The Neurobiology of Addiction

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What is Addiction?

• 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
Addiction is a Brain Disorder

• commonly associated with a chronic, relapsing course
• those who 1) have addictions and 2) who have a risk factor in childhood that predisposes to addiction
  – appear to be less able to ‘say no’, or inhibit automatic responses on behavioral tasks
  – particularly in the face of emotional or highly desired cues
  – this is reflected in neural correlates of these abnormalities
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 (Grant and Dawson, 1998; Grant et al, 2004).
• For alcohol, 51% (120 million) of people over the age of 12 were current users
• 7.7% (18 million) met the criteria for Substance Abuse or Dependence on Alcohol.
• For nicotine, in 2007, approximately 28.6% (70.9 million) Americans aged 12 or older were current (past month) users of a tobacco product
Addiction Involves Multiple Factors

- Biology/Genes
- Environment

Brain Mechanisms

Addiction

DRUG

NIDA
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 *Drug Addict*

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
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
- [http://www.youtube.com/watch?v=QX_oy9614HQ](http://www.youtube.com/watch?v=QX_oy9614HQ)
- Individuals (n=60) who were less able to delay gratification in preschool and consistently showed low self-control in their 20’s and 30’s performed more poorly than did high delayers on a Go / No-Go task when having to suppress a response to a desired cue but not a neutral or aversive cue.
- 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.

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>
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<tbody>
<tr>
<td>General public</td>
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<tr>
<td>Any Mood Disorder</td>
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<td>Any Anxiety Disorder</td>
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<td>Depression</td>
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<td>Mania</td>
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<td>Panic w/ Agoraphobia</td>
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<td>Panic w/out Agoraphobia</td>
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<td>Social Phobia</td>
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<tr>
<td>Generalized Anxiety</td>
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#### Prevalence of Nicotine Addiction

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percent</th>
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<tbody>
<tr>
<td>General public</td>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>Depression</td>
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</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
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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 mesocorticicolimbic reward circuit.
- All drugs of abuse share the ability to activate the this circuit.
  - increase extracellular dopamine (DA) levels in the NAc

Gilman et al. 2008

Alcohol:
dopamine transporters
Natural Rewards Elevate Dopamine Levels

Effects of Drugs on Dopamine Release

**Amphetamine**

- Accumbens
- DA (orange), DOPAC (light blue), HVA (green)
- 0 to 5 hours

**Cocaine**

- Accumbens
- DA (orange), DOPAC (light blue), HVA (green)
- 0 to 5 hours

**Nicotine**

- Caudate (blue)
- Accumbens (orange)
- 0 to 3 hours

**Morphine**

- Dose: 0.5, 1.0, 2.5, 10 mg/kg
- Accumbens
- 0 to 5 hours

*Di Chiara and Imperato, PNAS, 1988*
enhanced dopamine in the NA is responsible for acute high or initial reinforcing effects of drugs of abuse.

- In animals, lesioning the NA or impeding DA release diminishes drug-seeking behaviors and drug self-administration.

- 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
Is this Responsible for Addiction?

- 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
Why Can’t Addicts Just Quit?

Because Addiction Changes Brain Circuits

Adapted from Volkow et al., Neuropharmacology, 2004.
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

Control brain

Alcoholic brain
Reduction in Amygdala Size in Cocaine Users

Makris et al. 2004
Dopamine Transporters in Methamphetamine Abusers

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., 2007
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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

Guillotine Doors

esh
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.
Morphine CPP: Persistence of effect of drug-paired cues infrequent 15-min tests: no drug since training

Note the lack of extinction when test are widely spaced

Mueller et al., 2000
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.
**Basic Research ➔ Medication**

Opiate agonists stabilize brain function in heroin addicts

Smokers who are poor nicotine metabolizers smoke less

Stress triggers relapse in animal models of addiction and CRF antagonists interfere with the response to stress

Agonist Therapy
Methadone
Buprenorphine

Inhibitors of metabolizing enzymes

CRF Antagonists
Targeting addiction treatments to specific stages of the addiction cycle

Full recovery is a challenge but it is possible ...
Extended Abstinence is Predictive of Sustained Recovery

After 5 years – if you are sober, you probably will stay that way.

It takes a year of abstinence before less than half relapse.

Dennis et al, Eval Rev, 2007
It takes time, but the brain can recover

DAT Recovery with prolonged abstinence from methamphetamine

Treatment Reduces Drug Use and Recidivism

Delaware Work Release Therapeutic Community (CREST) + Aftercare 3 Years After Release (N=448)

* p < 0.05, compared to no treatment group
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!!!