Introduction to Neuroscience: The Basal Ganglia

Michal Rivlin
Basal Ganglia— a group of subcortical nuclei

- Striatum: caudate & putamen
- Globus pallidus (external & internal segments)
- Subthalamic nucleus
- Substantia nigra (pars compacta & pars reticulata)
Basal ganglia-thalamo-cortical loop

- Basal Ganglia receives robust input from the cortex

- Principal projection of the BG – via the thalamus back to cortical targets
Overview of BG organization

- **Input:**
  - Caudate and putamen (together, the striatum)

- **Intrinsic:**
  - Subthalamic nucleus (STN)
  - External segment of globus pallidus (GPe)

- **Output:**
  - Substantia nigra pars reticulata (SNr)
  - Internal segment of globus pallidus (GPi)

- **Neuromodulator:**
  - Substantia nigra pars compacta (SNc)
Striatum: Medium spiny neurons

- Caudate and putamen

- Medium spiny neurons
  - 95% of neurons; primary projection neurons
  - GABAergic; inhibitory
  - Very little spontaneous activity

Striatum: Intrinsic interneurons

2 principle types

- 3 GABAergic interneurons

- Tonically active neurons (TANs)
  - Cholinergic
  - Large cell bodies
Globus pallidus

Two segments

Internal (GPI): Principle output nucleus
External (GPE): intrinsic circuitry
Globus pallidus
Subthalamic nucleus

Glutamatergic; excitatory
Substantia nigra

- Midbrain

- SN pars reticulata (SNr)
  - GABAergic
  - high tonic firing rates
  - Output of BG

- SN pars compacta (SNC)
  - Neuromelanin-containing cells
  - Dopaminergic
  - Tonic/phasic firing
Direct and indirect pathways

Diagram showing the flow from Cortex to Striatum, then to GPe, STN, GPi/SNr, SNc/VTA, and Thalamus, with labels for excitation, inhibition, and dopamine modulation.
Direct pathway promotes action
Indirect pathway suppresses action
Hyperdirect pathway

[Diagram showing the hyperdirect pathway in the brain, indicating excitatory and inhibitory connections between structures like Cortex, Striatum, GPe, STN, GPi/SNr, Thalamus, and Brainstem.]
Role of Basal Ganglia

BG dysfunction has been associated with numerous conditions including Parkinson's disease, Huntington's disease, Tourette's syndrome, schizophrenia, attention-deficit disorder, obsessive-compulsive disorder, and many of the addictions.

• Motor control
• Learning
• Motivation and reward
• Cognitive tasks
Reinforcement learning

• Supervised learning –
  All knowing teacher, detailed feedback

• Reinforcement learning –
  Learn and relearn based on actions and their effects (rewards)

• Unsupervised learning –
  Self organization
Rescorla-Wagner rule (1972)

• The idea: error-driven learning
• Change in value is proportional to the difference between actual and predicted outcome

\[ \Delta V = \eta [R - V] \]

- Learning rate
- Outcome: Reward value
- Reward predicted
TD learning

\[ V_t^{\text{new}} = V_t^{\text{old}} + \eta (r_{t+1} + V_{t+1}^{\text{old}} - V_t^{\text{old}}) \]

`truer` value of current state:
Reward at present state +
Estimated value of next state

Estimated value
of current state

temporal difference prediction error \( \delta(t+1) \)

\( V_t = \) Estimated value of current state based on predicted future reward

\( r_t = \) reward given at time \( t \)

\( \eta = \) Learning rate
The computational machinery of the Basal Ganglia

The basal ganglia networks are built as Actor-Critic network and employ temporal difference algorithms.

Dopamine provides the pleasure prediction error.
Dopamine match surprise signal

Schultz et al., 1997
Dopamine match surprise signal

Dopamine signal = reward occurred – reward predicted
Dopamine neurons encode the (positive) mismatch between predictions and reality

Genela Morris et al., Neuron, 2004
Effects of dopamine

- Learning = plasticity
- Teaching = modulating synaptic plasticity
- Cortico-striatal synapses are known to undergo long-term changes in synaptic efficacy.
  - Long-term potentiation (LTP) is mediated by activation of dopamine D1 receptors
  - Long-term depression (LTD) is mediated by activation of dopamine D2 receptors
The strive for the dopaminergic reward

- Cocaine and amphetamines increase amount of dopamine by inhibiting its reuptake into the synaptic terminals.
- Opiate narcotics increase dopamine release by disinhibiting dopaminergic neurons.
- Nicotine increases striatal dopamine.
- A prolonged increase in dopamine levels may affect synaptic plasticity and provide the neural basis for drug addiction.
It’s not all about dopamine: balance between neurotransmitters
Parkinson’s disease (PD)

Clinical symptoms
• Akinesia/bradykinesia,
• Tremor,
• Muscular rigidity,
• Postural deficits
• Emotional and cognitive deficits

Epidemiology
• 3/1000 of total population
• Mean age of onset – 60 years
• 1/100 of >60 years

James Parkinson, 1817
Parkinson’s disease: depletion of dopamine

Tyrosine hydroxylase catalyzes L-DOPA, a precursor for dopamine
Effects of dopamine depletion on direct and indirect pathways

A Normal

B MPTP

Direct pathway promotes action
Indirect pathway suppresses action
1967-9, George C. Cotzias: L-DOPA (a precursor of dopamine that cross the blood brain barrier) is established as the gold-standard therapeutic agent for Parkinson's disease.

1970 – today: Dopamine replacement therapy (L-DOPA, post synaptic agonists, etc)
The limits of dopamine replacement therapy

Levodopa-induced dyskinesia
Dystonia
The MPTP model of Parkinson’s disease

MPPP (1-methyl-4-propionoxypiperidine)
- a reverse ester of meperidine and a potent narcotic
- easy to synthesize
- synthesis typically results in MPTP as byproduct.

1976: A college student synthesized and abused MPPP for 6 months.
- made a 'sloppy batch', and became severely Parkinsonian.
- Pathology: severe cell loss limited to the SN (Davis et al. 1979).

1982: MPPP was distributed en-mass in California as 'synthetic heroin'
- young drug abusers arriving in ER with advanced Parkinsonism.
- typical Parkinsonian rest tremor in about half (3-4/7) of MPTP patients (Langston et al. 1983, 1987, 1995).
The MPTP model of Parkinson’s disease
Appearance of neuronal oscillations

- The parkinsonian brain demonstrates oscillatory activity:
  - PD patients during brain surgery
  - MPTP primates

Neural oscillations (5-15 Hz)
Spontaneous activity

- Neuronal oscillations appear in the GP as well as in MI

- Tremor frequency differs from cortical frequency
Inactivation of the subthalamic nucleus ameliorates Parkinson symptoms of the MPTP monkey

Bergman, Wichmann and DeLong, 1990
Deep brain stimulation (DBS)

- Deep brain stimulation (DBS) is used as a treatment for advanced PD.
- An electrode is located in the STN/GPi and high frequency stimulation (~130 Hz) is given through the electrode.
BG hyperkinetic disorders

• Huntington’s disease
  – striatal projection neurons become dysfunctional and degenerate
  – causes defects in behavior and uncontrolled movements.
  – hereditary disease
• Hemiballismus
  – Reduced activity in the subthalamic nucleus
  – Repetitive, large amplitude involuntary movements of the limbs
BG non-motor disorders

- Tourette syndrome
- Obsessive-compulsive disorder
- Attention-deficit hyperactivity disorder (ADHD)
- Addiction