Introduction to Neuroscience: The Basal Ganglia

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Basal Ganglia— a group of subcortical nuclei

- Striatum: caudate & putamen (& nucleus accumbens in the ventral striatum).
- 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
  - 2 types: striatonigral (express D1 receptors) and striatopallidal (express D2 receptors).
Striatum: Intrinsic interneurons

2 principle types

– 3 GABAergic interneurons

– Tonically active neurons (TANs)
  • Cholinergic
  • Large cell bodies
Globus pallidus (=pale globe)

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 (=black substance)

- **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
Direct pathway promotes action
Indirect pathway suppresses action
Hyperdirect pathway

[Diagram showing the hyperdirect pathway in the brain, including connections between the cortex, striatum, thalamus, and various other brain regions. The diagram includes excitatory and inhibitory pathways, as well as dopamine modulation.]
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.
  Relies on the discrepancy between what was expected and what is actually observed.

• Unsupervised learning –
  Self organization
Classical (Pavlovian) conditioning

1. Before Conditioning
   - Neutral Stimulus
   - Ear Movement (Unconditioned response unrelated to meat.)

2. Before Conditioning
   - Unconditioned Stimulus
   - Salivation (Unconditioned Response)

3. During Conditioning
   - Salivation (Unconditioned Response)

4. After Conditioning
   - Conditioned Stimulus
   - Salivation (Conditioned Response)
Rescorla-Wagner rule for classical conditioning (1972)

- The idea: error-driven learning
- Change in value is proportional to the difference between actual and predicted outcome (=the prediction error).

\[ V_{\text{new}} = V_{\text{old}} + \eta(R - V_{\text{old}}) \]

- 0 < Learning rate ≤ 1
- Outcome: Reward value
- Reward predicted
TD learning

$V_t = \text{Estimated value of current state based on predicted future reward}$

$r_t = \text{reward given at time } t$

$\eta = \text{Learning rate}$

Sutton & Barto
Marr’s Tri-level hypothesis

• David Marr (1945-1980) proposed that to understand information processing systems three levels of analysis are required:

1. Computational Level: what problem does the system solve? **optimal prediction of future reinforcement**

2. Algorithmic Level: what is the strategy? **temporal difference learning**

3. Implementational Level: how it is actually done by networks of neurons? **does the brain use TD learning?**

Based on lectures by Yael Niv
The computational machinery of the Basal Ganglia
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

No prediction
Reward occurs

Reward predicted
Reward occurs

Reward predicted
No reward occurs

Schultz et al., 1997
Dopamine match surprise signal

Dopamine signal = reward occurred – reward predicted
Dopamine activity is proportional to reward value

Unexpected reward of different liquid volumes

Tobler et al., Science 2005
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, which are dopamine dependent.
  - 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.

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

True story of a British neurologist Oliver Sacks: Between 1915 and 1926, an epidemic of encephalitis lethargica (sleeping sickness) spread around the world; Oliver treated them with L-DOPA.
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
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 Parkinsonian 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 (nonvoluntary movement/vocal tics).
• Obsessive-compulsive disorder
• Attention-deficit hyperactivity disorder (ADHD)
• Addiction
Suggested reading

• Niv & Schoenbaum (2008) - Dialogues on prediction errors - a guide for the perplexed

• Barto (1995) - adaptive critic and the basal ganglia - TD learning in the basal ganglia