Addiction and the Brain
Antireward System

Koob & Moal 2008
What is drug addiction?

- Chronic relapsing disorder characterized by:
  - Compulsion to seek and take the drug
  - Loss of control in limiting intake
  - Emergence of a negative emotional state when access to the drug is prevented

- DSM-IV calls this SUD, dependence
Goal of neurobiological research

- Understand neurobiology that mediate the transition from occasional, controlled drug use and the loss of control over drug seeking and taking that defines chronic addiction.
Koob’s thesis

“A key element of the addiction process is the underactivation of natural motivational systems such that the reward system becomes compromised and that an antireward system is recruited to provide the powerful motivation for drug seeking associated with compulsive use.”
Opponent process theory

- A-process: occurs shortly after presentation of a stimulus, correlates closely with the stimulus intensity, quality, and duration of the reinforcer, and shows tolerance
- B-process: occurs after the a-process has terminated. Sluggish in onset, slow to build up to an asymptote, slow to decay, and gets larger with repeated exposure
Allostasis

- A state of chronic deviation of the regulatory system from its normal (homeostatic) operating level
- Drug addiction represents a dynamic break with homeostasis
- Changed set points that require increasing amounts of energy to defend a certain pathology
Allostasis is mediated by:

- **Within-system neuroadaptations:** change within a given reward circuit to accommodate overactivity of pleasure processing associated with addiction, resulting in a decrease in reward function.
- **Between-system neuroadaptations:** circuitry change where a different circuit is activated by excessive engagement of the reward circuit and has opposing actions, again, limiting reward function.
Motivation and addiction

- Drug addiction has aspects of:
  - Impulsivity
  - Compulsivity

- What’s the difference?
Reward

- Impulsivity: positive reinforcement
- Compulsivity: negative reinforcement
- Drug addiction has been conceptualized as such a disorder that can start as an impulse control problem, but progresses to a combination of the two
Reinforcement examples

- Scenario A: Lunch was at 12:00pm. You had a good meal, were satisfied, and are not noticeably hungry at 2:00pm when someone brought in a plate full of freshly baked cookies to CVT. You are motivated to eat the cookie because you remember how good cookies taste, and you decide to have one.
- Positive reinforcement
Reinforcement examples

- Scenario B: Lunch was at 12:00pm. You had a good meal, were satisfied. You then worked in the lab for 8 hours without eating. You are noticeably hungry and irritable. Someone brings in a plate full of freshly baked cookies. You are motivated to eat the cookie to relieve your hunger.

- Negative reinforcement
Different drugs, different reinforcement

- Opioids, nicotine, and marijuana dependence: the drug must be obtained to avoid severe dysphoria and discomfort
- Alcohol, psychostimulants (cocaine, amphetamines): the drug must be obtained to satisfy the craving of a high
Positive reinforcement

- Animals (and humans) will readily self-administer drugs in a non-dependent state
- How can we measure motivation?
  - Manipulate: dose, cost of responding, second-order schedules
- Brain reward thresholds: drugs of abuse decrease thresholds for brain stimulation reward
Negative Reinforcement

- During withdrawal, attractiveness of reward increases
- Brain reward thresholds are increased
- Rats will work harder to take drug and increase intake during withdrawal
- Drug taking in the presence of an aversive consequence
Craving

- Defined as memory of the rewarding aspects of drug use superimposed on a negative emotional state

- Measuring craving:
  - Lever pressing after extinction
  - Lever pressing when paired drug cue is reinstated
  - Lever pressing when paired with a stressor
  - Place aversions
Multiple Pathways to Addiction

- Mesocorticolimbic dopamine system: evidence to suggest that all major drugs of abuse activate this system
- Lesions of this system?
- Extended amygdala: evidence to suggest it has a role in positive reinforcement
<table>
<thead>
<tr>
<th>Drug of abuse</th>
<th>Neurotransmitter</th>
<th>Site</th>
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<td>Cocaine and amphetamines</td>
<td>Dopamine</td>
<td>Nucleus accumbens</td>
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<td>γ-aminobutyric acid</td>
<td>Amygdala</td>
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<tr>
<td>Opiates</td>
<td>Opioid peptides</td>
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<td>Dopamine</td>
<td>Ventral tegmental area</td>
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<td>Endocannabinoids</td>
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<td>Nicotine</td>
<td>Nicotinic acetylcholine</td>
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<td>Δ⁹-Tetrahydrocannabinol</td>
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Neural Basis of Dependence: Within System

- The same systems that are involved in positive reinforcement are disrupted during withdrawal.
- During withdrawal, decreased activity in:
  - Meocorticolimbic dopamine system
  - Opioid peptide
  - GABA
  - Glutamate in nucleus accumbens
Neural Basis of Dependence: Between System

- Different systems (e.g. stress modulation) become engaged in an attempt to overcome the chronic presence of a drug to restore normal function.

- HPA axis
  - releases adrenocorticotropic hormone in response to stressor
  - Measured in cortisol levels in blood or saliva
Extended Amygdala

- Regions of the basal forebrain consisting of the stria terminalis (BNST), the central nucleus of the amygdala (CeA) and a transition zone in the medial subregion of the nucleus accumbens

- This region plays a part in the negative effects of reward function produced by stress that may drive compulsive drug seeking
The Dark Side of Addiction

- Development of the aversive emotional state that drives negative reinforcement of addiction
- Long term persistent plasticity of neural circuits
- Critical problem of chronic relapse
Vulnerability to Addiction

- Many factors at play:
  - Comorbidity
  - Temperament
  - Personality
  - Genetic factors
  - Developmental factors
  - SES factors
  - Stress and other life events
- These factors *interact* with the neurobiological processes involved
Self Medication?

- Individuals are hypothesized to take drugs to medicate dysregulated affective states:
  - Inability to express personal feelings
  - Cope with painful/threatening emotions

- Comorbidity of subjects with current dependence:
  - 35% met lifetime for mood disorder
  - 45% met lifetime for anxiety
  - 50% met lifetime for conduct or ASPD
Genetics

- 40%-60% heritability of addictions
- Researchers have identified certain genes, chromosomes, and receptors that may be key to vulnerability
- Knockout studies
Changes in genes?

- “A dramatic feature of addiction is the striking longevity of the behavioral abnormalities which indicates that addiction processes produce long-term and probably permanent changes in specific circuitry in the brain.”

- Stress, trauma, prenatal stress, early-life rearing experiences may alter addiction pathology via gene expression changes
Nondrug addictions?

- Other impulse control disorders have similar characteristics
  - Kleptomania
  - Trichotillomania
  - Pyromania
  - Compulsive gambling

- Face validity with phenotype of addiction