Why We Can’t Stop Using Drugs

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Addiction Hijacks Survival Circuitry

Food!

Food!

Martini!
What Brain Circuits Get Hijacked?

Phases of Addiction

Social Use → Regulated Relapse → Compulsive Relapse

Reward Learning and Memory Retrieval

Reward Learning → Declarative Memory & Regulated Behaviors → Procedural Memory & Habits

Neurocircuitry

Dopamine → Cortex Glutamate → Habit Circuitry
Addiction Treatment Strategies

- Social Use
- Regulated Relapse
- Compulsive Relapse

Replacement Therapies

Restore Control (Reverse addiction pathology with pharmacotherapy)

Pharmacotherapeutic Interventions

Psychosocial Interventions
Addiction is a failure of the brain to update drug-seeking habits

Breiter, Neuron, 2000
Cocaine Addiction Reduces Prefrontal Metabolic Activity

Goldstein and Volkow, 2002
Finding the Problem with Cortical Connections and Curing Addiction
Self-administration of Cocaine, Heroin or Nicotine
Glutamate Synapses

Presynaptic Terminal

Dendrite

mGluR2/3

mGluR1/5

Glu Transport

Glia
Synaptic glutamate spillover during relapse

**Heroin** *(JNeurosci, 2008)*

**Nicotine** *(PNAS, 2013)*

**Cocaine** *(JNeurosci, 2003)*

**Alcohol** *(Addict Biol, 2010)*
Reduced Accumbens Glial Glutamate Transport (GLT-1) Characterizes Substance Use Disorders

Cocaine (Biol Psychiat, 2010)

Nicotine (PNAS, 2013)

Heroin (J Neurosci, 2014)

Alcohol (Neurosci, 2012)
Relapse to Drug Use
Down-regulated GLT1 causes synaptic spillover
Excessive mGluR5 stimulation?
Synaptic Learning: Long-Term Potentiation (LTP) and Long-Term Depression (LTD)
How have drugs changed synaptic learning (LTP & LTD)?

Nature Neuro, 2009
Drug use induces an enduring loss of LTP and LTD in prefrontal synapses.
N-acetylcysteine fixes the glutamate imbalance and restores LTP and LTD in prefrontal synapses.