Introducing Dopamine and Serotonin
Background: The Synapse
Receptor binding
DA and 5-HT

• One thousand times less common than the major neurotransmitters
• Mainly modulatory, slow
• Originate in brainstem, but released throughout the entire brain and spine
Glutamate

The most common excitatory neurotransmitter Glutamate is released by 80% of neurons

Learning

Memory
Dopamine

The Salience Neurotransmitter
Rewards sex, eating
Increases alertness, happiness
Serotonin (5-HT)

The Satiety Neurotransmitter
Feelings of fullness, contentment
Relieves depression
Serotonin

Dimethyltryptamine (DMT)

Ondansetron (Zofran)

Psilocybin
Serotonergic drugs II

Serotonin

Lysergic Acid Diethylamide
Topics to choose from:

- Appetite and obesity
- Parkinson’s disease *see psychosis
- OCD (Obsessive-Compulsive Disorder)
- Schizophrenia and psychedelic drugs
- Addiction
- Depression
- ADHD *see addiction
- Pain
Reuptake

Metabolism (destruction)
Antidepressant Mechanisms

Increase synthesis (Levodopa, 5-HTP)

Inhibit breakdown (MAOIs)

Antagonism (Mirtazapine)

Agonism (Pramipexole)

Release (Amphetamine)

Inhibit reuptake (SSRIs, TCAs)

Electroconvulsive therapy (Unknown mechanism)

Partial agonism (Buspirone)
**Key**

- ** Increases/causes OR excitatory (synapse)**
  Note: An arrow from one brain region to another is glutamate, unless otherwise noted

- ** Decreases/blocks OR inhibitory (synapse)**
  Note: A T-headed arrow from one brain region to another is GABA, unless otherwise noted

- ** Modulates**
  The relationship may be complex and/or poorly understood

**Entity**
- A brain region, cell, protein, or other entity

**Entity**
- Hypoactive, decreased, or dead

**Entity**
- Hyperactive, increased
The direct pathway

Amplifies activity in the cortex. It is thought that a plan for movement is a small flurry of activity in the cortex, and that neural activity (plan) is amplified by going through this loop several times until finally enough activity builds up and the movement is performed.
The indirect pathway

This inhibits activity in the cortex, rather than amplifying it like the direct pathway. This inhibitory loop may be important for eliminating plans that we do not carry out, so that only certain movements are chosen and executed.
Adding the substantia nigra

Dopamine from the substantia nigra pars compacta activates the direct pathway and inhibits the indirect pathway, both of which have the net result of reinforcing cortical activity.
Parkinson’s Disease

The substantia nigra pars compacta dopaminergic neurons die, leading to the pattern of hyper- and hypoactivity shown here, which ultimately leads to decreased activity in the areas of cortex necessary to initiate movement.
Treatments for PD
Surgical lesions or deep brain stimulation can inhibit the globus pallidus or subthalamic nucleus, hopefully reversing their pathological overactivity.
Synaptic structure

Dopamine from the substantia nigra pars compacta activates the direct pathway and inhibits the indirect pathway, both of which have the net result of reinforcing cortical activity.
There is too little DA in Parkinson’s Disease (PD). This causes symptoms directly through D1 and D2 receptors on the MSNs, but it also causes symptoms indirectly by elevating ACh.
Drugs that increase DA or decrease ACh can help alleviate the symptoms of PD.

**ACh and DA drugs for PD**

**Cortex**

**Striatum**

**Cholinergic interneuron**

**Medium spiny neuron (GABAergic)**

**Anticholinergics (M1 antagonists)**

**D2 agonists**

**D1, D2**

**Levodopa**

**GABAergic**

**Substantia nigra pars compacta**
Schizophrenia
This diagram shows the pathways that may be involved in schizophrenia.
Schizophrenia

Psychosis results when the pyramidal neurons are overly excited and fire too often.

Cerebral or limbic cortex

Pyramidal neuron

NMDA

Interneuron

GABA

ACh

NE

Glu

Glu

5-HT

DA

Ventral tegmental area

Dorsal raphe nucleus

Thalamic sensory relay

Basal forebrain nucleus

Locus ceruleus
Antipsychotics

Typical antipsychotics, also called neuroleptics, are antagonists at dopamine receptors.
Atypical antipsychotics

Atypical antipsychotics (second-generation antipsychotics) are often antagonists at both dopamine and serotonin receptors. Antagonists of $5$-$HT_{2A}$ receptors are especially popular.
Psychotomimetics

Psychotomimetics are drugs that cause psychosis. Drugs that increase 5-HT, DA, and/or NE are all psychotomimetics (amphetamine, cocaine, psychedelics). Drugs that block NMDA receptors (ketamine, PCP, dextromethorphan) and drugs that block muscarinic ACh receptors (anticholinergics) are also psychotomimetic.
Other psychosis treatments

- Benzodiazepines, which boost the inhibitory effect of GABA, can effectively suppress psychosis. (This was predicted by the diagram.)
- Clozapine increases ACh release, which helps alleviate psychosis (as predicted).
- Many antipsychotics block NE, which further helps treat psychosis.
Dopamine signals unexpected rewards

- Signal (bursts per second)
- Time (seconds)

Eats peanut
Dopamine signals predicted/expected rewards

First trial:

“Good monkey”

Eats peanut

Tenth trial:

“Good monkey”

Eats peanut

Time (seconds)
Dopamine signals error in prediction

Tenth trial:

“Good monkey”
Eats peanut

No peanut:

“Good monkey”
No peanut

Time (seconds)
The dopamine burst motivates the animal

The dopamine motivates the child, focuses the child’s attention on the goal, and facilitates the behavior (truck chasing) that will lead to reward.
Drugs of abuse mimic natural reward

First dose:
- Sees cocaine
- Snorts cocaine

Fiftieth dose:
- Sees cocaine
- Snorts cocaine
Why does seeing cocaine cause dopamine release?
Remember how conditioning normally works:

First trial:

Tenth trial:

“Good monkey”
Eats peanut

“Good monkey”
Eats peanut

Time (seconds)
Drugs of abuse mimic natural reward

When an addict sees cocaine, the dopamine burst produced by his own cells motivates him to get cocaine and snort it.

The pleasure an addict actually feels from snorting cocaine is decreased over time, due to tolerance.

Fiftieth dose:

Sees cocaine

Snorts cocaine

Time (seconds)
Drug addicts are insensitive to non-drug motivators

The incentive of freedom triggers a dopamine burst, which motivates the person to wash the car.

The addict has tolerance to both cocaine and their own dopamine, so they cannot be motivated by normal incentives.

What will the addict do?

Normal person: “Wash my car or go to prison”

Addict: “Stay clean or go to prison”

Time (seconds)
Liking versus wanting

Addicts don’t like doing drugs as much as they used to
Addicts want to do drugs
Addicts don’t want to do anything else
Speed of onset and addiction

Drugs which take effect quickly are more addictive, because a fast spike in dopamine more closely mimics natural rewards and the drug-taking behavior is more closely associated with the reward if they come close together.
Speed of onset and addiction

Faster onset, more addictive:
- Crack cocaine
- Injected heroin
- Smoked meth (ice)

Slower onset, less addictive:
- Powder cocaine (snorted, has an 11 minute absorption half-time)
- Snorted heroin (absorbed faster than snorted cocaine. Why?)
- Snorted meth (even less addictive: swallowed meth)
Speed of onset and addiction

Faster onset, more addictive:
Xanax (the fast elimination and need for more doses also increases addiction potential. Why do frequent doses lead to stronger addiction? Discuss.)

Slower onset, less addictive:
Klonopin, Librium
<table>
<thead>
<tr>
<th>Faster onset, more addictive:</th>
<th>Slower onset, less addictive:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snorted Ritalin</td>
<td>Oral Ritalin</td>
</tr>
<tr>
<td>Vicodin</td>
<td>OxyContin</td>
</tr>
<tr>
<td>Abused (chewed, crushed and snorted)</td>
<td>Properly used (intact time-release tablets)</td>
</tr>
<tr>
<td>OxyContin</td>
<td>OxyContin</td>
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ADHD

ADHD is treated with stimulants that boost dopamine (and norepinephrine), why does this work?

Dopamine normally facilitates goal-directed behavior by:

• Increasing motivation
• Focusing attention on the goal
• Providing energy to work towards the goal
• Speeding learning and reinforcing memory
ADHD

Why does dopamine speed learning and reinforce memory?
Discuss