The Neurobiology of Addiction

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ASAM Disclosure of Relevant Financial Relationships

No Relevant Financial Relationships with Any Commercial Interests
Addiction is a stress induced, genetically mediated, primary, chronic disease of brain reward, motivation, memory and related circuitry.

Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations.

This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors...
ASAM definition of addiction

- Addiction is a stress induced, genetically mediated, primary, chronic disease of brain reward, motivation, memory and related circuitry.
Addiction is *stress induced*
Stress = Drinking

- Older adults more vulnerable to effects of alcohol and medications
- Increased risks of comorbid diseases
- Increased risks of harmful drug interactions, injuries, depression, cognitive issues, liver and cardiovascular diseases
- Increased fall risks leading to bone fractures, internal bleeding and head injury
- Poor cognition interfere with ability to recall use history
- Withdrawal management challenges
At risk drinking and problem drinking are the largest classes of substance use problems in older adults.

At risk drinking defined by $\geq 3$ drinks per day and $\geq 7$ drinks per week in healthy men/women older than 65 y/o.

At risk drinking increases the potential for developing problems and complications.

Late onset problems may develop due to stressors related to older age (e.g., retirement, loss of income, loss of partner).

Most elderly patients with alcohol problems go unidentified by health care personnel.

Few elderly patients seek help.
Iatrogenic Addiction

• Adults > 65 y/o comprise 13% of the population and 36% of all prescription medications used in the United States

• 25% of older adults use psychoactive medications with abuse potential

• Greatest concerns are opioids and benzodiazepines

• Misuse and abuse of prescription drugs by older adults not typically done for euphoria

• Most abused medications are obtained by prescription

• Estimated nonmedical use of prescription drugs will increase to ~2.7 million by 2020 in 50+ age group
Plasticity of the Brain

- Brain **adapts** to experience
  - Changes in receptors and neurotransmitters
  - Changes in chemical reactions elicited by stimuli
  - “Rewiring” of nerve connections
  - *Changes in gene expression* aka **epigenetics**
Epigenetics

• Modifications of genes that affect gene expression - mask/unmask
• Environment and experience influence gene expression
• Heritable, reversible (?)
• Accounts for characteristics to be inherited without changes to DNA sequence
...genetically mediated...

• Genetic predisposition accounts for about 50% of the likelihood that an individual will develop addiction
Heritability of Addiction
Genetic Vulnerability vs. Resistance

- Numerous genetic differences and *endophenotypes*
- Low vs. high responders to alcohol effects
- Impulsiveness/behavioral disinhibition
- Personality styles
- Opioid receptors
- Alcohol metabolism

Mark Schuckit, MD, UCSD
Numerous genes associated with Addiction

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AC, adenylyl cyclase; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; DA, dopamine; DAT, dopamine transporter; DRD2, dopamine receptor D2; GABA, γ-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal axis; 5-HT, serotonin; LR, level of response; NPY, neuropeptide Y; PKC, protein kinase C.
Adolescents are highly vulnerable to addiction beyond their genetic predisposition.
Alcohol ages the brain

CORTICAL GRAY MATTER VOLUMES

57-year-old men

Alcoholic

Control Subject

Lifetime consumption of alcohol was

1866 kg or 625 gallons

60 kg or 20 gallons

Z-score

Prefrontal  Frontal  Ant Temporal  Post  Ant Parietal Occipital

Younger Alcoholics (N=33)

Older Alcoholics (N=29)

Control Subjects
...primary, chronic disease of...
Disease

- A “defect in an organ system that produces a consistent pattern of signs and symptoms”
An Evil Disease

- Doesn’t look like a disease
- Self-deception (denial) is a sign
- Affects genetically susceptible (vulnerable) people
- Has a highly variable prognosis
  - Poor prognosis if untreated
  - Some recover spontaneously
  - Chronic/relapsing
- Culturally & politically divisive: challenges societal values and norms.
Chronic Diseases......

- Treated, not cured
  - characterized by relapse and remission
- Outcomes depend on continuity of care over time
- Genetic plus environmental factors determine..... “vulnerability”
Relapse in Addiction

• Like other chronic diseases, relapse in addiction is common
• Relapse rate (for all substances) is 40-60%
Vulnerability to Addiction

**Risk Factors**

- **Biology/Genes**
  - Genetics
  - Gender
  - Mental disorders

- **Environment**
  - Chaotic home and abuse
  - Parent's use and attitudes
  - Peer influences
  - Community attitudes
  - Poor school achievement

- **Drug**
  - Early use
  - Availability
  - Cost

- **Brain Mechanisms**

- **Addiction**
...brain reward, motivation, memory...
80 – 100 billion neurons

Each nerve cell may have up to ten thousand connections. Each connection is called a **synapse**.

The brain has 100,000,000,000,000 synapses.
Synapse = nerve connection
Memory

• Simple model of memory:
  • Encoding
  • Storage
  • Retrieval
Brain Memory Pathways

cerebral cortex

to thalamus

amygdaloid body

olfactory bulb

cerebellum

locus coeruleus

caudal raphe nuclei

© CNSforum.com
Memory for Drugs and Related Cues

- Memory of prior euphoric experiences
- Both drugs and associated memories
  - Drug cues
- Cues motivate behaviors associated with drug use
  - Craving
  - Drug seeking
“Reward circuit” re-enforces survival behavior

- **Midbrain (VTA):** Reward driven, impulsive (motivation)

- **Nucleus Accumbens:** memory and learning associated with reward

- **Prefrontal cortex:** Executive function
  - Top down decision making
  - Inhibitory control: “Brakes and steering” (choice)
Neuroimaging (PET scan)

Shows activation of reward areas of human brain after exposure to cocaine.
Survival Brain (Limbic Area)

Brain connections ensure that we will repeat life-sustaining activities by associating those activities with pleasure.

Survival behaviors:

• Food/Fluid intake
• Relationships/nurturing
• Fight or Flight response
• Procreation
Reward system affects thinking

Prefrontal area – appropriate behavior. Think and act according to social norms and expectations.

WOW!!!
That feels amazing
(I will do THAT again!)
The Prefrontal Cortex (PFC)

PFC is known to mediate:\(^1\)

- Decision Making
- Planning
- Working Memory
- Inhibition
- Attention
- Salience
- Value
- “Brakes and Steering”

The Prefrontal Cortex in Addiction

Dysregulation of the PFC in addiction leads to compulsive, drug-seeking behavior

1. Impaired inhibition of unhealthy or drug-taking behavior (i.e. drinking)
2. Excessive salience attributed to alcohol and alcohol-related stimuli

**Impaired Response Inhibition and Salience Attribution (iRISA)**
Goldstein & Volkow 2002, 2011
“Thus, those who say ‘it was their own choice’ after a person dies of an overdose fail to grasp that an addicted person’s brain has a disrupted choice mechanism.”

“It isn’t enough to say that addiction is a chronic brain disease. ...the circuits that enable us to exert free will no longer function as they should.”

“...The good news is that behavioral therapies and medications can help addicted individuals repair their damaged self-control capacities, as long as they actively participate in treatment.”
"Thinking about Thinking"
Higher Reasoning
Executive Function

Prefrontal Cortex
9 Functions of the Prefrontal Cortex

1. Empathy
2. Insight
3. Response Flexibility
4. Emotion Regulation
5. Body Regulation
6. Morality
7. Intuition
8. Attuned Communication
9. Fear Modulation

Limbic Brain
1. Fight, flight, freeze stress response
2. Thinks, "Am I safe? Do people want me?"
3. Emotions live here
The “brakes” have failed
Substances *and behaviors* associated with dopamine release

- Alcohol/Sedative hypnotics
- Opioids
- Cocaine/Amphetamines
- Ecstasy (MDMA)
- Hallucinogens
- Dissociants
- Cannabinoids
- Nicotine
- Anabolic Steroids
- Food/sugar
- Sex/love
- People, “co-dependency”
- Gambling
- Exercise
- Achievement
- Collection/Accumulation
- Rage/Violence
- Media/Entertainment
Magnitude of Dopamine release determines the degree of reinforcement.

*Natural Rewards Elevate Dopamine Levels*

ALL drugs of abuse cause release of dopamine in the reward pathway that is **out of proportion** to natural rewards.

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**Natural Rewards Elevate Dopamine Levels**

- **Food**
  - NAc shell
  - Graph showing % of Basal DA Output over time (min) with points for Empty Box Feeding.

- **Sex**
  - Graph showing DA Concentration (% Baseline) over sample number with points for Female Present.

**Effects of Drugs on Amphetamine**

- Graph showing % of Basal Release over time (hr) for Accumbens, DA, DOPAC, HVA.

**Effects of Drugs on Nicotine**

- Graph showing % of Basal Release over time after drug (hr) for Accumbens, Caudate.
Opioids increase brain dopamine
✓ Dose dependent
✓ Long-lasting effect

Effects of Drugs on Dopamine Release

Di Chiara and Imperato, PNAS, 1988
So, why do people use drugs?

BECAUSE THEY LIKE THEM!

Energized + WOW! + Well-being = Euphoria
Like Becomes Need
Non-addict brain response to drug

No persisting brain changes

Baseline = Normal
Addicted Brain Response

- Brain chemistry is changing
- Brain is rewiring itself
- Genes are making new proteins
- Craving/desire for drug occurs

Baseline = Normal

The addicted person once used for pleasure, now uses out of desperation just to feel normal.
Repeated drug use changes the brain (MISERY)
ASAM definition of addiction

- Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations.
- This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors...
Psychosocial manifestations

• Inability to consistently **ABSTAIN**
• Impairment in **BEHAVIORAL CONTROL**
• **CRAVING**
• **DIMINISHED RECOGNITION** of problems with one’s behavior and interpersonal relationships
• Dysfunctional **EMOTIONAL RESPONSE**
Spiritual manifestations

• Distortion in meaning, purpose and values

• Distortion in connection w/ self, others & the transcendent
  - God, Higher Power, Absolute, Allah, Buddha, Brahman, Universal Spirit, etc.
All areas of life become unmanageable

Relationships

Mental

Health

Legal

Emotional

Social

Financial

Spiritual

Occupational

Addiction

prefrontal cortex

nucleus accumbens

VTA
Family Disease

Addiction

Worry

Frustration

Anger

Food

Sex

Drugs

Exercise

Shopping

PATIENT

FAMILY MEMBER
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- Media/Entertainment
Use of other drugs of abuse - supplementation or substitution

Once addiction is established, other substances which stimulate the reward system may satisfy cravings or stimulate them.

Dopamine Pathways

Ken Thompson - Caron Treatment Centers
Persistent brain changes
Persistent brain changes

Normal

Cocaine Addict (10 days abstinent)
Persistent brain changes

Normal

Cocaine Addict (10 days abstinent)

Cocaine Addict (100 days abstinent)
Summary

• Addiction is a chronic disease that affects the brain – it is not a lack of willpower or moral failing
• Addiction is a complex disease that requires a comprehensive solution
• Medication alone is insufficient to treat addiction
• Recovery is more than abstinence
• Recovery is a progression toward optimum wellness across biological, psychological, social, and spiritual dimensions.
• Recovery is a lifelong process
• We have much to learn