Introduction to Neuroscience: The Basal Ganglia

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Basal Ganglia anatomy – a short introduction

- 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

GABAergic; inhibitory
high tonic firing rates
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 pathways involving Cortex, Striatum, SNC/VTA, GPe, STN, GPI/SNr, Thalamus, and Brainstem, with arrows indicating excitation, inhibition, and dopamine modulation.]
Direct pathway promotes action
Indirect pathway suppresses action
Hyperdirect pathway
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

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

'truer' value of current state:

- Reward at present state +
- Estimated value of next state

Estimated value of current state

\[ V_{t} = \text{Estimated value of current state based on predicted future reward} \]

\[ r_{t} = \text{reward given at time } t \]

\[ \eta = \text{Learning rate} \]
The basal ganglia networks are built as Actor-Critic network and employ temporal difference algorithms.

Dopamine provides the pleasure prediction error
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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.

- Treatment of major emotional disorders (Schizophrenia, ADHD and major depression) is done by manipulation of dopamine transmission.

Electrical self-stimulation in neuronal pathways associated with dopamine. Olds and Milner, 1954
It’s not all about dopamine: balance between neurotransmitters

Mn109
M. Mulatta

AC+9.6
A:28.2
AC+4.8
A:23.7
AC+0
A:18.7
AC-4.8
A:13.3

Figure

Neural Pathways Involved in Movement

Substantia Niagra

DA

(-)
Basal Ganglia

ACh

(+)
GABA

(-)
Cortico-Spinal Tracts

Role of 5-HT

Raphe Nuclei

5-HT

(-)
Substantia Niagra

(-)
DA

(+)
Basal Ganglia

ACh

GABA

(-)
Cortico-Spinal Tracts

DA Blockade

(-)
Substantia Niagra

(-)
Basal Ganglia

ACh

(+)
GABA

(-)
Cortico-Spinal Tracts

Source: Leo RJ (2001)
Parkinson’s disease: depletion of dopamine

Parkinson

Normal

Substantia nigra

Striatum
Effects of dopamine depletion on direct and indirect pathways

Direct pathway promotes action
Indirect pathway suppresses action
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
Dopamine replacement therapy of Parkinson’s disease

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, MAO-B and COMT inhibitors, etc)
The limits of dopamine replacement therapy

Levodopa-induced dyskinesia
Dystonia
MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
- 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
Inactivation of the subthalamic nucleus ameliorates Parkinson symptoms of the MPTP monkey

Bergman, Wichmann and DeLong, 1990
Appearance of neuronal oscillations

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

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

- Tremor frequency differ from cortical frequency
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