Why We Fall Apart:
The Neuroscience and Neurophysiology of Aging

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Lecture 5:
PARKINSONS DISEASE
The Basal Ganglia
Cortical Motor System

Primary motor cortex
*Execution of movement*
Somatotopy in M1
Cortical Motor System

Pre-motor cortex
Movement planning/sequencing
Cortical Motor System

Posterior parietal cortex (PPC)
Sensory guidance of movement
Subcortical Motor System: Basal Ganglia
Basal Ganglia Circuit

- Gpi/SNr output is inhibitory
- Gpi/SNr input from the striatum is inhibitory, whereas input from the STN is excitatory
Parkinson’s Disease

- Decreased output of SNc dopaminergic projections
  - Decrease inhibition in direct pathway
  - Increase excitation in indirect pathway
- Net effect: more inhibition of thalamus and therefore less excitatory input to motor cortex

Diagram:
- M1, PM SMA → Cortex → Striatum → GPe → STN → SNc → Thalamus → GPi/SNr
- Excitatory (green) and inhibitory (red) pathways

Key structures:
- Cortex
- Striatum
- Thalamus
- M1, PM SMA
- GPe
- STN
- SNc
- GPi/SNr
So what is the basal ganglia circuit doing?

• “Brake” Hypothesis

B.G. essentially acts like a brake to prevent unwanted movement
Subcortical Motor System: Basal Ganglia

Behavioral effects when damaged can include:

- Resting tremor
- Akinesia (paucity of mov’t)
- Muscular rigidity
- Unstable posture
- Bradykinesia (slowness of voluntary mov’t)
- Tic-like involuntary movements
- Hemiballism (sudden involuntary large scale mov’t)
- Possibly obsessive compulsive disorder, Tourette’s, stuttering
- Assorted cognitive deficits (e.g., aphasia)

Parkinson’s disease
Huntington’s disease
What is Parkinson’s Disease?
Defining IPD

- Named after James Parkinson who published 'An Essay on the Shaking Palsy' in 1817, which established Parkinson's as a recognised medical condition.

- He studied at the London Hospital Medical College, qualifying as a surgeon in 1784 when he was 29.
The term "parkinsonism" refers to any condition that involves a combination of the types of changes in movement seen in Parkinson's disease, which happens to be the most common condition causing this group of symptoms.
Parkinson Disease (PD)

- Usually idiopathic
- Substantia nigra degeneration causes dopamine deficiency in striatum → motor symptoms
- *Dopaminergic therapy relieves motor symptoms*
• Male or Female
• Ages 50 – 80 (can be earlier than 20)
• 55,000 in Canada (0.2% of population)
• Reduces life expectancy due to increased incidence of infection associated with chronic immobility
Figure 1
Prevalence of Parkinson’s disease in household population, by age group and sex, population aged 45 or older, Canada excluding territories, 2010/2011

* significantly different from women (p < 0.05)
E use with caution

Table 1
Mean age at symptom onset and diagnosis of Parkinson's disease, by age group at symptom onset, household population aged 18 or older, Canada excluding territories, 2011

<table>
<thead>
<tr>
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<th>Age group at symptom onset</th>
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<tbody>
<tr>
<td></td>
<td>Younger than 50</td>
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<tr>
<td>Mean age at diagnosis</td>
<td>50.7**</td>
</tr>
<tr>
<td>Mean age at symptom onset</td>
<td>43.8</td>
</tr>
<tr>
<td>Mean years between symptom onset and diagnosis</td>
<td>6.9*</td>
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</tbody>
</table>

** significantly different from mean age of symptom onset (p < 0.01)
* significantly different from other age groups (p < 0.05)

Source: 2011 Survey of Living with Neurological Conditions in Canada.
PARKINSON'S DISEASE

Substantia Nigra

Normal Neuron

Parkinson's Affected Neuron

Dopamine

Normal Movement

Movement Disorders
• caused by progressive deterioration of dopamine producing nerve cells in the basal ganglia

• insufficient dopamine disturbs the balance between dopamine and other transmitters, such as acetylcholine.

• without dopamine, the nerve cells cannot properly transmit messages, and this results in the loss of muscle function.

• the exact reason that the cells of the brain deteriorate is unknown.
1. Dopamine producing neurons die
2. More Lewy bodies – abnormal proteins that inhibit regular brain function
Lewy Bodies in the substantia nigra region in brains of Parkinson's patients
Pathology

- Depletion of pigmented dopaminergic neurons in SN
- Reduced dopaminergic output from SN
- Inclusion bodies (Lewy bodies) develop in nigral cells
- Degeneration in other basal ganglia nuclei
- Neurons in subthalamic nucleus become more active than usual in inhibiting activation of the cortex

Bradykinesia
Dopamine

concentrated in very specific groups of neurons collectively called the basal ganglia
Nigrostriatal system: motor control

Mesolimbic: regulating emotional behavior

Mesocortical: executive control, reinforcement learning
PD Course and Prognosis

- Biochemical onset is much earlier than symptoms onset.
- Initial symptoms are subtle, i.e., non-motor symptoms or mild weakness, discomfort in the back, neck, and limbs, etc.
Defining IPD

- Parkinsonism
  - Multiple systems atrophy
  - Progressive supranuclear palsy
  - Drug-induced parkinsonism
  - Lewy body dementia
  - Vascular parkinsonism

IPD
Differential diagnosis of parkinsonism

- **Parkinson disease** (idiopathic or genetic)

- **Parkinson-plus degenerations** (dementia with Lewy bodies, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy)

- **Drug-induced parkinsonism** (anti-dopaminergics)

- Rare but treatable in young people: Wilson disease and Dopa-responsive dystonia

- Other: “vascular” parkinsonism, brain trauma, CNS infection
• Parkinson’s Disease not just a motor problem:

• Depression
• Dementia
• Hallucinations
• Overall mental deterioration
Parkinson disease: Common early complaints

- Resting tremor
- Writing smaller; harder to do buttons
- Slowness, “weakness”, limb not working well
- Stiff or achy limb
- Stoop, shuffle-walk, “dragging” leg(s)
- Trouble getting out of chairs or turning in bed
- Low or soft voice

- Non-motor: anosmia, dream enactment, constipation, anxiety, depression, “passiveness”
# Signs and Symptoms of PD

<table>
<thead>
<tr>
<th>Motor symptoms (TRAP)</th>
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<tbody>
<tr>
<td><strong>Tremor at rest</strong>: &quot;Pill rolling&quot;</td>
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<tr>
<td><strong>Rigidity</strong> (stiffness): &quot;lead pipe&quot; or like a &quot;cogwheel&quot;</td>
</tr>
<tr>
<td><strong>Akinesia</strong> (inability to move) or <strong>Bradykinesia</strong> (slow movement). Includes mask-like face micrographia, freezing, impaired swallowing</td>
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<tr>
<td><strong>Postural instability with gait problems</strong></td>
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</tbody>
</table>
Clinical features

- Bradykinesia
- Rigidity
- Postural instability
- Resting Tremor

IPD
Clinical features

Resting Tremor

- Present: At rest, when distracted
- Diminished: On action
- Pill-rolling at rest

Arms/legs/feet /jaw/tongue
Resting tremor
Tremor

- An involuntary movement which may affect the head, limbs, or entire body.
- Most apparent when limb is related and supported
- Increased with stress
- Ceased during sleep
- Decreased with intentional movements
- ‘Pill rolling tremor’ if most prominent in fingers and hand
- Most bothersome, yet least disabling of all symptoms
Clinical features

- Cogwheel rigidity (upper limbs)
- Flexed posture
- Lead pipe rigidity (legs)
- Increased tone when opposite arm moves actively
Clasp-knife rigidity
Rigidity

- Muscular stiffness and increased muscle tone
- Patients usually unaware of rigidity but troubled with slowness
- More apparent to doctor than patient
- Cogwheeling (affect when moving arms)
Clinical features

- Bradykinesia
  - Difficulty initiating movement
  - Reduced spontaneous blinking
  - Facial immobility (hypomimia)
  - Poor rapid fine movements (fingers)
Bradykinesia/Akinesia

- Akinesia: inability to move
- Bradykinesia: slowness of movement
Clinical features

- Loss of postural reflexes
- Postural instability
  - Difficulty making turns
  - Retropulsion
Postural Instability

- Impaired righting ability
- Toe-first walk develops
- Decreased arm swing when walking
- Posture stooped, knees flexed while walking
- Unsteadiness while turning
- Falls will occur
Clinical features

Gait:

i) Stooping
ii) Slow to initiate walking
iii) Shortened stride
iv) Rapid small steps (shuffling)
v) Tendency to run (festinating)
vi) Reduced arm swing
vii) Impaired balance on turning

• Falls common in later stages.
• Parkinson’s gait
Clinical features

• Speech

- Monotone → tremulous, slurring dysarthria.
- Soft, rapid, indistinct.

• Cognitive

- Cognitive impairment in 1/3 of patients (loss of executive functions including planning/decision-making/controlling emotions).
- Depression.
Clinical features

- Constipation/heartburn/dribbling/dysphagia/weight loss.
- Greasy skin.
- Micrographia (small cramped writing).
Clinical features

- Tremor
- Stooped posture
- Masklike facies
- Arms flexed at elbows and wrists
- Rigidity
- Hips and knees slightly flexed
- Short shuffling steps
**Postural Instability**
- Impaired righting ability
- Toe-first walk develops
- Decreased arm swing when walking
- Posture stooped, knees flexed while walking
- Unsteadiness while turning
- Falls will occur

**Non-Motor Symptoms**

- Psychological (i.e., depression, psychosis, anxiety, apathy, memory problems)
- Sleep (i.e., RLS, REM behavior disorder)
- Autonomic Dysfunction (i.e., constipation, drooling, decreased BP, temp regulation)
- Other (i.e., fatigue, speech, swallowing, seborrhea, pain, weight loss)
Stage 1

- Mild one sided tremor or rigidity
- Affected arm in semiflexed position with tremor
- Patient leans to affected side
Stage 2

- Bilateral involvement
- Early postural changes
- Slow, shuffling gait
- Decreased stride length
Stage 3

- Pronounced gait disturbances
- Moderate generalization disability
- Balanced is a major problem
- Server tremor, rigidity and/or brandykinesia
Stage 4

- Significant disability
- Limited ambulation with assistance
Stage 5

- Loss of ability to function independently
- Brandykinesia very severe
- Independent mobility impossible
Phases and Course of PD

Dopaminergic Neuron Number and Function

Asymptomatic

Symptomatic

Disease Severity

100%

50%

Diagnosis

Symptoms

Motor Complications

Cognitive Decline
## Motor Problems with Advancing PD

- **Dyskinesia** (abnormal involuntary movements)
  - **Chorea** (dance-like movements), mostly occurs with too much dopamine
  - **Dystonia** (sustained or spasmodic muscle contraction), mostly occurs with too little dopamine.

- **Akathisia** (motor restlessness) - patient feels he must constantly move
Motor Problems with Advancing PD

- Motor Fluctuations
  - Wearing off – dose wears off early
  - Random on/off – unpredictable offs

- Freezing (motor block) tends to occur suddenly and exacerbated by anxiety.
Treatment
Treatment of Parkinson’s Disease

• Since PD is related to a deficiency of dopamine, it would be appropriate to administer dopamine

• Problem: Dopamine cannot cross BBB
Levodopa

used to increase dopamine levels

can cross the blood-brain barrier

(dopamine cannot)

once in CNS metabolized to dopamine
PD: meds for motor symptoms

• L-dopa (with carbidopa) is most effective and usually best tolerated

• Dopamine agonists (ropinirole, pramipexole)

• Others have only modest benefits (MAO-B inhibitors, anticholinergics, amantadine)
Levodopa Therapy Motor Fluctuations

Dyskinetic

Normal

Akinetic

6:00 9:00 Noon 3:00 6:00
Debate as to why it works!
Alleviates motor symptoms
Not a cure!
Early PD: When to start meds?

• Drugs are symptomatic, not neuroprotective or neurotoxic

• Level of patient function is best guide

• Response to dopaminergic therapy (especially l-dopa) is the best available “test” for PD

** Remember the value of exercise! **
Which treatment to start?

• L-dopa most effective for motor symptoms in general (bradykinesia, tremor, gait changes)

• Family physicians can start levodopa !!

• Dopamine agonists cause more non-motor side effects, and are best avoided in patients above 70
Treatment pearls in early PD

• Fear not L-dopa. “Delaying L-dopa” is of no benefit long-term.

• Treat more for symptoms and function, and less for how the patient “looks”.

• Generics are fine.

• Allow adequate dose and time to work before concluding “failure” or “not PD”.

• Resting tremor may be medication refractory in some patients; don’t conclude “not PD”.
Levodopa

• Most effective overall for motor symptoms

• A fine option for initial therapy of PD

• By mid to late disease it is almost always needed

• Non-motor side effects include nausea, orthostasis, sleepiness, hallucinations; but not as much as other PD drugs

• Motor side effect: dyskinesias
Dopamine agonists (ropinirole, pramipexole, rotigotine)

• Can be monotherapy in early disease; need L-dopa in mid to late disease

• Can add to L-dopa to reduce OFF time

• Frequent side effects! Nausea, sleep attacks, hypotension, compulsive behaviors, LE edema 😞

• More prone than L-dopa to causing hallucinations and confusion. Caution in older or demented patients! 😞
Mid to late PD: a tricky business

- More motor complications including dyskinesias and ON-OFF fluctuations
- More drug-resistant motor symptoms (e.g. impaired balance with falls)
- More nonmotor symptoms (especially dementia and hallucinations)
- More medications, so more side effects

Managing these complexities requires experience.
“Motor complications” as PD progresses

• Fluctuations. Medication wears off before next dose. OFF periods worse as disease progresses.

• Dyskinesias (usually at the peak of ON).

• Need larger and/or more frequent med doses, or combinations of drugs.

• Deep brain stimulation an option for some patients with medically refractory motor complications.
Depression and anxiety

• It’s not just because of the stress of the diagnosis
• Motor symptoms and wearing off can interact with mood and anxiety levels
• Can misinterpret “poker face” as depression. Ask the patient!
• SSRI’s can work; avoid benzodiazepines
Depression and anxiety: other considerations

• Consider support services / psychotherapy for patients and caregivers

• Geriatric psychiatrists usually have better expertise in this population
REM sleep behavior disorder

- Typically in men, often years before motor symptoms
- Complex movements or fighting
- Usually early in the morning, varying frequency
- Patient or bed partner injury
Insomnia

- Can be primary or secondary
- Address sleep hygiene
- Review med list
- Treat nighttime motor symptoms
- Think about OSA
- Treat psychiatric comorbidities
- Sedative/hypnotics: melatonin, trazodone, mirtazapine, clonazepam (if RBD)
Hypersomnia

- PD increases sleep need for many patients
- Poor sleep at night (many causes)
- Think about OSA
- Review med list (make special note of dopamine agonists, anticholinergics, benzos, other sedatives)
Fatigue

• “Tired”, “Wiped out”, “No energy”
Is it:
Sleepiness? Wearing off? Motor? Mood?
• Isolated fatigue can be disabling
• No established treatment, though anti-depressants and stimulants have been tried
• Encourage light exercise, hobbies, etc
• We badly need better treatments for this
Hallucinations & Dementia in PD

- Complicate many longstanding PD cases
- Hallucinations are usually visual
- Main contributors are disease progression (brain pathologic changes), age, and meds
- Older patients much more at risk
- \textit{Marker for increased morbidity, mortality, and institutionalization}