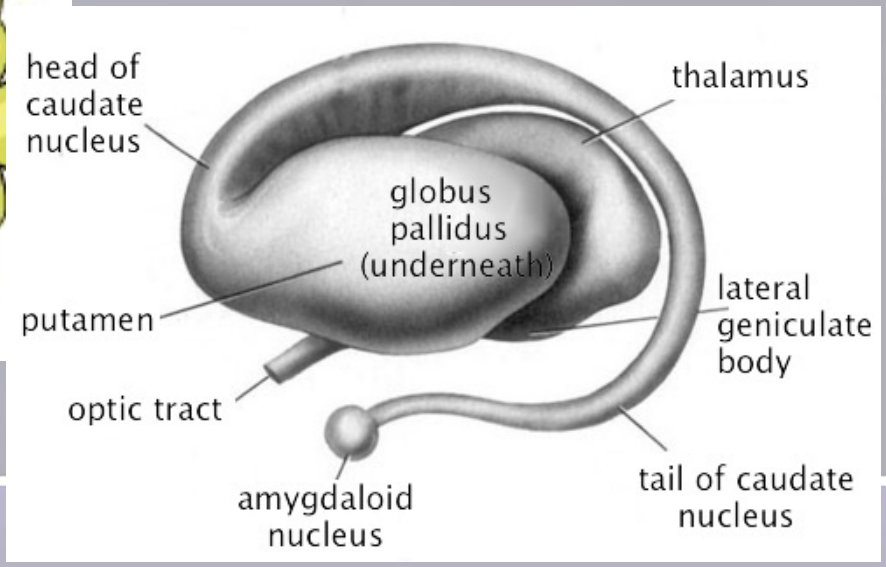
- Caused by damage to the substantia negra
  - Normally provides outflow pathway from basal ganglia to the cortex and a feedback loop to the caudate and putamen

- Impairs flow of motor programs from the basal ganglia
  - Causes bradykinesia (slow movement) and difficulty initiating movement
- Loss of feedback loop expresses itself as resting tremor
- Gradual loss of dopamine-producing cells

- Typically idiopathic
  - Known to result from lesion by toxins
- Symptoms
  - Muscle rigidity, bradykinesia, palsy (resting tremor), tiredness and weakness, poor balance, dementia

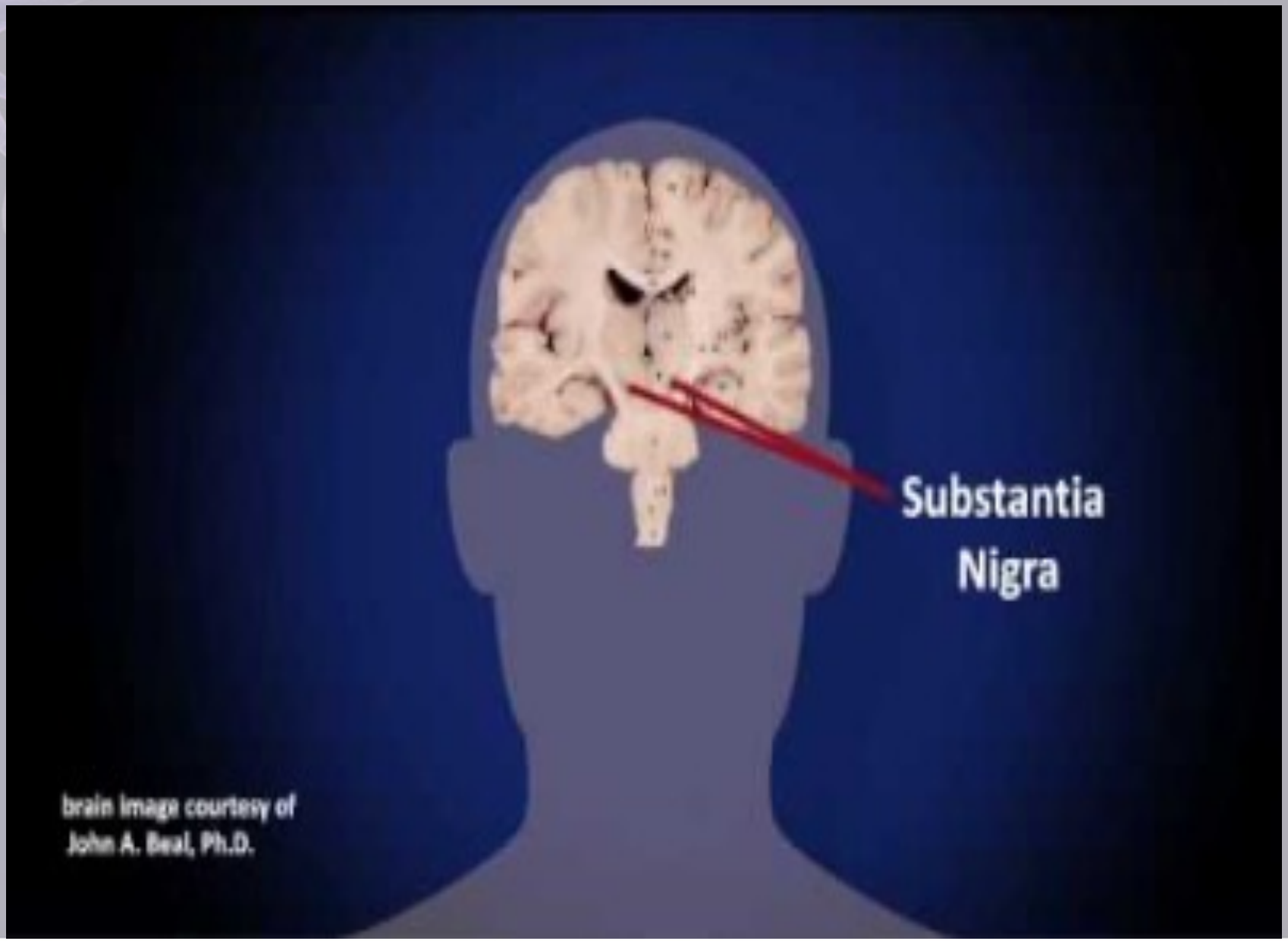
Figure AB-18: Basal Ganglia





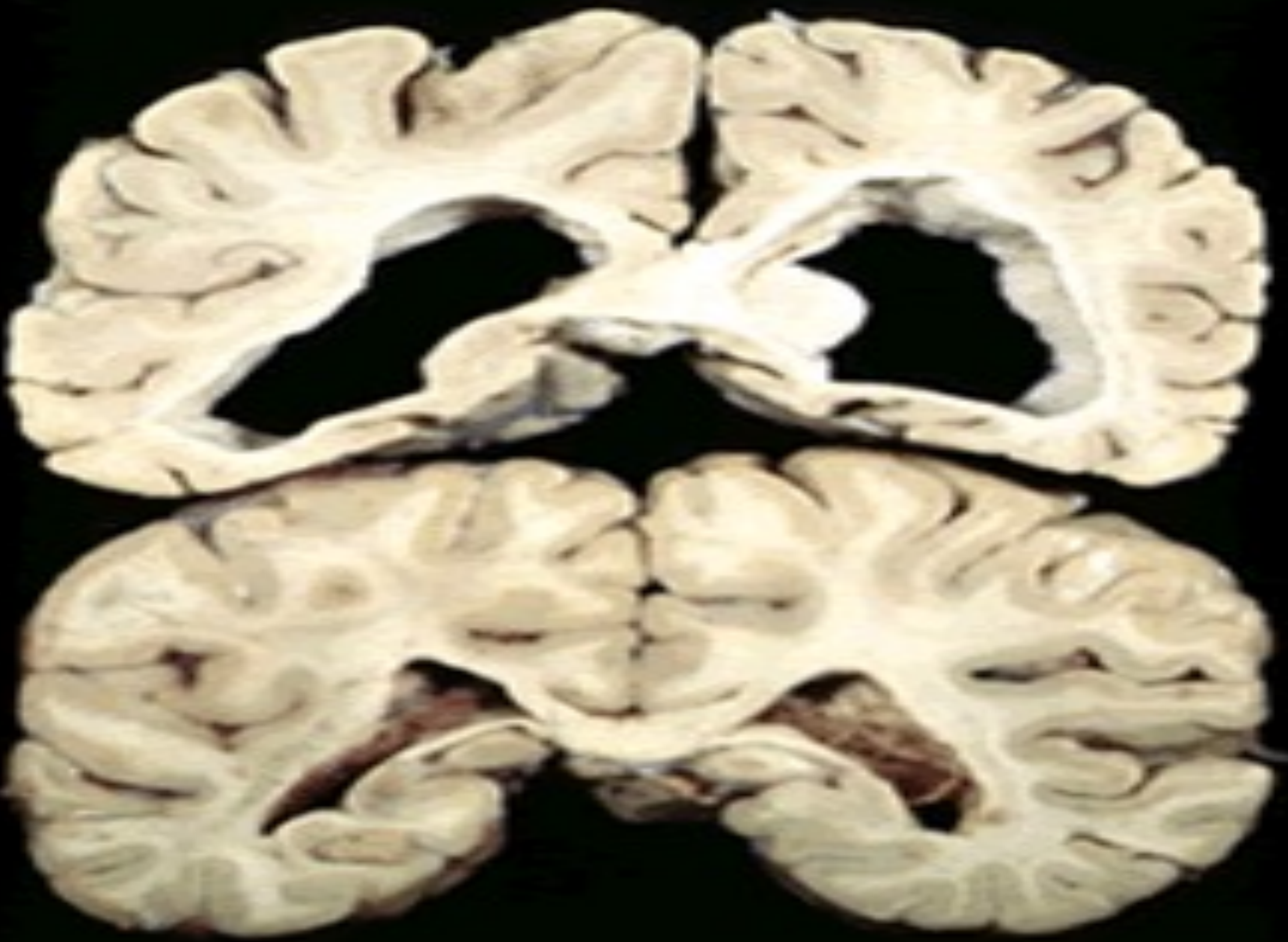
- Degenerative disorder of the basal ganglia
  - Usually in men over 50
  - One million cases in USA
- S & S
  - Four classic symptoms:
    - Resting muscle tremor
    - Slowness of voluntary movement – bradykinesia
    - Impaired postural reflexes – simian posture
    - Inability to maintain balance when being shoved or bumped
  - Other symptoms:
    - Increased muscle tone or rigidity
    - Small “steppage” gaits
    - Frozen facial expression – “masked face”
    - Handwriting changes - micrographia

- Diagnosis
  - No classic diagnostic tests or lab studies
- Treatment
  - Dopamine is used for the first five years
  - Anticholinergic drugs, MAO inhibitors, Symmetryl
  - The meds do not stop the progression, they only provide symptomatic relief
  - Surgical treatment is currently experimental
    - Implanting cadaver or fetal basal ganglion cells


Substantia
Nigra
brain image courtesy of
John A. Beal, Ph.D.

Huntington's Disease

- Characterized by dominant genetic defect on chromosome 4
- Dementia consists of progressive loss of cognitive function
- Massive cellular loss from caudate and putamen
  - Course of disease is about 15 years
- Symptoms: rapid, writhing contortions of hands, arms, face, trunk and profound dementia



The human brain, showing the impact of HD on brain structures in the basal ganglia region of a person with HD (top) and a normal brain (bottom).

http://kobiljak.msu.edu

- Huntington Disease
  - Also known as “chorea”
  - Autosomal dominant hereditary-degenerative disorder
  - Severe degeneration of the basal ganglia (caudate nucleus) and frontal cerebral atrophy
    - Depletion of gamma-aminobutyric acid (GABA)

Cerebral Palsy

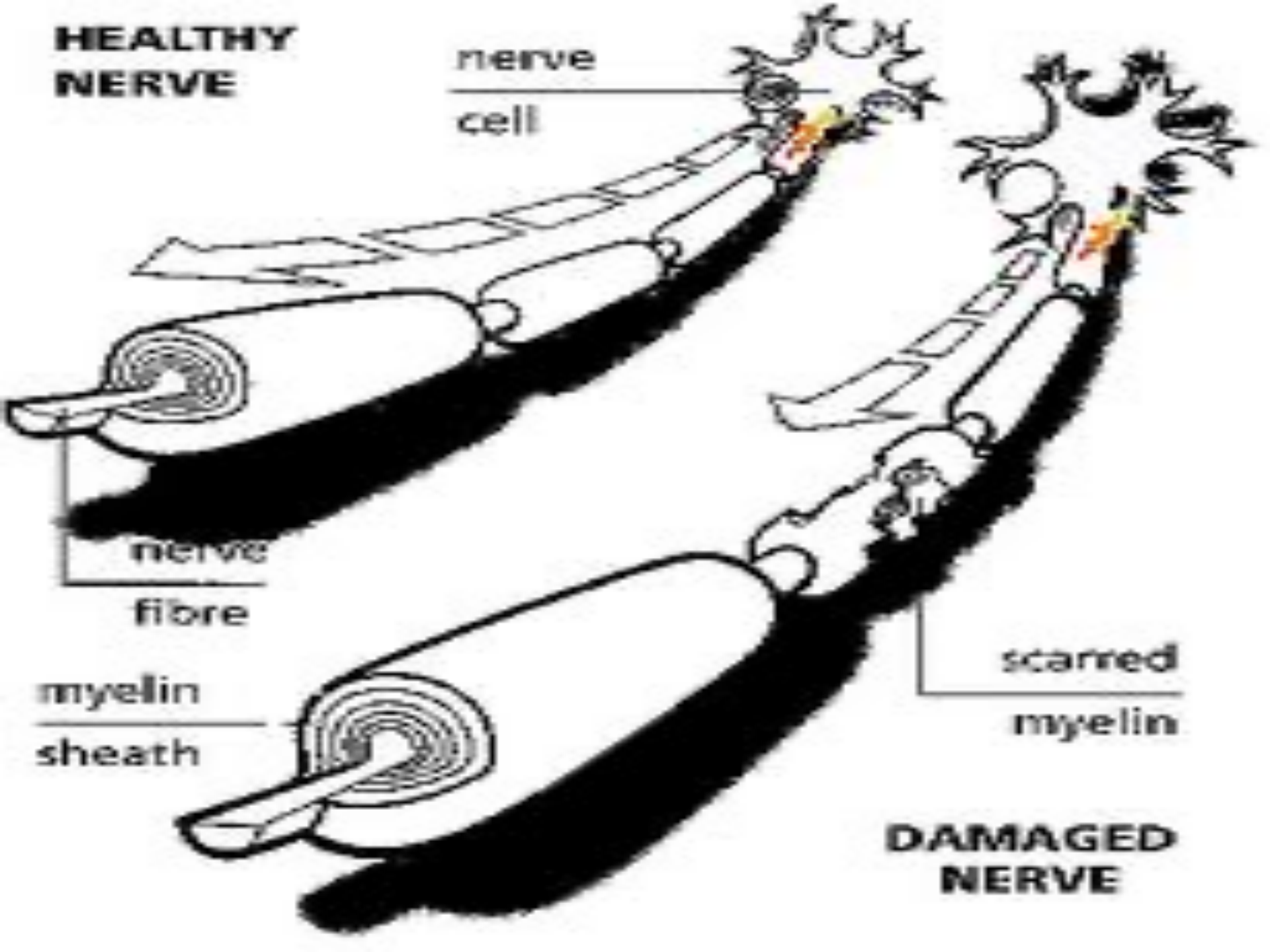
- General term that applies to disabilities that derive from perinatal brain injury
- Movement problems, sensory and cognitive impairment
- CP is commonly classified based on the area of the body most affected
  - Quadriplegic CP – all 4 limbs affected
  - Diplegic CP – lower limbs affected more than upper
  - Monoplegic CP – only 1 limb affected

Demyelinating Disorders

- Multiple sclerosis (MS)
  - MS is a progressive, inflammatory, demyelinating disorder of the CNS
  - Types
    - Mixed (general)
    - Spinal
    - Cerebellar

Multiple Sclerosis (MS)

- Possibly caused by an interaction between a viral illness in teen years and a genetic predisposition
- Arises through a single mechanism of lesion
  - Focal, chronic, progressive
- Areas of demyelination are called **plaques**
  - Confined to white matter
- **Optic neuritis** is often the first symptom
- Chronic exacerbation and remission
  - Triggers: infection, medication, stress, fatigue


HEALTHY NERVE
nerve cell
nerve fibre
myelin sheath
scarred myelin
DAMAGED NERVE

Demyelination in MS