PARKINSON DISEASE

James Parkinson, 1817
affects older adults, ≥ 55 years
second most common
movement disorder
(after essential tremor)

hypokinetic defects
present unilaterally

patients have greatest difficulty
in two simultaneous or
sequential movements
sequential program

Petri net
bradykinesia (slow movement)

akinesia (absent movement)

masked face

d↓ eyeblinks
d↓ facial expressions
d↓ head movements

muscular rigidity

leadpipe (unyielding)
cogwheel (ratcheting)

loss of postural adjustment

Parkinsonian stance

stumbles become falls

marche à petit pas (festinating gait)
handwriting
micrographia
large amplitude, fast → small, slow

large fast
Eduard small slow

can reconstruct PD onset from dated handwriting samples

speech
↓ volume hypophonic
↓ pitch, cadence changes
monotonous, robotic
<table>
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<th>NT</th>
<th>neuron survival</th>
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<tbody>
<tr>
<td>SNC</td>
<td>DA</td>
<td>-</td>
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<tr>
<td>VTA</td>
<td>DA</td>
<td>+/-</td>
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<tr>
<td>locus coeruleus</td>
<td>NE</td>
<td>+/-</td>
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progressive loss of catecholamine neurons often asymmetric
cognitive and personality changes

30% PD patients have comorbid depression

20% PD patients develop dementia and/or psychosis

(cf. 100% for HD)

dementia absent at onset

most PD patients work \geq 5 years after diagnosis

idea neuron death in VTA may cause dementia/psychosis
L-tyrosine → tyrosine hydroxylase → DOPA decarboxylase

L-DOPA → DOPA decarboxylase → dopamine β-hydroxylase

DA, dopamine → dopamine β-hydroxylase → NE, norepinephrine (≡ noradrenaline)

NE, norepinephrine → epinephrine (≡ adrenaline) → N-methyl transferase
1970s: partial animal model of PD by microinjection of 6-hydroxydopamine along nigrostriatal projection.

1982: four young adults in San Jose, CA develop Parkinsonism from neurotoxin MPTP that contaminates batch of street Demerol (meperidine).

in DA neurons

MPTP $\xrightarrow{\text{MAO}}$ MPP$^+$

inhibits mitochondrial oxidative metabolism, kills neurons

similar insecticide rotenone
drug-induced Parkinsonism

D2R blockers (anti-psychotics)
bilateral onset
symmetric course

drug-induced choreoathetosis

dopamine precursor L-DOPA
or dopamine agonists
first improve PD symptoms but
later cause dyskinesia
electrical self-stimulation

James Olds  Peter Milner  1950s

electrodes placed near the medial forebrain bundle
reinforce virtually any operant behavior
examples: location in box lever-press

animals ignore food, water to lever-press to point of exhaustion
originally "pleasure centers" in brain
today axon tracts of midbrain dopamine neurons
Dopamine connection

DA antagonists block electrical self-stimulation

DA agonists (cocaine) are drugs of addiction
Allocortex

VTA

Nucleus accumbens

Cocaine, amphetamine ↑ DA action

MFB

Opiates, nicotine ↑ DA release
Primary goals/drives presented in hypothalamus mesolimbic DA system distributes credit for goal attainment stamps in that behavior credits a hierarchy of secondary goals over lifetime drugs of abuse bypass the need for success of the primary goal reinforce all actions linked to drug consumption
Cortex, Brainstem

Striatum - Pallidum

Midbrain Dopamine
allocortex
prefrontal cortex
motor cortex
Aside

Executive-motor cortical hierarchy of the frontal lobe has a matching mesostriatal hierarchy of reward

Challenge

Integrate two views of BG

1. Sequential control and communication in well-learned behavior

2. Learning behavioral plans