The Neurobiology of Addiction

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What is Addiction?

• commonly associated with a chronic, relapsing course

• Drug addiction is a chronically relapsing disorder that has been characterized by
  – (1) compulsion to seek and take the drug,
  – (2) loss of control in limiting intake, and
  – (3) emergence of a negative emotional state (eg, dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented
How Common is Addiction?

- 15.6% (29 million): nonmedical or illicit drug use at some time in their lives
- 2.9% (5.4 million): substance dependence on illicit drugs
- 7.7% (18 million): meet the criteria for abuse or dependence on Alcohol.
- 28.6% (70.9 million): current (past month) users of a tobacco product
- 48% (>100 million): report having used marijuana at some time in their life
Addiction Involves Multiple Factors

- Biology/Genes
- Environment

DRUG

Brain Mechanisms

Addiction
Addiction is Like Other Diseases...

➢ It is preventable
➢ It is treatable
➢ It changes biology
➢ If untreated, it can last a lifetime

Decreased Brain Metabolism in *Cocaine-addiction Patient*

Healthy Brain
Diseased Brain/ Cocaine Abuse

Decreased Heart Metabolism in *Heart Disease Patient*

Healthy Heart
Diseased Heart
Advances in science have revolutionized our fundamental views of drug abuse and addiction.
Your Brain on Drugs in the 1980’s

this is your brain on drugs.
Today’s Talk

• Who gets Addicted?
• The Addiction Cycle
  – Role of Dopamine/Reward in Addiction
  – Role of Impaired Inhibition in Addiction
• Changes in the Brain that Occur
• Treatment and Recovery
Vulnerability

Why do some people become addicted to drugs while others do not?
Individual Variability

• Inhibitory control abnormalities? Reward Responsivness/Anhedonia? Stress sensitivity Resilience?
• Mood, anxiety, psychotic disorders are clear risk factors
• Those with schizophrenia have cognitive impairments such as diminished prefrontal cortical control over behavior and increased limbic drive similar to those with addictions, perhaps conferring dual risk
• 40-60% of the risk for addiction attributed to genetic factors.
• Genetic factors also present in treatment response
Who is Predisposed to Addiction?

• The Marshmallow Test: Behavioral and Neural Correlates of Ability to Delay Gratification: 40 Years Later

• 4 year-olds who were able to resist eating one marshmallow in exchange for two marshmallows 15 minutes later showed lower rates of substance use 40 years later.
Individual Differences in Response to Drugs: 
DA Receptors influence drug liking

As a group, subjects with low receptor levels found MP pleasant while those with high levels found MP unpleasant

Adapted from Volkow et al., Am. J. Psychiatry, 1999.
Addiction is a Developmental Disease that starts in adolescence and childhood.

% in each age group who develop first-time dependence

Age at **tobacco**, **alcohol**, and **cannabis** dependence per DSM IV

What Other Biological Factors Contribute to Addiction--Comorbidity

Prevalence of Drug Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>General public</td>
<td>10.0</td>
</tr>
<tr>
<td>Any Mood Disorder</td>
<td>20.0</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>25.0</td>
</tr>
<tr>
<td>Depression</td>
<td>30.0</td>
</tr>
<tr>
<td>Mania</td>
<td>35.0</td>
</tr>
<tr>
<td>Panic w/ Agoraphobia</td>
<td>40.0</td>
</tr>
<tr>
<td>Panic w/out Agoraphobia</td>
<td>20.0</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>25.0</td>
</tr>
<tr>
<td>Generalized Anxiety</td>
<td>30.0</td>
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</tbody>
</table>

Prevalence of Nicotine Addiction

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>General public</td>
<td>10.0</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>80.0</td>
</tr>
<tr>
<td>Depression</td>
<td>30.0</td>
</tr>
</tbody>
</table>
Why do Mental Illnesses and Substance Abuse Co-occur?

• **Self-medication**
  – substance abuse begins as an attempt to alleviate symptoms of mental illness

• **Causal effects**
  – Substance abuse may increase vulnerability to mental illness

• **Common or correlated causes**
  – the risk factors that give rise to mental illness and substance abuse may be related or overlap
Addictiveness by Drug Type

Comparative Prevalence of Dependence Among Different Drug Users

Percent of users who Become addicted

- Tobacco
- Alcohol
- Cannabis
- Cocaine
- Stimulant
- Analgesics
- Psychodelics
- Heroin
- Prescription Opiates

* Nonmedical Use

Cannabis in the 1960’s-2000’s: THC 1-3%
Cannabis today: THC 80%

Meier, 2017; Raber et al., 2015
Borodovsky et al., 2016; Schauer, King et al., 2016; Wang et al., 2016; Weiss, 2015
Marijuana growers have worked to make the drug as potent as possible.

- In 1960s-70s average THC concentrations were 1-2%. Today, they are as high as 25%
Marijuana Users, especially those who use before the age of 16, do not learn as much, or as efficiently, as non-users.

- Early-onset users recall fewer words initially, and never catch up!

**SOURCES:** Schuster and Gilman et al, 2016, *Neuropsychology*
Stopping cannabis use in adolescents is associated with improved memory after 1 week.
Fig. 1. Mortality rates from unintentional drug overdoses. (A and B) Mortality rates for (A) individual drugs and (B) all drugs. Detailed data for individual drugs are only available from 1999 to 2016, although additional data for all drugs are available since 1979 (this area is grayed out). The exponential equation and fit are shown for all drugs. (Synth Opioids OTM: synthetic opioids other than methadone. This category includes fentanyl and its analogs.)

SOURCES: Jalal et al., Science 361, 2018
The Opiate Epidemic

SOURCES: Jalal et al., Science 361, 2018
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The addiction cycle

Koob and Volkow 2010
The addiction cycle

Koob and Volkow 2010
The addiction cycle

Koob and Volkow 2010
Reward, Dopamine, and the Nucleus Accumbens (NAc)

- Reward: stimulus that induces subjective feelings of pleasure.
- Rewarding stimuli activate the mesocorticolimbic reward circuit.
- All drugs of abuse share the ability to activate this circuit.
  - Increase extracellular dopamine (DA) levels in the NAc

Alcohol:

Gilman et al. 2008
dopamine transporters
Natural Rewards Elevate Dopamine Levels

Effects of Drugs on Dopamine Release

**Amphetamine**
- Accumbens
- % of Basal Release
- Time After Drug 0, 1, 2, 3, 4, 5 hr
- DA, DOPAC, HVA

**Cocaine**
- Accumbens
- % of Basal Release
- Time After Drug 0, 1, 2, 3, 4, 5 hr
- DA, DOPAC, HVA

**Nicotine**
- % of Basal Release
- Time After Drug 0, 1, 2, 3 hr
- Accumbens, Caudate

**Morphine**
- % of Basal Release
- Time After Drug 0, 1, 2, 3, 4, 5 hr
- Dose 0.5 mg/kg, 1.0 mg/kg, 2.5 mg/kg, 10 mg/kg

*Di Chiara and Imperato, PNAS, 1988*
Reward

- Enhanced dopamine in the NA is responsible for acute high or initial reinforcing effects of drugs of abuse.

- Drugs of abuse are able to more rapidly and markedly elevate DA levels to supraphysiological levels for sustained periods of time compared with natural rewards.

- Drugs outcompete natural reinforcers and end up “hijacking” and corrupting the initial process of reward processing.

Roberts & Koob, 1980
Behaviors persist despite **tolerance** to the positive effects of drugs over time.

Individuals maintain use of substances through negative reinforcement to **avoid negative states** such as withdrawal states or to attempt to self-medicate for underlying psychic distress.

Degree of euphoria of a substance does not necessarily predict its addictiveness (i.e. nicotine).

(Berridge et al., 2009)
The Switch from Reward to Negative Reinforcement/Withdrawal

- Enhanced dopamine in the NA is responsible for acute high or initial reinforcing effects (i.e., positive reinforcement) of drugs of abuse.
- All major drugs of abuse activate the brain stress systems
  - Elevated corticotrophin releasing factor (CRF) in the amygdala

George, Le Moal, and Koob, 2012
Executive Function Component

- loss of control, impulsivity, and impaired decision-making capacity
- Involves:
  - Orbitofrontal cortex (OFC): assigns a motivational value based on a prediction of reward
  - Anterior cingulate (ACC): role in inhibitory control of behaviors
Abnormal Activity in Two Brain Systems:

1) **Reward** (drive to meet goals) – Strong urge to use drugs over natural rewards, associated with impulsivity

2) **Inhibition** (control of goal-directed behavior) – Reduced control over behavior despite negative consequences

~Both abnormalities are worsened by stress

Baler & Volkow, 2006; Koob & Volkow 2009
Inhibition: Just Say No?

Ability to ‘stop’ a response, even when it is habitual and includes:

- Motor actions
- Higher-order responses (i.e., thoughts, memories, or emotions)

Critical for stopping both automatic and habitual behaviors to help us meet our goals

Related to impulsiveness in the healthy population

Cools, 2008; Jentsch and Taylor, 1999; Nigg et al. 2005; Avila and Parcet, 2001; Logan et al., 1997; but see Enticott et al., 2006
Just Say No??

• Addiction: loss of control over intense urges despite adverse consequences.

The model is:

Greater reinforcing (rewarding) properties of drugs/diminished reinforcement from natural rewards = greater drive to use drugs

Diminished inhibitory control over behavior as evidenced by reduced prefrontal cortical activity during decision-making tasks = greater use of drugs despite serious negative consequences

Volkow & Fowler, 2000; Koob & Volkow, 2010
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Structural Effects of Addiction

Pfefferbaum et al. 1997

Gilman et al. 2008
Reduction in Amygdala Size in Cocaine Users

Makris et al. 2004
Dopamine Transporters in Methamphetamine Abusers

Normal Control

Methamphetamine Abuser

Motor Task
Loss of dopamine transporters in methamphetamine abusers may result in slowing of motor reactions.

Memory Task
Loss of dopamine transporters in methamphetamine abusers may result in memory impairment.

Certain brain regions such as the Insula are especially important in the maintenance of addictive behavior.

Patients with damage to the INS were able to quit cigarette smoking “easily, immediately, without relapse, and without persistence of the urge to smoke”

Navqi et al., *Science*, 2007
Substance use is particularly damaging to the adolescent brain

- high amounts of alcohol/cannabis exposure during adolescence:
  - disrupts processes of brain maturation
  - worsens neurocognitive functioning.

### Table 1

<table>
<thead>
<tr>
<th>Overview of consequences of repeated adolescent exposure to ethanol (EtOH), nicotine (NIC), cannabinoids (CBs) and MDMA and methamphetamine stimulants (STIM).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Age Vulnerability</strong></td>
</tr>
<tr>
<td><strong>Cognitive/behavior</strong></td>
</tr>
<tr>
<td>Spatial memory</td>
</tr>
<tr>
<td>Conditional discrim./pattern learning</td>
</tr>
<tr>
<td>Attention</td>
</tr>
<tr>
<td>Obj. recogn./working memory</td>
</tr>
<tr>
<td>Pre-pulse inhibition</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
</tr>
<tr>
<td>Risk preference</td>
</tr>
<tr>
<td>Impulsivity/disinhibition</td>
</tr>
<tr>
<td>Retent. of adoles.-typical phenotypes</td>
</tr>
<tr>
<td><strong>Affective/Social behavior</strong></td>
</tr>
<tr>
<td>Depression-like behaviors</td>
</tr>
<tr>
<td>Social interactions</td>
</tr>
<tr>
<td>Social anxiety-like behaviors</td>
</tr>
<tr>
<td>Other anxiety-like behaviors</td>
</tr>
<tr>
<td>Later self-adm. (same/different drugs)</td>
</tr>
<tr>
<td><strong>Neural</strong></td>
</tr>
<tr>
<td>Neurogenesis</td>
</tr>
<tr>
<td>Cell death</td>
</tr>
<tr>
<td>Spines/dendritic branching</td>
</tr>
<tr>
<td>Electrophysiol. Alterations</td>
</tr>
<tr>
<td>Neuroimmune activation</td>
</tr>
<tr>
<td>Histone acetylation/epigenetic regul.</td>
</tr>
<tr>
<td><strong>Alterations in:</strong></td>
</tr>
<tr>
<td>Ach</td>
</tr>
<tr>
<td>Glutamate/GABA</td>
</tr>
<tr>
<td>DA</td>
</tr>
<tr>
<td>5HT</td>
</tr>
<tr>
<td>CB</td>
</tr>
<tr>
<td><strong>Affected brain regions:</strong></td>
</tr>
<tr>
<td>PFC</td>
</tr>
<tr>
<td>HPC</td>
</tr>
<tr>
<td>nAc</td>
</tr>
<tr>
<td>AMYG</td>
</tr>
</tbody>
</table>

References are provided in text and cited reviews: ↓ impaired/attenuated; ↑ enhanced; • no notable exposure effects; Y alterations reported (often complex)."^"data interpreted as decreased cautiousness/attenuated threat evaluation (which are likely similar but may not be the same construct as impulsivity).
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Science Has Generated Much Evidence Showing That...

Prolonged Drug Use Changes the Brain In Fundamental and Long-Lasting Ways
These changes are long-lasting.

Conditioned Place Preference

- White Wall
- Center Choice Chamber
- Guillotine Doors
- Steel Grid
- Wire Mesh
Morphine-induced CPP: Movement patterns during a 15-min test before and after four pairings of the left compartment with morphine 10 mg/kg, s.c.

German & Fields, 2006
Morphine CPP: Persistence of effect of drug-paired cues in frequent 15-min tests: no drug since training

Note the lack of extinction when test are widely spaced

Mueller et al., 2000
Who Gets Treatment??

8.3% of Americans have diabetes
Any diabetes treatment  16%
No treatment      84%
9.5% of Americans have a mood disorder in a given year
Any MH treatment  No treatment

59%  41%
7.4% of Americans have a substance use disorder in a given year
Any addiction treatment  9%

No treatment  91%
WHY?? People can’t afford treatment

How People Pay for Treatment

- 48.4% Own savings and earnings
- 34.8% Private health insurance
- 26.7% Medicaid
- 26.1% Public assistance other than Medicaid
- 19.2% Medicare
- 15.9% Funds from family members

(note: individuals could report multiple sources of funding for treatment)
WHY?? Not enough doctors! (ex: Suboxone)

**Train more psychiatrists?**
- <1% are current prescribers
- Many psychiatric clinics will not prescribe buprenorphine

**Train more PCPs?**
- <0.01% are prescribers
- Majority of primary care clinics will not prescribe buprenorphine

**Train more addiction psychiatrists?**
- About 20-40 new board-certified addiction psychiatrists per year in the US
Addiction is Similar to Other Chronic Illnesses Because:

• It has biological and behavioral components, both of which must be addressed during treatment.
• Recovery from it—protracted abstinence and restored functioning—is often a long-term process requiring repeated episodes of treatment.
• Relapses can occur during or after treatment, and signal a need for treatment adjustment or reinstatement.
• Participation in support programs during and following treatment can be helpful in sustaining long-term recovery.
Full recovery is a challenge but it is possible ...
It takes time, but the brain can recover

DAT Recovery with prolonged abstinence from methamphetamine

Conclusions

• Addiction is a brain disease, with both biological and behavioral risk factors
• Addiction consists of specific stages, that each involve different brain regions and different neurotransmitters
• Addiction disrupts brain circuits involved in judgment and decision-making, so that “saying no” becomes very difficult
• These disruptions of brain circuitry are long-lasting
• Specific treatments of addiction exist, and those treatments work to help patients maintain abstinence

• Thank you for your attention!!!