Dual Diagnosis: Chicken or Egg?

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Dr. Gold has no disclosures to report.
Most Cited MSG Articles and Citation Classics

**Citation Classics**
1. New concepts in cocaine addiction: the dopamine depletion hypothesis CA Dackis, MS Gold - Neuroscience & Biobehavioral Reviews, 1985 - Elsevier
3. Problematic internet use: proposed classification and diagnostic criteria...., ST Szabo, M Lazoritz, MS Gold... - Depression and ..., 2003 - Wiley Online Library
5. Neurobiology of food addiction DM Blumenthal, MS Gold - Current Opinion in Clinical Nutrition & ..., 2010 - journals.lww.com

**High Citation Recognition:**
2. Comorbid cigarette and alcohol addiction: epidemiology and treatment NS Miller, MS Gold - Journal of addictive diseases, 1998 - Taylor & Francis
5. Body mass index and alcohol use KD Kleiner, MS Gold, K Frostpineda... - Journal of addictive ..., 2004 - Taylor & Francis
Examine the biological underpinnings of co-occurring substance abuse and psychiatric disorders
Do Psychiatric Diseases Cause Addiction or Vice Versa or Both?
Epigenetics: Drug Experiences Change the Brain, Make Recovery Challenging and Comorbidity the Rule—Where Drugs Meet the Genome

Drug Use Trends

- In 1962, only 2% of the U.S. population over the age of 12 years had tried an illegal drug
- By the mid 1980s, nearly 50% of the population had experimented with an illegal drug
- In 2013, an estimated 9.4% of the population had used an illicit drug in the past month—up from 8.3% in 2002
  - Increase reflects a recent rise in use of marijuana, the most commonly used illicit drug

At Least 1 in 3 Women Use Drugs “Recreationally”
42% Used Painkillers like Oxy “Recreationally”
35% Used Adderal or similar
33% Used Xanax or similar
24% Used Cocaine
63% Take Drugs when also Drinking
16% Have Blacked out
>10% “I’m a daily MJ smoker”
Evidence Base has been Established But

CASA REPORT- Where is the Funding for US

MD Education, Residency, and Fellowships?

- 10 year work on panel
- Too little medical and provider education
- Absence of Fellowship slots to train interested MDs
- Too few MDs trained and Board Certified
- Too few addiction treatment providers
- Too many children, adolescents, college age, young adults, adults, and even geriatric addicts
- Training of MDs needed and only 1/10th the number of ASAM-ABAM MDs as needed

National Advisory Commission on Treatment Addiction. Addiction Medicine: Closing the Gap between Science and Practice. JUNE 2012 CASA
Website http://www.casacolumbia.org/addiction-research/reports/addiction-medicine
Education, Prevention, Training

- Prevention PSAs
- Ad Council
- Media Partnership
- NIDA-NIAAA
- CADCA
- Treatment-adding to church basements

- One of the original ASAM, (AMSAOD) Fellowship Directors and trained 80 ASAM Boarded MDs
- ASAM Textbook
- UpToDate
- APA Council on Addictions
- Practice Guidelines
Drug Rewards Sensed by Animal Brains

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human</th>
<th>Animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Heroin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Yes</td>
<td>Some</td>
</tr>
<tr>
<td>Inhalants</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Brain Changes During Cocaine Craving

Cue-Induced Craving

Amygdala

Anterior Cingulate

Cocaine Video

Yale’s Psychiatry and Pharmacology
Professor Bob Byck –3 Major Factors Drive Drug Use

The Drug
● The drug itself
● Route of administration
● Dose
● Duration
● “Fit” in the brain
● Gold added neurotoxic effects & residual deficits

The User
● Pre-existing vulnerabilities
● Psychiatric diseases- self medication
● Age of first use
● Genetic & epigenetic factors
● Second-third hand exposure in utero or environment
● Personal characteristics (social standing, risk-taking, age, etc.)
● Post-use comorbidities

The Environment Connecting the Drug and the User
● Availability and price
● Stigma or Accepted--The culture in which this connection takes place
● Trauma & PTSD
Dopamine Deletion Theory: New Concepts in Cocaine Addiction

- Euphoric properties of cocaine lead to the development of chronic abuse, and appear to involve the acute activation of central DA neuronal systems. This is based upon known effects of cocaine on DA neurons, and the role played by DA in reward states and self-stimulation behavior.

- With chronic cocaine use, neurotransmitter and neuroendocrine alterations occur. DA depletion is hypothesized to result from overstimulation of these neurons and excessive synaptic metabolism of the neurotransmitter.

- DA depletion may underlie dysphoric aspects of cocaine abstinence, and cocaine urges. Neurochemical disruptions caused by cocaine are consistent with the concept of "physical" rather than "psychological" addiction.

- Possible pharmacological interventions in cocaine addiction are outlined and the psychological approach to these patients is discussed.

Drugs of Abuse and Dopamine: Cocaine Model Extrapolated to Other Drugs

- Hypothesized that cocaine releases 10 X more dopamine than natural rewards
- Smoked = injected drugs release dopamine quickly
- Cocaine effects last much longer than natural rewards
- Cocaine reward motivates people to take drugs again
- Cocaine depletes dopamine or causes a functional dopamine depletion with resultant drive for more cocaine
- Drug abuse is learned and triggered by dopamine-induced OR chemical reward
- Bupropion in cocaine, cigarette smoking, and depression
- Post-addiction, persistent anhedonia, depression, suicidality, sleep, and appetite changes

Clonidine to Naltrexone - 1979

- Detox works
- Induction onto naltrexone works
- Patients have multiple comorbidities—medical, neurological, endocrinological, psychiatric, trauma, addictions
- Patients stop and relapse
- Only MDs, mandated to treatment, continue
## Naltrexone: The “Perfect” Drug—Ten Reasons to Take

<table>
<thead>
<tr>
<th>Reason</th>
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<tbody>
<tr>
<td>1.</td>
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<td>3.</td>
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<td>5.</td>
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<td>7.</td>
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<td>8.</td>
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<tr>
<td>9.</td>
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<tr>
<td>10.</td>
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</tbody>
</table>

- Common Answers—"I don’t need it”
- “It costs too much”
- “I won’t use again”
- Denial after denial
- Anesthesiologists and work place data we collected suggests it is a good transition reducing death rates
Approaches to Pharmacotherapy of Substance Use Disorders

- Detox and acute abstinence
- Protracted abstinence
- Decrease craving
- Block reinforcement
- Produce toxic reaction
- Treat comorbid conditions
Treating Addiction as a Human Process

- "Edward Khantzian has been a consistent voice for the role of psychiatry and psychiatrists in the evaluation and longterm treatment of addicts. This new book brings together a substantial portion of his previous work in one volume. ...Khantzian has been a vocal advocate for the inner world of addicts, and in this book he offers his extensive experience as a clinical psychiatrist who has spent his career developing insights into psychodynamic understanding of the addict. By bringing more psychiatry to the addict, Khantzian has been a champion for parity and treatment access and has supported patient advocacy efforts to reduce stigma and shame.

- Khantzian does not minimize neurochemical, genetic, and other biological findings and theories but tries to apply them to his psychodynamic model. Khantzian has extended Freudian theory, which views drug use as a displaced addiction to masturbation. Freud may have been describing himself and his relationship to his pipe and tobacco while also predicting that drugs of abuse are taken because they hijack the brain systems normally quiet and reserved for reinforcement of primary drives, like sex.

- Khantzian is always asking, Why do people take drugs? One answer he provides is, Because they have to. Addicts suffer from subclinical or DSM-IV deficits and diseases that they learn to self-medicate with a preferred drug. The self-medication hypothesis leads to Khantzian’s overall view of addicts as people with considerable lack of self-care and self-governance who destroy themselves as a consequence of not knowing how to regulate or care for themselves. Thus, addiction is not pleasure seeking but remedial action to relieve suffering.

- In his earliest work, Khantzian explored the treatment implications of self-medication and combining psychotherapeutic and psychopharmacological treatments for alcoholics. He advocated the targeting and treating of depression and anxiety, which he judged to be important to the development of alcohol dependency. Khantzian has changed his theory from the concept that all alcoholics uniformly suffer from pathological ego and self-formations to the idea that alcoholics have a degree of abnormality and difficulty in self-regulation. This evolution came from treating patients who had benefited from therapy in 12-step programs and showed great flexibility, strength, and resiliency.
Addictive Conditions as a Self-Regulation Disorder

- Notwithstanding the absence of empirical evidence, clinical observations (practice-based evidence) suggest that there is a considerable degree of preference specificity for an individual’s drug-of-choice. I would emphasize that it is a range of painful, unbearable or confusing feeling states that individuals self-medicate that might or might not be associated with psychiatric disorders. Few would argue that intense feelings of rage, aggression and violence predominate with PTSD and BPD. In my experience, it is these intense emotions that heroin-dependent individuals self-medicate. Based on the evaluations of many heroin-dependent individuals, they repeatedly indicate that their main drug preference remains heroin, albeit they use many other substances.

- I have adopted an overarching understanding of addictive conditions as a self-regulation disorder and, in my experience, other drugs are then employed to self-medicate all the other psychological and behavioral dysregulation induced by the heroin dependency. It is worth mentioning here that my thinking was influenced by the fact that in the mid-1960s, in the middle of my psychiatric training, our nomenclature for the then psychotropic medications changed from referring to them as ‘minor tranquilizers’ (e.g. Librium) or ‘major tranquilizer’ (e.g. Thorazine) to designating the medications by their specific action (e.g. antianxiety, antidepressant, antipsychotic drugs).

- Although, for instance, antidepressants have a broader action, such as reducing anxiety, few would dispute that the main action is an antidepressant one. Similarly, it is not too much of a stretch to similarly consider how the main effect of opiates is countering rage and aggression, but it is not limited to that action. It also has a modulating or ameliorating effect on all the other unpleasant and troubled emotions, and co-occurring conditions that predispose to, and result from, opiate dependence. Certainly, one might wonder how addiction could possibly be seen as an attempt to relieve suffering when there is so much of it as a consequence of drug use. In part, it is related to the compulsive nature of addiction, much like compulsive disorders in general.

- I and other psychodynamic investigators have emphasized that the painful, repetitious aspects of addiction are displaced attempts to deal with the vague, confusing and inaccessible feelings that render the person powerless, helpless and out of control. In such instances, the operative changes from one of relieving suffering to controlling it. This driven and destructive aspect of addiction is further compounded by self-regulation deficits in self-care wherein they fail to anticipate and avoid the dangers and damage associated with addictive behavior.

Recent clinical observations and psychiatric diagnostic findings of drug-dependent individuals suggest that they are predisposed to addiction because they suffer with painful affect states and related psychiatric disorders.

The drugs that addicts select are not chosen randomly. Their drug of choice is the result of an interaction between the psychopharmacologic action of the drug and the dominant painful feelings with which they struggle.

Narcotic addicts prefer opiates because of their powerful muting action on the disorganizing and threatening affects of rage and aggression.

Cocaine has its appeal because of its ability to relieve distress associated with depression, hypomania, and hyperactivity.

From Self-Medication to Intoxication: Time for a Paradigm Shift

- Trauma and psychopathology may be risk factors for the initiation of substance use and the subsequent development of addiction, just as family dysfunction, unemployment, chronic pain, genetic predisposition and access to substances are risk factors for the above; but none of these causes addiction. Addiction results from the complex interplay between risk factors, the reinforcing properties of the substances themselves and the learned behavior and rituals associated with habitual use.

- Self medication hypothesis (SMH) undermines the treatment of addiction by ignoring the intrinsically reinforcing properties of addictive substances, misdirecting treatment away from treatment for addiction and contributing to the current epidemic of prescription medication abuse. Addictive substances are reinforcing. They work through both positive reinforcement (the pleasure associated with use) and negative reinforcement (the pain associated with cessation of use). Reinforcement is a well-documented biological phenomenon that occurs with chronic administration of all addictive substances. The negative reinforcement of withdrawal is often confused with the psychological distress implied by the SMH, encouraging addicted individuals to regard symptoms of withdrawal as evidence of an underlying psychiatric condition, which ‘justifies’ their ‘need’ for continued use of substances.

It is hard to imagine comprehensive evaluation and care without a strong Psychiatric component.
Heroin Use is Part of a Larger Substance Abuse Problem

- Single drug use is rare
- Even for opioids, other drug use-abuse-dependence common
- Heroin use is on the rise in the US
- 96% heroin users also used at least one other drug, according to researchers at the CDC

What is the Role for Psychiatry and Psychiatrists in Addiction Evaluation and Treatment?

- Evaluation, comprehensive neuro-psychiatric & multi-system and specialty evaluation of the patient on admission, generation of a complete problem list, other testing, and a plan to treat.
- In psychological testing, neuropsychological testing, addiction, psychiatric, medical, neurological, GYN, and others common comorbid diseases, syndromes, and problems that are important to identify and address.
- Is the accidental drug poisoning or overdose truly an accident or is it a suicide attempt or wish to die? Many patients say they would have been fine if they died. Others are agitated and angry when rescued by naloxone.
Family History, Exposure
Personal History

- Kurt's family history of suicide was significant. Two of his uncles took their own lives, and his great-grandfather committed suicide in front of his family.

- Family history of depression and alcohol abuse, and many in the field feel there is a strong genetic component to depression and addiction. Exposed to so much suicide in his family and in his hometown, he was already talking about taking his own life as a young teen.

- Kurt came upon a suicide victim himself when he was in middle school, discovering a man who had hanged himself in a tree. That vision was most certainly indelible in Kurt’s young brain—he extensively talked about it with his childhood friends—and the sheer happenstance of that discovery became yet another horrific part of his history.

- Kurt Cobain is better known now for his suicide than for anything else. Even those who know nothing about Nirvana, or music, or Kurt’s personal artistry know he took his own life in April 1994 with a shotgun. He is one of the most famous people to ever commit suicide. Any search for suicide on the Internet immediately yields Kurt’s name near the top, along with Sylvia Plath, Vincent Van Gogh, and Hunter S. Thompson.

- Kurt's suicide made front-page news around the world, made the cover of many magazines (Newsweek’s headline read “Suicide: Why do people kill themselves?”), was reported on every major television news broadcast, was the subject of round-the-clock coverage on MTV, and was the topic of days of discussions on talk radio.

- Suicide is the second leading cause of death for adults of either gender 27 years of age, after only car accidents.
## Likelihood of a Suicide Attempt

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Increased Odds of Attempting Suicide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine use</td>
<td>62 times more likely</td>
</tr>
<tr>
<td>Major depression</td>
<td>41 times more likely</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>8 times more likely</td>
</tr>
<tr>
<td>Abuse, separation, or divorce</td>
<td>11 times more likely</td>
</tr>
</tbody>
</table>

NIMH/NIDA ECA Evaluation
Selected Manner and Cause-of-Death Rates per 100,000 Population: US, 1999-2013. The year-specific self-injury 1 death rate = total suicide rate, +0.7 and 0.8 of respective accidental and undetermined drug-intoxication death rates for ages 15 years and older. The corresponding self-injury 2 death rate substituted constants of 0.8 and 0.9.

Rockett IRH, Caine ED. *JAMA Psychiatry*. 2015;72(11):1069-1070. Date of download: 3/8/2016 Copyright © 2016 American Medical Association. All rights reserved.
Suicide Rates Increased from 1999 through 2014, with Greater Annual Percent Increases After 2006

- Age-adjusted suicide rate in 2014, 13.0 per 100,000 population, was 24% higher than the rate in 1999 (10.5).
- The average annual percent increase in the age-adjusted suicide rate was about 1% per year from 1999 through 2006 but increased to 2%/yr from 2006-2014.
- In 2014, the age-adjusted rate for males (20.7) was more than 3x than for females (5.8).
- From 1999 -2014, the % increase in the age-adjusted suicide rate was greater for females (45% increase) than males (16% increase), resulting in a narrowing of the gender gap in suicide rates (as measured by rate ratios). The ratio of male to female suicide rates was lower in 2014 (3.6) than in 1999 (4.5).

Double Trouble: Relationship of Alcohol & Drug Problems to Severe Suicidality (n = 12,196)

<table>
<thead>
<tr>
<th>Alcohol or Drug Problems</th>
<th>% With Severe Suicide Rating</th>
<th>ODDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n=4853)</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>Mild (n=1022)</td>
<td>10.0%</td>
<td>1.23</td>
</tr>
<tr>
<td>Moderate (n=2391)</td>
<td>20.0%</td>
<td>1.18</td>
</tr>
<tr>
<td>Severe (n=3930)</td>
<td>30.0%</td>
<td>2.00</td>
</tr>
</tbody>
</table>

Walds = 235.41  p < .001

ODDS adjusted for age & gender

Volkow N, 2010
Protracted Abstinence – Longlasting

- Poor concentration & memory
- Sleep dysregulation
- Hyperphagia - appetite
- Hypersexuality
- Dysphoria – depression

- Anhedonia - Extreme Sports Activities - Risk Taking
- Suicidal ideation
- Irritability and aggression
- ADD-ADHD
- Cravings
- Relapse
Addictions Neuroclinical Assessment: A Neuroscience-Based Framework for Addictive Disorders

Genetic Variables
- Genes and family history
- Pharmacogenomics
- Sexuality
- Psychiatric disorders
- Methylyomics
- Metabolomics

Agent use history
- Onset
- Type & mode
- Pattern
- Rx
- Polydrug use
- Withdrawal severity

Environmental Variables
- Education
- SES
- Activity levels
- Culture
- Stress exposure
- Nutrition

Executive Function

Negative Emotionality

Incentive Salience

Outcomes
- Problems with:
  - Law
  - Home
  - Work
  - Physical health

Anhedonia and Abstinence

Drugs produce sense of well being and euphoria

Drugs of abuse change the brains set point for reward and pleasure

Drug withdrawal produces depression and anhedonia
All Drugs of Abuse Change the Brain

Table 1

<table>
<thead>
<tr>
<th>Process</th>
<th>Possible disruption in addiction</th>
<th>Probable PFC region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-control and behavioral monitoring: response inhibition, behavioral coordination, conflict and error prediction, detection and resolution</td>
<td>Impulsivity, compulsivity, risk taking and impaired self-monitoring (habitual, automatic, stimulus-driven, and inflexible behavioral patterns)</td>
<td>DLpFC, dACC, IFG, and vIFPFC</td>
</tr>
<tr>
<td>Emotion regulation: cognitive and affective suppression of emotion</td>
<td>Enhanced stress reactivity and inability to suppress emotional intensity (for example, anxiety and negative affect)</td>
<td>mOFC, vmPFC, and subgenual ACC</td>
</tr>
<tr>
<td>Motivation: drive, initiative, persistence, and effort to pursue the goal</td>
<td>Enhanced motivation to procure drugs but decreased motivation for other goals, and compromised purposefulness and effort</td>
<td>OFC, ACC, vmPFC, and DLpFC</td>
</tr>
<tr>
<td>Awareness and introspection: feeling one’s own bodily and subjective state, insight</td>
<td>Reduced salience, denial of illness or need for treatment, and extremely oriented thinking</td>
<td>mACC and dACC, mPFC, OFC, and vIFPFC</td>
</tr>
<tr>
<td>Attention and flexibility: set formation and maintenance versus set-shifting, and task switching</td>
<td>Attention bias towards drug-related stimuli and away from other stimuli and reinforcers, and inflexibility in goals to procure the drug</td>
<td>DLpFC, ACC, IFG, and vIFPFC</td>
</tr>
<tr>
<td>Working memory: short-term memory enabling the construction of representations and guidance of action</td>
<td>Formation of memory that is biased toward drug-related stimuli and away from alternatives</td>
<td>DLPFC</td>
</tr>
<tr>
<td>Learning and memory: stimulus-response associative learning, reversal learning, extinction, reward devaluation, latent inhibition (suppression of information), and long-term memory</td>
<td>Drug conditioning and disrupted ability to update the reward value of non-drug reinforcers</td>
<td>DLPFC, OFC, and ACC</td>
</tr>
<tr>
<td>Decision making: valuation (coding reinforcers) versus choice, expected outcome, probability estimation, planning, and goal formation</td>
<td>Drug-related anticipation, choice of immediate reward over delayed gratification, discounting of future consequences, and inaccurate predictions or action planning</td>
<td>IOFC, mOFC, vmPFC, and DLpFC</td>
</tr>
<tr>
<td>Salience attribution: affective value appraisal, incentive salience, and subjective utility (alternative outcomes)</td>
<td>Drugs and drug cues have a sensitized value, non-drug reinforcers are devalued and gradients are not perceived, and negative prediction error (actual experience worse than expected)</td>
<td>mOFC and vmPFC</td>
</tr>
</tbody>
</table>

Reprinted with permission [13].

Orbitofrontal cortex (OFC) includes Brodmann area (BA) 10, 14, 47, and inferior and subgenual regions of anterior cingulate cortex (ACC) (BA 24, 25 and 32) in the ventromedial prefrontal cortex (vmPFC). ACC includes rostral ACC (rACC) and dorsal ACC (dACC) (BA 24 and 32, respectively), which are included within the medial PFC (mPFC). The mPFC also includes BA 6, 8, 9 and 10; dorsolateral PFC (dLpFC) includes BA 6, 8, 9 and 46; and the inferior frontal gyrus (IFG) and ventrolateral PFC (vIFPFC) includes inferior portions of BA 8, 44 and 45. These various processes and regions participate to a different degree in craving, intoxication, bingeing and withdrawal. IOFC, lateral OFC; mOFC, medial OFC; PFC, prefrontal cortex.

Prefrontal Cortical Regulation of Brainwide Circuit Dynamics and Reward-Related Behavior

- The drive to seek and experience reward is conserved across species and, in mammals, involves interactions between subcortical dopaminergic systems and limbic structures such as the striatum. Impairment of this process, observed across a number of psychiatric conditions, is the clinical symptom of anhedonia (loss of enjoyment).

- The neural mechanisms underlying anhedonia are unknown but could result from abnormal interactions between cortical and subcortical reward circuits.

- We sought to test the hypothesis that elevated medial prefrontal cortex (mPFC) excitability (a clinical feature associated with anhedonia) exerts suppressive control over the interactions between two distant subcortical regions: the dopaminergic midbrain and the striatum.

Illuminating Anhedonia Optogenetics and fMRI Reveal the Brain Circuitry of Anhedonia

**Reward circuitry.** Shown are approximate anatomical relationships in the human brain between the midbrain dopamine (DA) pathways from the ventral tegmental area (VTA) to the nucleus accumbens (part of the ventral striatum) and the vmPFC, and reciprocal influences (mediated by glutamate) of the vmPFC. The vmPFC includes the medial orbitofrontal cortex and parts of the ventral cingulate cortex, including the subgenual cingulate cortex. Ferenczi et al. show that the rewarding effects of optogenetic stimulation of the VTA were counteracted by optogenetically-induced hyperexcitability of the vmPFC to mimic behavioral anhedonia-like symptoms in rats, presumably via descending pathways to the subcortical regions including the striatum and VTA.

Prospective Associations Between Marijuana Use and Nucleus Accumbens (NAcc) Activation During Reward Anticipation

A. Time 1 to time 2 results
B. Time 2 to time 3 results

Figure Legend:
Prospective Associations Between Marijuana Use and Nucleus Accumbens (NAcc) Activation During Reward Anticipation

- A, Past-year marijuana use at age 20 years (time 1) and NAcc activation during reward anticipation at 22 years (time 2).
- B, Past-year marijuana use at 22 years (time 2) and NAcc activation during reward anticipation at 24 years (time 3).

Both partial regression plots controlled for all covariates included in cross-lagged analyses. Circles indicate data points for each participant; horizontal line, coefficient line.
Methamphetamine Causes Microglial Activation in the Brains of Human Abusers

- Methamphetamine (MA) is associated with multiple neuropsychiatric adverse events and toxic to the dopaminergic and serotonergic systems of the brain.
- MA-induced neuropathology is associated with increased expression of microglial cells thought to participate in either pro-toxic or protective mechanisms in the brain.
- Although reactive microgliosis has been observed in animal models of methamphetamine neurotoxicity, no study has reported on the status of microglial activation in human methamphetamine abusers.
- 12 abstinent MA abusers, 12 age-, gender-, and education-matched control subjects who underwent positron emission tomography using a radiotracer for activated microglia. Compartment analysis was used to estimate quantitative levels of binding potentials of [(11)C](R)-PK11195 in brain regions with dopaminergic and/or serotonergic innervation. The mean levels of [(11)C](R)-PK11195 binding were higher in MA abusers than those in control subjects in all brain regions (>250% higher; p < 0.01 for all). Binding levels in the midbrain, striatum, thalamus, and orbitofrontal and insular cortices (p < 0.05) correlated inversely with the duration of MA abstinence.
- Results suggest that chronic self-administration of MA can cause reactive microgliosis in the brains of human MA abusers, a level of activation that appears to subside over longer periods of abstinence.

Methamphetamine Causes Microglial Activation in the Brains of Human Abusers

- Mean levels of [11C](R)-PK11195 binding potential (BP) in control subjects and methamphetamine (MA) abusers
- [11C](R)-PK11195 BP levels were significantly higher in all brain regions of MA abusers (p < 0.01 for all by Mann-Whitney U test). Error bars represent SD
- Correlations between [11C](R)-PK11195 BP and the duration of MA abstinence in representative brain regions in MA abusers
  - Midbrain: Kendall’s $\tau = -0.657$, $p = 0.004$; Thalamus: $\tau = -0.743$, $p = 0.001$.

Methamphetamine (MA) addiction is a growing epidemic worldwide. Chronic MA use has been shown to lead to neurotoxicity in rodents and humans. MRI studies in MA users have shown enlarged striatal volumes and PET studies have shown decreased brain glucose metabolism in the striatum of detoxified MA users. The study examines structural changes of the brain, observes microglial activation, and assesses changes in brain function, in response to chronic MA treatment.

Compared with controls, chronic HD MA-treated rats had enlarged striatal volumes and increases in [3H]PK 11195 binding in striatum, the nucleus accumbens, frontal cortical areas, the rhinal cortices, and the cerebellar nuclei.

These results corroborate clinical findings of MA-induced brain damage and help further examine the mechanisms behind MA-induced neurotoxicity.

The increased microglial response extends beyond the striatum, to distinct dopamine-poor brain regions, not showing volumetric changes. BGluM changes in DA-related regions (globus pallidus, striatum) may be the result of a response to MA by the dopaminergic system. In contrast, the changes in BGluM in other areas (cerebral cortex, hippocampus) suggest MA effects on other neurotransmitter pathways.

Hitler was an Amphetamine Addict with Delusions and a Persistent Thought Disorder…or Two

- In 1999, Yale psychiatrist Fritz Redlich published a well-received book, Hitler: Diagnosis of a Destructive Prophet, which relied on written and oral statements made by Hitler and those around him, particularly the records of Hitler’s chief personal physician, Theodor Morell. Redlich’s analysis painted a picture of Hitler in power as a man with a laundry list of maladies, some more severe than others.

- In the end, Redlich drew a conclusion that has been repeated frequently ever since: that “Hitler abused amphetamines, particularly between 1939 and 1943, (and) was temporarily impaired by such abuse.” Morell’s notes reveal that he put Hitler on a regimen of Vitamultin—a preparation containing glucose, vitamins, and sometimes the methamphetamine Pervitin—and prescribed dietary restrictions, bloodletting, leeching, enemas, and the morphine derivative Eukodal to relieve the GI symptoms. Sedatives (for sleep) and testosterone (for sexual potency) were also among the considerable number of drugs (over 40 different kinds) Hitler took over the course of his adult life.
The Psychoactive Designer Drug and Bath Salt Constituent MDPV Causes Widespread Disruption of Brain Functional Connectivity Neuropsychopharmacology (2016), 1–14

The abuse of ‘bath salts’ has raised concerns because of their adverse effects, which include delirium, violent behavior, and suicide ideation in severe cases. The bath salt constituent 3,4-methylenedioxypyrovalerone (MDPV) has been closely linked to these and other adverse effects. The abnormal behavioral pattern produced by acute high-dose MDPV intake suggests possible disruptions of neural communication between brain regions.

Therefore, we determined if MDPV exerts disruptive effects on brain functional connectivity, particularly in areas of the prefrontal cortex. Male rats were imaged following administration of a single dose of MDPV (0.3, 1.0, or 3.0 mg/kg) or saline. Resting state brain blood oxygenation level-dependent (BOLD) images were acquired at 4.7 T. To determine the role of dopamine transmission in MDPV-induced changes in functional connectivity, a group of rats received the dopamine D1/D2 receptor antagonist cis-flupenthixol (0.5 mg/kg) 30 min before MDPV. MDPV dose-dependently reduced functional connectivity. Detailed analysis of its effects revealed that connectivity between frontal cortical and striatal areas was reduced. This included connectivity between the prelimbic prefrontal cortex and other areas of the frontal cortex and the insular cortex with hypothalamic, ventral, and dorsal striatal areas. Although the reduced connectivity appeared widespread, connectivity between these regions and somatosensory cortex was not as severely affected. Dopamine receptor blockade did not prevent the MDPV-induced decrease in functional connectivity. The results provide a novel signature of MDPV’s in vivo mechanism of action. Reduced brain functional connectivity has been reported in patients suffering from psychosis and has been linked to cognitive dysfunction, audiovisual hallucinations, and negative affective states akin to those reported for MDPV-induced intoxication. The present results suggest that disruption of functional connectivity networks involving frontal cortical and striatal regions could contribute to the adverse effects of MDPV.
What Drugs Do Have in Common: They Affect Dopamine Signaling in Brain

- Dopamine: Cognition, reward, movement, motivation, inhibits prolactin, sleep, mood, attention, working memory, learning.
- Dopamine: Implicated in Parkinson’s disease, substance abuse, schizophrenia, ADHD, narcolepsy
- Dopamine transporter: Regulates dopamine by sequestering it, terminating its signal
Nucleus Accumbens (NAc)

- A major node in networks regulating motivated behavior
- Integrates VTA (DA) and PfC (Glu) input to determine motivational response to environmental stimuli
- Regulates both drug-taking and -seeking behaviors
Normal Controls
Cocaine Abusers

DA D2 Receptors
Bmax/Kd

Age (years)
Cocaine-addicted patients have reduced frontal metabolism, diminished gray matter & poor performance on neuropsychological tests of frontal function.

**PET O-15 Hypoactivity**

**Reduced Gray Matter**
Hypofrontality in Cocaine Dependent Patients

Reduced metabolic activity at baseline in cocaine dependent subjects
Prescriptions Quadrupled

From 1999 to 2013, the amount of prescription painkillers prescribed & sold in the U.S. nearly QUADRUPLED.

Yet there has not been an overall change in the amount of pain that Americans report.
Primary Prescription Opioids of Abuse—MDs and Lack of Education Caused this Epidemic

Oxycodone: 30%
Hydrocodone: 20%
Methadone: 5%
Hydromorphone: 5%
Morphine: 5%
Buprenorphine: 5%
Oxymorphone: 5%
Tramadol: 5%
Fentanyl: 5%
First Drug Used

Heroin Summary

- Highly addictive; withdrawal symptoms extreme
- Addiction hard to treat
- Relapse is rapid, frequent, recurring
- Many consequences: Poor health, infections, brain impairment
- Overdoses frequent; Death rates very high
Complications of IV Use: Overdose

- MOR control heart rate, breathing
- Opioids suppress breathing
- Oxygen deficits in brain hypoxia
  - Psychological
  - Neurological
  - Permanent brain damage

(Courtesy: M. Herkenham, NIH)
### Heroin and Death

<table>
<thead>
<tr>
<th>Description</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death rate <em>cf</em> with non user</td>
<td>6 – 20x greater</td>
</tr>
<tr>
<td>Death rate: 20 years</td>
<td>25%–50%</td>
</tr>
<tr>
<td><strong>Death rate by region, yearly</strong></td>
<td><strong>Asia (3%)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Western Europe (2%–3%)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>North America (1%–2%)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Australia (less than 1%)</strong></td>
</tr>
<tr>
<td><strong>Death rate by cause</strong></td>
<td><strong>If HIV/AIDS prevalent, AIDS</strong></td>
</tr>
<tr>
<td></td>
<td><strong>In US, overdose &gt; suicide &gt; trauma</strong></td>
</tr>
</tbody>
</table>
Premature Death Rates Highest With Opioid Use Disorder

National Overdose Deaths: Number of Deaths from Prescription Opioid Pain Relievers

Despite the fact that opioid discontinuation after overdose is associated with lower risk for repeated overdose, almost all patients continue to receive prescription opioids after an overdose.

Substance Abuse and Suicide

- How many accidental drug overdoses are suicide attempts?
- Could depression and suicide be post SUD comorbidities on the basis of drug-related damage to the brain’s reward system-threshold, pleasure-mood systems?
Drug addiction represents a dramatic dysregulation of motivational circuits that is caused by a combination of exaggerated incentive salience and habit formation, reward deficits and stress surfeits, and compromised executive function in three stages. The rewarding effects of drugs of abuse, development of incentive salience, and development of drug-seeking habits in the binge/intoxication stage involve changes in dopamine and opioid peptides in the basal ganglia. The increases in negative emotional states and dysphoric and stress-like responses in the withdrawal/negative affect stage involve decreases in the function of the dopamine component of the reward system and recruitment of brain stress neurotransmitters, such as corticotropin-releasing factor and dynorphin, in the neurocircuitry of the extended amygdala. The craving and deficits in executive function in the so-called preoccupation/anticipation stage involve the dysregulation of key afferent projections from the prefrontal cortex and insula, including glutamate, to the basal ganglia and extended amygdala. Molecular genetic studies have identified transduction and transcription factors that act in neurocircuitry associated with the development and maintenance of addiction that might mediate initial vulnerability, maintenance, and relapse associated with addiction.
Changes in Glutamatergic Synapses in the Nucleus Accumbens During Relapse After Long-term Use of Cocaine, Heroin, or Nicotine. The upper drawing is the control situation where glial glutamate uptake via glial glutamate transporter 1 (GLT1) is normal, thereby limiting access of synaptically released glutamate to extrasynaptic glutamate receptors, including metabotropic glutamate receptors (mGluRs) and N-methyl-D-aspartate (NMDA) receptors expressing the GluN2B subunit. After long-term drug use, glutamate uptake via GLT1 is downregulated. Thus, when an addict experiences drug-associated stimuli that can precipitate relapse, the corresponding release of glutamate more readily overflows the synaptic cleft to stimulate postsynaptic mGluR5 and NMDA receptors, which in turn increases AMPA signaling (elevated number of AMPA receptors) and synapse size, thereby potentiating synaptic activity. Supporting excessive presynaptic glutamate release, signaling via inhibitory presynaptic mGluR2 autoreceptors is reduced after long-term drug use. N-acetylcysteine restores GLT1, thereby normalizing synaptic potentiation by drug-associated stimuli and inhibiting relapse. Increases and decreases in signaling and glutamate uptake are indicated by larger or smaller arrowheads, respectively.
Environment as a Risk factor

- Perception of Risk
- Parents, Family
- Access
- Peer Networks
- Community Attitudes
- Intrauterine & Early Exposure
- Teen Experimentation

Monitoring the Future study, the University of Michigan. Available at http://www.monitoringthefuture.org/.
Questions & Answers