Neuroscience of Relapse & Recovery

CAADE 4/19/13

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CATC V

Addictions Recovery Center &
CNS Production, Inc.

Preventing Relapse, Promoting Long-Term Sobriety

Presented by: Darryl S. Inaba, PharmD., CADC III
Director Clinical & Behavioral Health Services - ARC
Director of Research & Education - CNS

Addiction Relapse Associations

• Stigma by both addicts & “normies”
• Great shame, guilt and hopelessness in both addicts and their families
• Progression of disorder, each successive event results in worse consequences
• Relapse is a feature of all chronic persistent disorders: annually 40-50% of those in treatment for Diabetes, Hypertension or Asthma experience relapses

**Slip and Relapse**

Slip = momentary, short-lived, isolated and limited use of addictive substance or practice of compulsive behaviors after a period of abstinence (Slide?)

Relapse = return to persistent and compulsive drug use or behavioral practice after a period of abstinence

The frequency that a single use of drug or addictive behavior (Slip) results in a Relapse of a recovering addict is 95%

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**Relapse Related Brain Circuits and Processes**

- Stay Stopped (Slip Decisions)
- Emotional Memory (Cravings)
- Stress Hormone Cycle (Hypersensitivity)

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**Slip/Stay Stopped Brain Anomalies**
**Relapsers, Nonrelapsers Make Decisions Differently**

During a decision-making exercise, nonrelapsers activated five brain regions that relapsers did not.

**Memories**

**Formation & Role In Drug Cravings**
Neuro-development of Memories

Dendritic spines, bumps or protrusions

Dendritic Memory Spines

- Amygdala process emotional memories, hippocampus all other memories
- Also known as Bumps, Spikes – I like the term memory protrusions = less triggering
- 4 to 6 sensory inputs of the same stimulus per hour results in development of a semi-permanent memory protrusion
- The more often a memory protrusion is activated the larger it grows and the more permanent it becomes

All Addiction Memories are processed as emotional memories via the amygdala, these are faster and have a more powerful influence on behavior than hippocampal regular memories
Meso-Limbic Reward-Reinforcement Circuitry of the MFB

- **Phase I** – Endogenous/Environmental Cue or memory triggers the Ventral Tegmental Area to release dopamine which activates core of Nucleus Accumbens Septi = anticipation of use **ON A MISSION!** If initiated difficult to stop

- **Phase II** – Cues or actual use of addictive drug activates dopamine “go” switches of lateral hypothalamus and Nucleus Accumbens (core and shell): **COMPULSION FOR MORE!**

- **Phase III** – Control circuitry of the prefrontal cortex is disrupted, is inactivated and releasing glutamate: results in **LOSS OF CONTROL, CONTINUE DESPITE NEGATIVE CONSEQUENCES**
New NIH Details on Addiction Craving Brain Pathway

- Hippocampal memory process activates
- Lateral Septum via glutamate and this in turn activates
- Ventral Tegmental Area (VTA) via gamma-aminobutyric acid (GABA) that then activates
- Nucleus Accumbens Septi (“go Switch”) via dopamine

Luo, AH, et al. Science 7/15/11

Hypersensitivity of Stress Hormone Cycle in Addiction

1. Stress activates hypothalamus release of corticotropin releasing factor (CRF)
2. CRF activates pituitary release of adrenocorticotropic hormone (ACTH)
3. ACTH activates kidney adrenal glands to release cortisol
Addiction is a stress-induced defect in midbrain’s ability to perceive pleasure – Dr. Kevin McCauley

- CRF & ACTH are neurotransmitters as well as hormones they modulate novelty-seeking and dopamine activity in the brain
- Severe stress increase risk-taking behaviors in all and suppress dopamine’s ability to perceive reward, survival reinforcement, “pleasure” resulting in anhedonia since
- CRF & ACTH as neurotransmitters produce the unpleasant emotional reactions associated with stress
- Cortisol usually turns off these secretions to terminate a stress reaction but extreme stress overrules cortisol

Addictive drugs first release of dopamine in the midbrain fools it as being a coping mechanism for the relieve of stress

- Opiates & endorphins shown to also inhibit CRF & ACTH as cortisol would naturally do
- But, withdrawal from opiates cause increase release of CRF, ACTH and creates hypersensitivity to stress that overrule cortisol’s regulation of cycle = craving
- Cocaine directly releases the CRF and ACTH mistaken as part of or covered by the rush, stimulant withdrawal also activates the stress mechanism = craving
- Research: metyrapone validation (shuts off cortisol production increasing CRF & ACTH) and CP-154,526 treatment (blocks CRF and thus suppresses ACTH release)

Also Neural Crux of Relapse with Stress March 2013

VTA’s (ventral tegmental area): GABA-releasing neurons, dopamine-releasing neurons and Kappa opioid receptors interaction in stress. Drugs and natural satiations release dopamine in the VTA. GABA applies a brake to this via strengthening synapses (known as long-term potentiation or LTP) but stress interrupts this process leading to unabated dopamine reinforcement. Nor-BNI blocks Kappa receptors in the VTA and prevents stressed out rats from relapsing to cocaine use

Grassino, Peltier, Briand, Pierce, Kauer (2013), J. Neuron
Challenges to Maintenance of Continued Abstinence

- Cognitive Impairment (30-80%)
- Endogenous Craving (Allostasis)
- Environmental Triggers or Cues
- Post Acute Withdrawal Symptoms (PAWS)
- Unaddressed Mental Health and/or other Medical Treatment Needs

Cognitive Impairment During Addictive Behavior and in Early Recovery

Cognitive Impairment

11.3% of Limbic system of which 7.8% of Hippocampus plus 24% of dopamine transporters

- Attention, memory, understanding problems
- Word meaning, problem solving, Strop paradigm
- Inflexibility, abstract thinking, judgment
- Temporal processing: planning, processing goals, delayed discounting
Brain Imaging:
Impact of Addiction Pathology

Portable fMRI Halo Systems
Multiple Brain Imaging Techniques

Brain on Cocaine
Minutes after shooting or smoking

15 year old male non-drinker
15 year old male heavy drinker
Nicotine Evokes Addictive Brain Changes With Just One Puff

Brain Imaging Revealing Anomalies Of Process Addictions: Gambling

Internet Including Gaming and Gambling On-Line
Sex Addiction

Endogenous or Intrapersonal Addiction Cravings via Neural-Physiological Allostasis

**ENDOGENOUS CRAVING**
Analogous to diabetes, hypothyroidism, et. al., an *allostasis* develops with continued use of an addictive substance. When abstinence is initiated, the brain craves the substance in an effort to maintain its imbalanced state through a variety of mechanisms: amygdala via emotional memories, attachment and bonding via the cingulate gyrus facilitated by delta fosB transcriptase and hypo-functioning of PFC.

CK Himmelsbach 1941, Inaba & Cohen 1986, Fredrick Von Stieff 2011
Brief Review: Brain Cells and their communication processes

Neuron Homeostasis: Brain in Dynamic Equilibrium

Courtesy, Takeichi Laboratory, Nagoya, Japan
By Age 6 100 Billion Neurons and Development of a Quadrillion Synapses

The Synapse

- Neuronal transmission
- Neurotransmitter CNNs
- Neuromodulation
- Neuropeptide
- Neurotransmitters
- Neurotransmission

Cell Body
Myelin Sheath of Axon
Dendrite
Synapse
Dendritic Spine
Axon
Electrical transmission
Nucleus
Synapse
Terminal
Dendrite
Cell body
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Psychoactive Drugs Affect Perception, Mood, and States of Consciousness by mimicking or Disrupting the Natural Chemistry of the Brain

Expanded Definition = Any Behaviors (e.g. Gambling) that Alter Moods and Affect the Brain's Addiction Circuitries and Pathways

**Neurotransmitters**
- Acetylcholine
- Substance "P"
- Norepinephrine
- Anandamide
- Epinephrine
- Glycine
- Dopamine
- Histamine
- Endorphin
- Nitric oxide
- Enkephalin
- Glutamic acid
- Serotonin (5HT)
- Cortisone
- GABA
- Aspartic Acid

Synapse @ 50,000x Electron Microscopy

Courtesy of Thomas Deerinck, NCMIR/Photo Researchers, Inc.
Drugs Mimic, Disrupt, or Block Neurotransmitters

SOME EXAMPLES -
UPPERS: Catecholamines (Norepinephrine, Epinephrine, Dopamine) + Serotonin and Acetylcholine
DOWNERS: Endorphin, Enkephalin, GABA, Serotonin
PSYCHEDELICS: Serotonin, Acetylcholine, Alpha Psychosin, Norepinephrine, Dopamine, Anandamide & endocannabinoids

Taking one: Uptown, Downtown and “Outatown”

- CNS Stimulants increase the electrical and chemical activity of the brain (caffeine to ‘ice’)
- CNS Depressants decrease the electrical and chemical activity of the brain (‘booze’ to ‘benzos’ to opioids)
- All Arounders (Psychedelics) distort and interfere with brain perceptions to produce delusions, illusion, hallucinations, & synesthesia (DXM: ‘Robo’ to ‘paka-lo-lo’ to Sylvia d)
- Misc: Inhalants, Anabolic Rhoids, Behaviors

All Addictive Substance Involve Dopamine Activity
2012 UCSF Research Confirms Role of Endogenous Opioid Neurotransmitters in Reward Circuitry as well as Dopamine

Beta Endorphin  Met-Enkephalin

Also Excess Nor Epinephrine (Nor Adrenaline) and Less Transporters in Pathological Gamblers

Noradrenaline

Expanding Role of GABA & Glutamate

Inhibitory  Excitatory
Serotonin aka 5-hydroxytryptamine also involved with all addictions?

Dopamine Depletion in Addiction = Endogenous Craving and Anhedonia

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<tr>
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Courtesy of Volkow, Wang, & Begleiter, et al.)
Any Negative Mood State can initiate a Craving Reaction

- HALT – Hungry, Angry, Lonely, Tired
- RIID – Restless, Irritable, Isolated, Discontent
- BAAD – Bored, Anxious, Angry, Depressed

Environmental or Interpersonal Triggers and Cues

- Any Sensory Input to addiction memories: visual, odor, auditory, physical withdraw, etc. – PTSD?
- Thoughts of using or of withdrawal
- Other Interpersonal factors: relationship problems, social/vocational pressures, no support system, negative life events, untreated dual diagnoses
Environmental or Interpersonal Triggers and Cues via Dendritic Emotional Memory “Spines, Bumps, or Protrusions”

Craving can be caused by the sight, smell, and taste of:
* a using partner
* a using place
* a dealer
* cash
* the drug itself
MEMORIES
Both Endogenous & Environmental Triggers activate memory neural pathways that then trigger the brain’s Addiction (aka Reward) Pathway:
The Neurons then search for the most convenient way it resolved the issues or needs in the past:
USE DRUGS!

Brain Reward Pathways

Physiology of Craving
• Increased heart and pulse rate
• Specific electrical changes in skin activity and spindle effects on EEG
• Increased peristalsis activity of gut
• Pupil dilatation and cortisone stress reaction
• Two degree or more core temperature drop
  Childress AR, McLellan T, O’ Brien CP. Br. J. of Addict. 1986
Craving and Relapse: Cue-Induced Brain Activity

- Brain regions activated while viewing alcohol-related cues

Craving Extinction &
The Resilient Brain


Key: Never Initiate any action to use
~ 95% of Slips = Relapse

Stop Signal Test (SST) Research
  inhibition in alcohol dependence and problem

• London, Edythe, Director Center for Addictive and Biobehavioral Sciences, UCLA
Relapse Prevention
“tool kits”
Other Effective Relapse Prevention Tools

- Emotional Freedom Techniques (EMDR, Brain Spotting, Tapping, Elastic Snapping)
- Yoga Breaths, Somatics, Figure 8 Pacing
- Mindfulness meditation & other grounding interventions, acupuncture
- Consequence Reminders (family photo, car keys, consequence cards)
- Paradoxical Interventions (emptied Librium capsules, empty Copenhagen can, turn shirt inside out, wash off and reapply makeup, et al.)

Gender Variance in Craving and Relapse?

Women: brain areas associated with craving are more activated by stress on MRI scans. Intrapersonal, Endogenous triggers

Men: drug cues/triggers activate craving areas of the brain more = Environmental, Interpersonal triggers

Potenza, Marc et al. (2012) Am. J. of Psychiatry

But: David Sacks’ most common causes of relapse in women: Romantic relationships too soon and Unrecognized love, relationship or sex disorders

Sacks, David (2012), Psych Central

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Graziane, Pelser, Briand, Pierce, Kauer (2013), J. Neuron

Role of GABA & Glutamate during Stress at VTA kappa (nor-BNI)

PAWS: Post Acute Withdrawal Syndrome & Protracted Withdrawal Syndrome: Role in Evoking Slips and Relapses
Post Acute Withdrawal Syndrome (PAWS) – episodic or recurrent

- Sleep Disturbances – insomnia, nightmares
- Memory Problems – Short-term, learning
- Thought Problems – concentration, rigidity, repetitive thoughts/behaviors, abstract thinking & problem solving difficulties
- Anxiety, irritability, hypersensitivity to stress
- Inappropriate emotional reactions, mood swings
- Physical and coordination difficulties, fatigue
- Syndrome persists for 3-6 months, sleep problems maybe longer – can be up to 2 years

PAWS Cause is Unknown
Projected Etiology

- Slow reversing tolerance and tissue dependence
- Returning neurotransmitter allostasis back to homeostasis
- Developed hyperexcitability of neuronal pathways


PAWS Treatment

- Clinical: CBT “grounding exercises”
- acamprosate for alcohol PAWS
- carbamazepine (Tegretol)
- Trazodone
- naltrexone
Mental Health and/or other Medical Conditions Must be Stabilized and Medically Managed During Recovery

May be Pre-Existing or Addiction-Induced?

Co-Occurring Disorder, Dual Diagnosis, MICA

- Prevalence depends on population studied
- 44% alcohol abusers and 64.4% other substance abusers met diagnoses for at least one major psychiatric disorder.
- 29% - 34% of those in mental health treatment met diagnostic criteria for an addiction and related disorder. Regier et al., 1990; Merikangas, Stevens, & Fenton, 1996
- Recovery difficult if MH disorders are not addressed

- Need for “Rule-Out” careful diagnosis: Substance Induced vs. Pre-Existing
- Best Outcomes when both disorders treated at the same time in one treatment system
- Same neurochemical imbalances involved with both disorders
- Major MH disorders: Thought, Affective, Mood, Anxiety, and Personality
Dr. Kenneth Minkoff
Four Quadrant Treatment Model

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Conclusion – Questions?
Hope! Though the challenges to maintaining sobriety are daunting, developments in treatment continue to improve outcomes. Remember, the qualities in those that makes one vulnerable to addiction are also qualities we look for in our charismatic leaders.

Recovery
• Continued Abstinence
• Discovery of Natural Highs
• Recovery of neurotransmitters and of natural brain functions
• Positive lifestyles and quality of life enhancements
• Remember: Not an Event but a Process

One does not cure addiction, you treat it and manage it like any other chronic persistent medical disorder
Treatment Works!

- 3 to 5 Yrs. Continued sobriety = 50% (1yr 80%)
- Decrease Crime = 75%
- $7-$12 Savings for every $1 Spent
- Positive results from 6-8 mo. Treatment
- Coerced treatment better than voluntary
- Decreased Psychiatric (40%), Family/Social (50-60%), Medical (15-20%), Employment Problems (15-20%)
- Culturally consistent better than generic treatments

Belenko, et al. 2005

RECOVERY

The Resilient Brain

8-10 Months Rigorous Uninterrupted Treatment for Reasonable Outcomes
Implies time needed for brain to become functional
Takes up to 2 years for greater functioning to return

Courtesy of Nora Volkow (Volkow, Hitzmann, Wong, et al 1992)
**ADDICTION CAN BE TREATED**

Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence

![Brain scan images](image)


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**Dopamine Transporter Binding (DAT) Recovery in Meth Addiction**

DAT Recovery with prolonged abstinence from methamphetamine

![Brain scan images](image)

Volkow et al. J. of Neuroscience 2001

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**Dr. Ken Blum’s patented: Synapta GenX, KB220Z**

Neuronutrient complex "normalization" of caudate, accumbens and putamen regions of heroin addicts demonstrated by MRI Scan

![Brain scan images](image)
Video Presentation (31 minutes)
CNS Productions, Inc.

Neurochemistry of Relapse & Recovery

Questions/Comments?

Thank You!
Darryl Inaba, PharmD.,
CADC III

Addictions Recovery Center
and CNS Productions, Inc.

Break: Reality Bites!
Fantasy Vs. Reality!