ADDICTION AND THE BRAIN: INSIGHTS FROM NEURODEVELOPMENT

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Flow of the presentation

• What is addiction?
• How are concepts of addiction evolving?
• Vulnerable periods during neurodevelopment
• Why early life stress (including prenatal drug exposure) increases the risks
• How brain plasticity during adolescence works against us when it comes to developing drug habits and addiction
Addiction — Chronic relapsing disorder characterized by a compulsion to seek and take a substance, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) when access is prevented (the Koob “dark side” of addiction)
Three Stage Model of Addiction
(aka, Koob’s Merry-Go-Round of Misery)

Koob GF, Le Moal M. 2008
Annu. Rev. Psychol. 59:29–53
Evolving concepts

• Concepts of addiction and how it develops have long leaned toward the male phenotype and the role of dopamine, the reward system and positive reinforcement.

• Sexual differentiation in the brain during adolescence leads to differences in motivation to use substances, responses to substances, the time course of development of addiction, and the nature of symptoms.

• We have also learned that dopamine is not a “pleasure molecule” per se and the reward system might be more important to addiction in males than females.

• As addiction unfolds there is a natural shift toward using the drug to cope (negative reinforcement) than to enhance (positive reinforcement).
Contribution of prenatal drug exposure

• Early exposure to alcohol/other drugs/other forms of stress increases the tone of stress circuitry (Conradt et al., 2018)

• Elevated cortisol levels, heightened sensitivity of the amygdala to cortisol, blunted cortisol response to stressor, longer time to recover, impaired regulation of the stress response (Hellemans et al., 2008; Buckingham-Howes et al, 2016)

• Such programming could increase likelihood of anxiety, depression, conduct problems during adolescence

• Might increase motivation for negative reinforcement putting offspring on a slippery slope toward addiction.

• Do changes in stress circuitry contribute to sex differences in substance use and development of substance use disorders?
“Women who use opioids while pregnant are also more likely to use other substances, such as nicotine, alcohol, antidepressants, and benzodiazepines compared to pregnant women who aren't using opioids (Heberlein et al., 2012; Winklbaur et al., 2009). Furthermore, they are more likely to experience a range of psychiatric comorbidities in addition to their substance use disorder such as anxiety, depression, and bipolar disorder (Whiteman et al., 2014). Given the high rates of poly-substance use and mental health comorbidities among women with opioid use disorders it is necessary to examine the shared mechanisms underlying development of these disorders.”

**Source:** Conradt et al., 2018
Humans like drugs because they add pleasure or reduce pain. Sometimes drugs are used to produce a positive state.
Humans like drugs because they add pleasure or reduce pain.

Sometimes drugs are used to fix a negative state.
Positive and negative reinforcement both shape our behaviors.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Behavior</th>
<th>Consequence</th>
<th>Change in behavior</th>
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<tbody>
<tr>
<td>Use of positive</td>
<td>Behavior (Studying)</td>
<td>Positive reinforcer (Teacher approval) is <em>presented</em> when student studies</td>
<td>Frequency of behavior <em>increases</em></td>
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Penn State PSYCH 484: Work Attitudes and Job Motivation.  
https://wikispaces.psu.edu/display/PSYCH484/3.+Reinforcement+Theory
Accidental discovery of the reward system and its role in positive reinforcement

- Dr. Olds accidentally placed an electrode into the circuitry that provides positive reinforcement for behavior.
- Stimulating the circuitry with electrical current shapes behavior.
The reward system was discovered to include two main brain areas – the Nucleus Accumbens and the Ventral Tegmental Area (VTA). Dopamine is released by VTA neurons onto cells in the Nucleus Accumbens.
Natural rewards increase dopamine levels in the Nucleus Accumbens

**FOOD**

![Graph showing % of Basal DA Output over time for NAc shell](image)

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**SEX**

![Graph showing DA Concentration and Copulation Frequency](image)

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*Di Chiara et al., Neuroscience, 1999*

*Fiorino and Phillips, J. Neuroscience, 1997*

Drugs increase dopamine levels more than natural reinforcers

Di Chiara and Imperato, PNAS, 1988

NICOTINE

AMPHEMETAMINE

Cocaine and amphetamine increase dopamine in the Nucleus Accumbens.

Heroin increases dopamine in the Nucleus Accumbens

Dopamine – Less about pure pleasure and more about novelty detection, learning and incentive salience

- Prefrontal cortex areas learn about the value (incentive salience) of stimuli and make decisions to either approach or avoid them.
- Drugs trick the brain into thinking they are extremely important (have high incentive salience).
Dopamine and reward – Would that it were so simple

Initially, when a reward is presented, dopamine neurons fire upon receipt of the reward.

If a cue precedes the reward, dopamine neurons fire in response to the cue not the reward.

If the cue is presented but the reward does not follow, dopamine neurons become less active, signaling the inconsistency.

Error detection and craving

Drug cues trigger dopamine release.

But when the expected reward does not come there is a drop in dopamine, signaling an error in the expectation.

Does the drop in dopamine here contribute to craving and motivation to seek the reward?

Is dopamine really the “reward molecule” or the “learning about reward” molecule?
All drugs of abuse increase dopamine but there is more to the story than dopamine

Alcohol increases opioid release in the Nucleus Accumbens

- Pleasure produced by alcohol and many other drugs likely stems from activation of opioid receptors in reward areas in addition to the increase in dopamine.

“So, if indeed it is the case that adolescent animals have lower basal rates of dopamine release, then perhaps adolescents initially seek out more stimulation (rewards) that will increase dopamine release; once stimulated, however, the adolescent will show greater dopamine release that subsequently contributes to a reinforcing feedback cycle that motivates additional reward-seeking behavior.”
Reward (monetary here) activates ventral striatum more strongly in adolescents than children or adults.

FIGURE. Ventral striatal activity to reward and association with risk-taking. Note: Ventral striatum (left) is activated with reward (middle) and correlated with risk-taking (right) (adapted from Galvan et al.\textsuperscript{6} and Galvan et al.\textsuperscript{16}). Such findings could mean that adolescents are more motivated for reward and more reinforced by it.

Cocaine abusers show larger brain response to cocaine than erotic films


Signal Intensity (AU)

Cocaine Film
Erotic Film

Controls Cocaine Users

Cingulate
Ant. Cing.
IFG
Heavy drinking teenagers show strong response to alcohol cues (i.e., incentive salience)

We know the brain undergoes widespread sexual differentiation during adolescence

**Females develop more interhemispheric communication**

Brain networks show increased connectivity in males (Upper) and females (Lower)

**Females and males develop different densities of gray matter in cortical areas**

Areas with more gray matter in female (RED) or in male (BLUE) adult brains

**Females have more functional brain connectivity at rest**

Brain activity at rest in women (A) involves broader and more densely connected networks than in men (B)

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**Source:** Madhura Ingalhalikar et al (2014) Sex differences in the structural connectome of the human brain. PNAS, 111, 823-828


But we know very little about how sex-related brain differences contribute to and are affected by alcohol and other drug misuse.

Out of 230 structural neuroimaging studies on substance use:

- 79% included both sexes but only 26% of those evaluated sex effects.
- 85% of the studies that did stratify by sex reported different effects of substances on brain volumes, indicating the importance of sex comparisons.
Alcohol induces less dopamine release in female than male Nucleus Accumbens

(PET) imaging using the D2/3 radiotracer $[^{11}C]$ raclopride.

Delta BP = relative reduction in DA D2/3 receptor availability for $[^{11}C]$ raclopride binding.

Decreased D2/3 binding reflects displacement by endogenously released dopamine

Increase in substance use correlates with developmental increase in sensation seeking.

Sensation seeking increases in mid-teens.

Alcohol and drug use often begins here.

% Past month alcohol use (NSDUH 2012)

- Current Use (Not Binge)
- Binge Use (Not Heavy)
- Heavy Alcohol Use

Romer et al (2010)
Prevention Science, 11, 319-30.
Sensation seeking and impulse control contribute to substance use – but probably more for males than females

“The findings suggest that the window of heightened vulnerability to risk-taking during adolescence may be greater in magnitude and more protracted for males than for females.” – Shulman et al, 2015

Shulman et al. Sex Differences in the Developmental Trajectories of Impulse Control and Sensation-Seeking from Early Adolescence to Early Adulthood. J Youth and Adolescence, 2015, 44, 1-17
Females might be more motivated to drink or do other drugs for negative reinforcement

“The results from the largest drinking motive study conducted to date suggest that gender-specific prevention should take differences in the motivational pathways toward (heavy) drinking into account, that is, positive reinforcement seems to be more important for boys and negative reinforcement for girls.” (Kuntsche et al., 2015)

“In a recent study of college students, male binge drinkers were characterized by their higher scores on impulsivity and sensation seeking compared to non-binge drinking males, and this pattern was not seen in females… Adolescent males are also more likely to report drinking for positive reinforcing effects as well as sensation and risk seeking.” (Dir et al, 2017)

In a sample of 6238 Norwegian adolescents aged 16–18 years, “Increasing severity of anxiety symptoms primarily associated with the alcohol consumption measures among girls. Anxiety and depression more closely related to early onset of alcohol use in girls than for boys.” (Johannessen et al., 2017)

Adolescents tend to rely more on the amygdala than frontal lobes to interpret facial expressions.

Role of amygdala and negative reinforcement in addiction

- Amygdala attaches emotional valence to stimuli, including threatening stimuli.
- Activation of some areas causes fear and anxiety.
- Calmed by some drugs, leading to negative reinforcement by reducing discomfort.
- Becomes overactive during withdrawal, contributing to negative affect and drive to use again.

Alcohol suppresses the amygdala – Negative reinforcement via anxiety reduction

**FIGURE.** Alcohol effects on amygdala activation to social signals of threat. **A)** Right lateral amygdala activation to Threat (> Non-threat) faces is present during the PBO session but absent during the ALC session. **B)** Mean BOLD Response (β weights ±SEM) extracted from amygdala ROIs showing activation to Threat (> Non-threat) faces in the PBO session but no activation during the ALC session. PBO, placebo; ALC, alcohol. **C)** Mean BOLD Response showing alcohol attenuates (PBO>ALC) activation to Threat (Angry, Fearful) faces but does not affect responses to Non-threat (Happy Faces).

Source: Sripada et al., 2011, Neuroimage, 55, 371-380.
Hypothesis: Brain wiring during adolescence leads to sex differences in reinforcing effects of alcohol and probably other drugs.

“We propose that males and females have different pathways of vulnerability to substance abuse: in adolescent boys sensation seeking and impulsivity may drive drug and alcohol use, while stressful experiences and comorbid internalizing disorders may mediate substance use in adolescent girls.”

Recent increases in depression among adolescent females

“The trends in adolescents were different among boys and girls. This aligns with past studies that also found a larger increase in depressive symptoms in girls than boys in more recent years, and recent data on trends in suicide in the United States that identified a greater increase among adolescent girls and young women.”

Mojtabai, R., Olfson, M., & Han, B. (2016). National Trends in the Prevalence and Treatment of Depression in Adolescents and Young Adults. Pediatrics, 138(6), e20161878.
Data from the Monitoring the Future study, funded by the National Institute on Drug Abuse, reveal that long-standing gender gaps in alcohol use between male and female 8th, 10th, and 12th graders have disappeared and, for 8th and 10th graders, actually reversed.
Transition in brain from goal directed to habit circuits facilitates the emergence of compulsivity.

Progressive decrease in inhibitory control by prefrontal cortical areas over drug seeking behavior.

Often furthered by damage to frontal lobe circuits following prolonged substance use.

Abnormal gray matter volume loss in heavy versus light drinking college students

Gray matter volumes decreased more over 2 years in sustained heavy drinking (average 48 drinks/month) compared to sustained light drinking (average 2 drinks/month) college students beginning at average age 18.5

“This pattern of greater gray matter decline in heavy users occurred largely in regions responsible for emotion, memory, mental flexibility, and decision making, all of which might have a direct impact on student college success.”


Source: Meda SA et al (2017) Heavy drinking in college students is associated with accelerated gray matter volumetric decline over a 2 year period. Frontiers Behav Neurosci 11:176:
Enter the “Dark Side” -- Shift from producing pleasure to reducing discomfort as tolerance develops.

From: Koob GF and Le Moal M, Neuropsychopharmacology, 2001, 24:97-129.
Addiction is a brain disorder that manifests in a three stage cycle.

Koob GF, Le Moal M. 2008
Annu. Rev. Psychol. 59:29–53
In summary

• Drugs are reinforcing because they add pleasure or reduce pain
• Reinforcement increases the odds of repeating drug use
• Repeating drug use leads to tolerance and dose escalation
• Tolerance leads to withdrawal and a shift in motivation for use toward reducing pain and away from adding pleasure
• Over time the brain shifts control over drug use from conscious choice to habit, making it much harder to regulate or stop
• Tolerance, withdrawal, and habit formation trap a person in the Koob cycle of addiction (i.e., anticipation/intoxication/negative affect)
• Impact of prenatal exposure to substances on tone of stress circuitry could increase the likelihood of anxiety, depression, conduct disorder and substance use later in childhood and adolescence
Thank You!

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Dr. Trish Powell