Is Addiction Really a "Disease?"

"Choice" vs. "Disease"
- Free Will exists
- Responsibility
- Can stop
- Punishment and Coercion DO work
- BEHAVIORS
- No Free Will
- No Responsibility
- Can’t stop
- Punishment and Coercion DON’T work
- SYMPTOMS

The Neurobiology of Addiction and Recovery

Kevin McCauley, MD
New Roads Treatment Center, Utah
Dawn Farm Education Series
Ypsilanti, Michigan
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The most evil disease imaginable
- Wouldn’t look like a “disease” at all
- Genetic, but with variable penetrance (genotype ≠ phenotype)
- Repulsive symptoms easily confused with “willful badness”
- Self-deception as a clinical feature
- Poor prognosis if untreated, but some will get better (inexplicably)
- Chronic and relapsing (not acute, nor cured)
- Culturally & politically divisive (would tap into society’s deepest prejudices, stigma, superstitions and attack its core values)
- Would only submit to "weird" solutions: peer support, patient accountability, personal evaluation, and spiritual

"Choice" vs. "Disease"

Long-Term Course of Opioid Addiction

Yih-Iang Hser, Ph.D.
UCLA Integrated Substance Abuse Programs
Addiction Seminar (Psychiatry 434)

Supported by the National Institute on Drug Abuse (P50DA004852)
Life Course Perspective on Drug use
1. Life course theory recognizes the importance of time, timing, and temporal processes in the study of human behavior and experience over the life span, characterized by trajectories, transitions, and turning points.
2. Persistence of drug use resembles chronic diseases: high relapse rates, non-compliance, require long-term management!
3. Critical life events often lead to or explain changes.
4. Social capital, situational choice are additional key concepts.

Gene Heyman, PhD
- Addiction is not a chronic disease.
- Most addicts do stop on their own, without treatment, and do not display relapse chronicity.
- Remission ("maturing out") is the rule, not the exception.
- Addicts do not need lifelong treatment.
- Remission rates lower for legal drugs than illegal.

A 33-year Follow-up of Heroin-Dependent Sample
- A cohort of 581 male heroin addicts admitted to the California Civil Addicts Program (CAP) in 1962-64 has been followed up and interviewed over more than 30 years.
- The CAP was the only major publicly-funded drug treatment program available in California in the 1960s.
- The CAP provided a combination of inpatient and outpatient drug treatment to narcotics-dependent criminal offenders committed under court order.

Longitudinal Approach to Study Drug Use over Time
- Figure 14: Five distinctive drug use trajectories (N = 1,797).

Likelihood of Remitting as a Function of Time Since Onset of Dependence
- Figure showing cumulative probability of remission.
- Equation: Cum Rem = 0.50 - e^{-0.17t}.
Marc Lewis, PhD: Addiction as a Developmental Stage

- Brain changes per se do not indicate pathology
- Plasticity (learning) is a normal function of the brain and addiction is a particularly deep form of learning
- Motivated repetition remodels the brain causing intense desire for drugs (craving), strong cues to repeat, over-valuation of drug, narrowing of focus,
- The very thing that got a person into addiction (plasticity) can get them out (development past addiction into recovery)

Getting to “core issues” is important

ASAM Addiction Definition (Aug 2011)

A stress-induced (HPA axis), genetically-mediated (polymorphisms, epigenetic mechs.) primary, chronic and relapsing brain disease of reward (nucleus accumbens), memory (hippocampus & amygdala), motivation and related circuitry (ACC, basal forebrain) that alters motivational hierarchies such that addictive behaviors supplant healthy, self-care behaviors
Addiction is a disorder of ... 
5. ... CHOICE (motivation) 
4. ... STRESS (anti-reward system) 
3. ... MEMORY (learning) 
2. ... REWARD (hedonic system) 
1. ... GENES (vulnerability) 

Five Theories of Addiction 
5. Pathology of Motivation and Choice (Kalivas & Volkow) 
4. Stress and Allostasis (Koob & LeMoal) 
3. Pathology of Learning & Memory (Hyman, Everitt & Robbins) 
2. Incentive-sensitization of Reward (Robinson & Berridge) 
1. Genetic Vulnerability (Schuckit et al) 

What goes into a “choice?”
- Valuation 
- Risk Taking 
- Novelty-seeking 
- Impulsivity 
- Empathy/Narcissism 
- Memory/Stress/Trauma 
- Social Status 

A “Disease” of Volition 
- Could such a thing exist? (ontologic argument) 
- What would happen if such a thing existed? (teleologic argument) 
- What is the nature of volition/free will/choice? 
- Is there something special (non-material) about “choice”? 
- If so, what is it? 
- If not, how is “choice” realized in the 

Addiction is a disorder of ... 
5. ... CHOICE (motivation) 
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2. ... REWARD (hedonic system) 
1. ... GENES (vulnerability) 

Individual characteristics that predict high vulnerability to drug-seeking behavior 
- High stress reactivity 
- High novelty-induced locomotor activity 
- High novelty-seeking 
- High trait impulsivity
Stanford Marshmallow Experiment
- Mischel, Shoda & Rodriguez, 1989
- Children offered a choice between
  1. One small immediate reward
  OR
  2. Two small delayed rewards
- Children that could delay gratification had better life outcomes (higher SAT scores, higher educational attainment, lower BMI)

Orbitofrontal Cortex (OFC)
- Decision-making guided by rewards
- Integrates sensory and emotional information from lower limbic structures
- Flexible assignment of value to environmental stimuli to motivate or inhibit choices & actions
- Self-monitoring and social responding

Anterior Cingulate Cortex (ACC)
- Works with OFC: decision-making based on reward values
- But also generates new actions based on past rewards/punishments
- Appreciation and valuation of social cues
- MRI: active in tasks

Insular Cortex (IC)
- Abrupt cigarette smoking cessation with IC lesions (Naqvi et al)
- Important in emotional awareness, empathy, interoceptive representation
- Impairment is one part of craving

Prefrontal Cortex (PFC)
- EXECUTIVE DECISION-MAKING
- Motivation for goal-directed activity
- Planning and problem-solving
- Attention to tasks
- Inhibition of impulsive responses
- Weighing consequences of future actions
- Flexibility of responses (rule shifting)
- Reflective decision-making
  Gives us the capacity to use past experience and knowledge to make sense of our current behavior

Addiction is a disorder of …
5.
4.
3.
2.
1. … GENES (vulnerability)
Genetic Vulnerability vs Resilience

- Genetic difference determine "low responders" vs. "high responders" to the effects of alcohol (low responders are more likely to become alcoholics)
- There are genetic differences in how people respond to methylphenidate (Ritalin) injections (some like it, some don't care) implying different vulnerabilities
- For addicts, drugs really do "feel" different than they do to non-addicts

Epigenetics

- Modifications (DNA methylation, Histone acetylation) that effect gene expression
- Tells the cell what genes to express
- Heritable (but reversible) changes in gene expression due to environmental factors
- Allows passage of information from generation to generation that is not encoded in DNA
- Inheritance without DNA sequence change

Epigenetics

- Overklix study: Starvation during adolescence increased the prevalence of diabetes in grandchildren
- Holocaust survivors with PTSD: their children also had PTSD without having been exposed to trauma
- A mechanism exists to transmit environmental exposure information from one generation to the next to the next

Strategies to deal with the GENETIC (VULNERABILITY) component of addiction

- Careful framing (vulnerability > adaptation)
- Adaptive strategies
- Risk assessment and stratification for all future medications
- Pharmacogenomics

Addiction is a disorder of ...

5.
4.
3.
2. ... REWARD (hedonic system)
1. ... GENES (vulnerability)
Addiction Neurochemical #1: Dopamine

- All drugs of abuse and potential compulsive behaviors release Dopamine.
- Dopamine is the first chemical in the cascade of chemicals that generate a rewarding experience.
- DA is the chemical of salience (survival importance).
- DA is more about “wanting” than “liking”.
- DA is more about expectation than consumption.
- DA signals reward prediction error - it tells the brain when something is “better than expected”.

Incentive-Sensitization (Robinson & Berridge)

- Distinguished between a “liking” and a “wanting” role for Dopamine (it’s more about “wanting”).
- Created hyper-dopaminergic Dopamine Transporter “knock-down” mice (mice with increased synaptic Dopamine).
- Observed increased intake of reinforcing substances in these mice and greater thwarting of obstacles to get them (i.e. more “wanting”).
- But did not observe greater “liking” of these substances by these mice.

DA NAc neurons do more than encode receipt of reward

- Expectancy of reward
- Amount of reward
- Delay of reward
- Errors in reward prediction
- Motivation for drug seeking
- Contribute to synaptic neuroplasticity that underlies the acquisition of addictive behaviors.

Computational Neuroscience

- Computational models of human decision-making and addiction
- How do agents process information to make a decision?

Dopamine-Releasing Chemicals

- Alcohol & Sedative/Hypnotics
- Opiates/Opioids
- Cocaine
- Amphetamines
- Entactogens (MDMA)
- Entheogens/Hallucinogens
- Dissociants (PCP, Ketamine)
- Cannabinoids
- Inhalants
- Nicotine
- Caffeine
- Anabolic-Androgenic Steroids
Drugs cause Dopamine Surges in the midbrain reward system

Dopamine-Releasing Behaviors
- Food (Bulimia & Binge Eating)
- Sex
- Relationships
- Other People
  - (“Codependency,” Control)
- Gambling
- Cults
- Performance
  - (“Work-aholism”)
- Collection/Accumulation
  - (“Shop-aholism”)
- Rage/Violence
- Media/Entertainment

The Full Spectrum of Addiction
- Alcohol & Sedative/Hypnotics
- Opiates/Opioids
- Cocaine
- Amphetamines
- Entactogens (MDMA)
- Entheogens/Hallucinogens
- Dissociants (PCP, Ketamine)
- Cannabinoids
- Inhalants
- Nicotine
- Caffeine
- Anabolic-Androgenic

Functionally...
Dopamine D2 Receptors are Decreased by Addiction

Periodic Table of the Intoxicants
ASAM Definition: Relapse

- Persistent relapse / and risk thereof
- Even after periods of abstinence
- Triggered by:
  1. Brief re-exposure to drug itself (DA release in NAc) 
     drug-induced reinstatement
  2. 
  3.

Strategies to deal with the DOPAMINE (REWARD) component of addiction

- Daily "dopamine load" assessment
- Take out the Dopamine "spikes"
- Nicotine cessation
- Avoid cross-addiction
- Put normal Dopamine releases (normal, competing rewarding activities) back in
- Judiciously chosen medications

Addiction is a disorder of …

5.
4.
3. … MEMORY (learning)
2. … REWARD (hedonic system)
1. … GENES (vulnerability)

Addiction Neurochemical #2: Glutamate

- The most abundant neurochemical in the brain
- Critical in memory formation & consolidation
- All drugs of abuse and many addicting behaviors effect Glutamate which preserves drug memories and creates drug cues
- And … glutamate is the neurochemical of “motivation” (it initiates drug seeking)
The hypofrontal/craving brain state represents and imbalance between 2 brain drives

<table>
<thead>
<tr>
<th>Amygdalar-Cortical Circuit</th>
<th>Cortico-Striatal Circuit</th>
</tr>
</thead>
<tbody>
<tr>
<td>“GO!”</td>
<td>“DON’T GO!”</td>
</tr>
<tr>
<td>Impulsive</td>
<td>Organized, Attentive</td>
</tr>
<tr>
<td>Non-reflective</td>
<td>Sensitive to consequences</td>
</tr>
<tr>
<td>Poorly conceived</td>
<td>Well-planned</td>
</tr>
<tr>
<td>Socially inappropriate</td>
<td>Socially appropriate</td>
</tr>
</tbody>
</table>

THERE’S TOO MUCH OF THIS (Behavioral Impulsivity)

THERE’S TOO LITTLE OF THIS (Failure of Behavioral Inhibition)

Strategies to deal with the GLUTAMATE (MEMORY) component of addiction

- Prepare for triggers
- Avoid triggers as much as it is possible to do so (avoiding old places, playmates, etc)
- Self-talk in moments of craving (CBTx)
- Peers, behavioral barriers, frequent monitoring
- Medications

ASAM Definition: Relapse

- Persistent relapse / and risk thereof
- Even after periods of abstinence
- Triggered by:
  1. Re-exposure to drug itself (DA release in NAc) 
     drug-induced reinstatement
  2. Exposure to drug cues (GLU release in Amygdala/Hipp) 
     cue-induced reinstatement
  3. Exposure to Envir Stress (CRF release in Amygdala) 
     stress-induced reinstatement

Addiction is a disorder of ...

5. ...
4. ... STRESS (anti-reward system)
3. ... MEMORY (learning)
2. ... REWARD (hedonic system)
1. ... GENES (vulnerability)

Hedonic Allostasis Theory (Koob & LeMoal)

- With continued drug use and withdrawal, the "anti-reward" system is recruited to counterbalance excess Dopamine (with the stress hormone CRF)
- Brain is unable to maintain normal "homeostasis"
- So the brain reverts to "allostasis" - change of the hedonic "set point" under stress in a desperate attempt to maintain stability
- Current Rx/Tx focus: CRF1-antagonists as anti-craving drugs
**Hypothalamic-Pituitary-Adrenal (HPA) Axis**

- Hypothalamus releases Corticotropin-Releasing Factor (CRF)
- CRF goes to Pituitary Gland to release ACTH (and ß-endorphin)
- Cortisol goes to Adrenal Glands to release Glucocorticoids and Cortisol
- Glucocorticoids and Cortisol mobilize the stress system
- Glucocorticoids feed-back to Hypothalamus to slow the release of CRF

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**CHRONIC, SEVERE STRESS = ↑CRF**

and ↑CRF = ↓DAD2 receptors

and ↓DAD2 receptors = Anhedonia

**Anhedonia:** Pleasure “deafness”

(the patient is no longer able to derive normal pleasure from those things that have been pleasurable in the past)

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**Addiction is a disorder of ...**

1. ... GENES (vulnerability)
2. ... REWARD (hedonic system)
3. ... MEMORY (learning)
4. ... STRESS (anti-reward system)
5. ... CHOICE (motivation)

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**Orbitofrontal Cortex (OFC)**

- Decision-making guided by rewards
- Integrates sensory and emotional information from lower limbic structures
- Flexible assignment of value to environmental stimuli to motivate or inhibit choices & actions
- Self-monitoring and social responding

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**Strategies to deal with the STRESS component of addiction**

- Safe housing
- Recognize unconscious aspects of relapse
- Ritualistic, daily (hourly) stress management activities
- Supportive peers
- Medication (alpha- and beta-blockade)
- Minimize social dominance
**damage to Orbitofrontal Cortex (OFC)**

- Causes a loss of a crucial behavioral guidance system
- Responses are impulsive and inappropriate
- Deficits of self-regulation
- Inability to properly assign value to rewards (such as money vs. drugs)
- Tendency to choose small & immediate rewards over larger but

**Anterior Cingulate Cortex (ACC)**

- Works with OFC: decision-making based on reward values
- But also generates new actions based on past rewards/punishments
- Appreciation and valuation of social cues
- MRI: active in tasks

**damage to Anterior Cingulate Cortex (ACC)**

- Just as with OFC damage: causes a loss of a crucial behavioral guidance system
- Inflexibility/inability to respond to errors in the past with regard to rewards/punishments
- Deficits in social responding due to decreased awareness of social cues

**Prefrontal Cortex (PFC)**

- EXECUTIVE DECISION-MAKING
- Motivation for goal-directed activity
- Planning and problem-solving
- Attention to tasks
- Inhibition of impulsive responses
- Weighing consequences of future actions
- Flexibility of responses (rule shifting)
- Reflective decision-making
  Gives us the capacity to use past experience and knowledge to make sense of our current

**damage to Prefrontal Cortex (PFC)**

- Failure of Executive Functioning
- Premature, unduly risky, poorly conceived actions
- Emotional crises
- Emotions inappropriate to the situation
- Lack of emotional expression (alexithymia)
- Sensation seeking
- Deficits in attention, lack of perseverance
- Insensitivity to consequences

**Strategies to deal with the FRONTAL CORTEX (CHOICE) component of addiction**

- Medical/craving/psychiatric stabilization
- Abstinence
- Peer support (small, single-gender, long-term)
- Agency-building exercises
- Service work, working with newcomers
- Purposeful, meaningful goals
- Subject > Object
Addiction is a disorder of …

6. … MEANING (spirituality?)
5. … CHOICE (motivation)
4. … STRESS (anti-reward system)
3. … MEMORY (learning)
2. … REWARD (hedonic system)
1. … GENES (vulnerability)

AA: using NON - Rational Concepts

• TRIBE ("the fellowship of alcoholics")
• MYTH (Bill’s Story, etc.)
• RITUAL ("what it was like, what happened, and…")
• FAITH ("Keep coming back, it works")
• HOPE (The Promises)
• ACCEPTANCE ("…the answer to all my problems")

References:


Dennis ME, Scott CR. Four-year outcomes from the early intervention (ERI) experiment using recovery management checkups (RMCS). Drug and Alcohol Dependence 121 (2012) 10-17.


