It’s in Your Mind: Addiction as a Chronic Brain Disease

Marvin D. Seppala, MD
Chief Medical Officer

Hazelden Betty Ford Foundation
Addiction is Characterized by:

- Compulsion to seek and take the drug
- Loss of control in limiting intake
- Diminished recognition of significant problems
- Emergence of negative emotional state
- Craving
- Chronicity and relapse
Addiction is a Brain Disease

NOT:

- Secondary to another psychiatric illness
- A moral or ethical problem
- A personality disorder
- A choice
Genetic Vulnerability

- Estimated genetic risk 40-60%
- Multiple genes are involved with drug responses
- A few genes have been identified that are protective
Environmental Risk Factors Consistently Related to Risk of Self Administration

- Low socioeconomic class
- Poor parental support
- Drug availability
Environmental Risk Factors

- **Stress** is a common feature among environmental risk factors, both for initiation of use and relapse.

- Co-occurring *psychiatric illness* and a history of *trauma* increase the risk of addiction and of relapse.
“C’mon, Sylvia … where’s your spirit of adventure?”
The Brain
The Human Brain – A Detailed Examination
Brain Reward Center

Mesolimbic Dopamine System (Median Forebrain Bundle)
NEURONS & NEUROTRANSMISSION
“An Irreproducible System”

- A human may have 100 billion neurons, with an estimated 100 trillion (100,000,000,000,000) connections

- “Neuron and nerve cell are synonyms that refer to the major information-conveying cells in the nervous system.”
The Neuron: Its Four Parts

1. Dendrites: “receives signals from other nerve cells and relay them to the cell body”
   - Dendrites can vary from 2 or 3 up to 10,000 in a purkinje cell in the cerebellum, which can have as many as 150,000 connections

2. Cell body: Nucleus with genes of the cell

3. Axon: “carries the message from the cell body”

4. Terminal: “relay the message to the dendrites, cell body, or even terminals of the next cell”
Neurons (Nerve Cells)
Signal Conduction

- Neurons do not touch each other in conducting a signal from one to the other

- A “synapse, synaptic gap” or “synaptic cleft” exists between them

This gap is 15-50 nanometers (nm)
A nanometer is one billionth of a meter
A million synaptic gap widths added together barely total an inch
Signal Conduction

- Signals are transmitted electrically within the neuron.
- But once the signal reaches the synapse, it stops, so a microscopic chemical called a neurotransmitter crosses the synapse.
- Neurotransmitters are produced in the neuron, stored in sacs called “vesicles”.
The Most common Neurtransmitters

- Acetylcholine
- Norepinephrine
- Epinephrine
- Dopamine
- Endorphin
- Enkephalin
- Serotonin
- GABA

- Substance “P”
- Anandamide
- Glycine
- Histamine
- Nitric oxide
- Glutamic acid
- Cortisone
The Synapse

1. Incoming electrical signal
2. Neurotransmitters
3. Vesicles
4. Synaptic gap
5. Ion gate
6. Chlorine ion
7. Sodium ion
8. Transmitted signal
9. Reuptake port
10. Auto receptor
Two Types of Neurotransmitters

- “Excitatory” neurotransmitters: augment the potential for signal propagation in the post-synaptic neurons; they increase the likelihood of an electric signal.
- “Inhibitory” neurotransmitters, prevent the propagation of the action potential; they decrease the likelihood of an electric signal.
- The specificity of a particular neurotransmitter (whether it acts in an excitatory or inhibitory fashion) is normally an inherent property of the neurotransmitter itself.
Dogs and alcohol: the tragic untold story
THE NEUROTRANSMITTERS ROLE IN ADDICTION
Addictive Drugs Are Associated With Specific Neurotransmitters

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Neurotransmitter System Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Facilitates GABA receptor function</td>
</tr>
<tr>
<td></td>
<td>Inhibits NMDA (Glutamate) receptor function</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Agonist at CB(_1) and CB(_2) cannabinoid receptors</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Indirect agonist of dopamine receptors by inhibiting dopamine transporters</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Indirect agonist of dopamine receptors by stimulating dopamine release</td>
</tr>
<tr>
<td>Opiates</td>
<td>Agonist at MU, delta and kappa receptors</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Agonist at nicotinic acetylcholine receptors</td>
</tr>
</tbody>
</table>
Normal Dopamine Release
Dopamine Release Due to Cocaine
Alcohol and Neurotransmitters

GABA
- Primary inhibitory neurotransmitter
- Decreases with chronic use

Glutamate:
- Primary excitatory neurotransmitter
- Increases with chronic use

Opioids:
- Alcohol stimulates endorphin release

Dopamine:
- Alcohol stimulates release, directly and via endorphins
Neuroadaptation (Neuroplasticity)

Repeated exposure

Changes in nuclear function

Altered transcription of target genes (abnormal proteins or receptors)

Altered activity of the neuron (neurotransmitter dysregulation)

Altered reward circuitry

Altered behavior (Loss of control)
"Hey! Look what Zog do!"
Addiction is a Disorder of…

- Incentive salience
- Reward deficit
- Stress surfeit
- Executive function
Addiction ≠ Casual Use

- Compulsion to seek and take the drug
- Loss of control in limiting intake
- Diminished recognition of significant problems
- Emergence of negative emotional state
- Craving
- Chronicity and relapse
Acute Intoxication: Primarily Reward Circuitry

- A Hedonic activity
- Positive reinforcement
- All drugs of abuse enhance dopamine release
- Mesolimbic dopamine system
Neurochemical Circuits in Drug Reward (Acute)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Where</th>
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</thead>
<tbody>
<tr>
<td>Cocaine/Amphetamine</td>
<td>Release dopamine by direct action on dopamine terminals</td>
<td>Nucleus Accumbens Amygdala</td>
</tr>
<tr>
<td>Opioids</td>
<td>Activate opioid receptors</td>
<td>VTA, Nucleus Accumbens Amygdala</td>
</tr>
<tr>
<td></td>
<td>Facilitate dopamine release</td>
<td>VTA, Nucleus Accumbens</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Actives GABA receptors or GABA release</td>
<td>VTA, Nucleus Accumbens Amygdala</td>
</tr>
<tr>
<td></td>
<td>Facilitates release of opioid peptides</td>
<td>VTA, Nucleus Accumbens Amygdala</td>
</tr>
<tr>
<td></td>
<td>Facilitates release of dopamine</td>
<td>Nucleus Accumbens</td>
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<tr>
<td>Nicotine</td>
<td>Actives nicotine acetylcholine receptors</td>
<td>VTA, Nucleus Accumbens Amygdala</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Actives cannabinoid CB&lt;sub&gt;1&lt;/sub&gt; receptors</td>
<td>VTA, Nucleus Accumbens Amygdala</td>
</tr>
<tr>
<td></td>
<td>Facilitates release of dopamine</td>
<td>Nucleus Accumbens</td>
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Establishment of the Addictive Cycle

- Positive Reinforcement from the drug diminished
- Negative Reinforcement from the drug increases
- Motivational withdrawal syndrome established
- Incentive salience narrows the individual's focus
The Addictive Cycle

Three Stages

The transition to addiction from casual drug use involves the brain areas associated with these three stages:

- Binge / Intoxication
- Withdrawal / Negative Affect
- Preoccupation / Anticipation (craving)
Neural Circuits of the Binge/Intoxication Stage


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**Incentive Salience**
- euphoria
- intoxication
- cue learning
- habits
Neural Circuits of the Withdrawal/Negative Affect Stage

Negative Affect
- dysphoria
- anxiety
- irritability
- malaise
Neural Circuits of the Preoccupation/Anticipation “Craving” Stage

Executive Dysfunction
- impulsivity
- compulsivity
- sleep disturbances
- impaired decision making
Addiction is a chronic brain disease and the manifestations that we find so puzzling are best understood by examining the neurobiological underpinnings. We can come to understand the behaviors associated with addiction by understanding the brain pathology.
Resources

- Neurocircuitry of Addiction

- Dynamics of Neuronal Circuits in Addiction
  Koob Pharmacopsychiatry 2009; 42 (Suppl 1): S32

- Neuropathology of Substance Use Disorders
  Cadet, Bisagno, Milray Acta Neuropathol (2014) 127; 91-107