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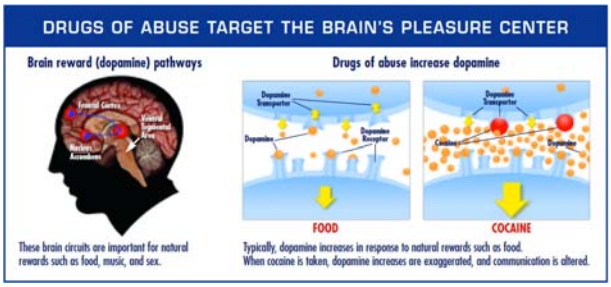
New Theories of Addiction:
Beyond Dopamine and the Reward Center

Jennifer Buckman, PhD
Fiona Conway, PhD

Old Theory of Addiction



New theory # 3

- A few things to know about these authors
  - 2 authors are the directors of
    - National Institute on Alcohol Abuse and Alcoholism (NIAAA)
    - National Institute on Drug Abuse (NIDA)
  - Koob (PhD, Behavioral Physiology) is an animal scientist who now oversees how alcohol research funds are dispersed.
  - Volkow (MD, psychiatry) is a human neuroimager who now oversees how drug research funds are dispersed.
- Both are neuro-focused, not behavior-focused

Three Stages of Change Theory

- Let's look at the language/tone of this paper compared to others.

- *Neurocircuitry*
- *Chronically relapsing disorder*
- *Neuroadaptive changes*
- *Neuroplasticity*
- *"genetic/epigenetic, cellular, and molecular mechanism that mediate the TRANSITION …"*
- *Psychiatric-motivational framework*

This model is more grounded in animal science.

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The Use, Abuse, Dependence Cycle

1. Compulsion to seek and take a drug.
2. Loss of control in limiting intake.
3. Emergence of a negative emotional state (dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented.

Psychological dependence develops through consistent and frequent exposure to a stimulus and involves emotional–motivational withdrawal symptoms (dysphoria and anhedonia)

It relates to the duration of psychological vs. physical dependence

Perhaps an attempt to disentangle dependence from addiction

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Psychiatric-motivational framework

- Addiction involves both positive *and* negative reinforcement
  - Positive reinforcement – getting praise/a reward
  - Negative reinforcement – removal of something unpleasant

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Psychiatric-motivational framework

- Addiction is
  - An impulse control disorder
    - ❖*increasing tension/arousal before committing an act*
    - ❖*pleasure/gratification/relief upon committing the act*

    Associated with positive reinforcement.
  - A compulsive disorder
    - ❖ *characterized by anxiety and stress before/without a repetitive behavior*
    - ❖ *relief from stress by performing compulsive behavior*

    Associated with negative reinforcement.

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The 'composite' addiction cycle

- Collapsing the cycles of impulsivity and compulsivity = addiction
- This cycle has 3 stages

1. Binge/intoxication
2. Withdrawal/negative affect
3. Preoccupation/anticipation

These stages interact, become more intense, and ultimate lead to "pathological condition known as addiction"

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The 'composite' addiction cycle

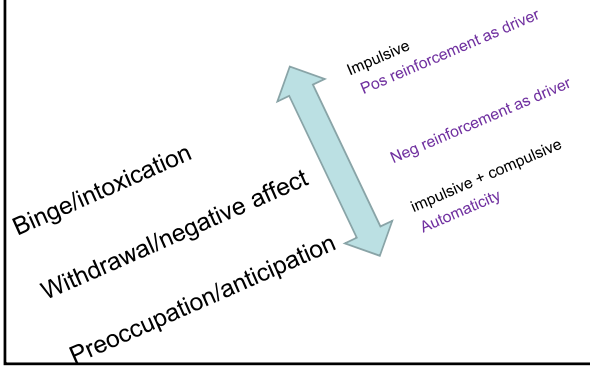

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Table 1 Definitions

Addiction	Assumed to be identical to the syndrome of Substance Dependence (as currently defined by the *Diagnostic and Statistical Manual of Mental Disorders*; American Psychiatric Association, 1994), and Substance Dependence on Alcohol is assumed to be identical to alcoholism. In this paper, we favor the term 'addiction' rather than dependence to avoid confusion with 'physical dependence,' which refers to the physical adaptations that result in largely somatic withdrawal symptoms when drugs such as alcohol, heroin, and benzodiazepines are abruptly discontinued. The adaptations associated with physical drug withdrawal are distinct from the motivational changes of acute withdrawal and protracted abstinence.
Impulsivity	Defined behaviorally as 'a predisposition toward rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to themselves or others' (Moeller *et al.* 2001). Impulsivity is often measured in two domains: the choice of a smaller, immediate reward over a larger, delayed reward (Rachlin and Green, 1972) or the inability to inhibit behavior by changing the course of action or to stop a response once it is initiated (Logan *et al.* 1997). Impulsivity is a core deficit in substance abuse disorders (Allen *et al.* 1998).
Compulsivity	Defined as elements of behavior that result in perseveration in responding in the face of adverse consequences, perseveration in responding in the face of incorrect responses in choice situations, or persistent reinitiation of habitual acts (Everitt and Robbins, 2005). The elements of compulsivity are represented in many of the symptoms outlined in the DSM-IV: continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem and a great deal of time spent in activities necessary to obtain the substance (American Psychiatric Association, 2000).
Positive reinforcement	Defined as the process by which presentation of a stimulus, usually pleasant (eg, the drug itself), increases the probability of a response.
Negative reinforcement	Defined as the process by which removal of an aversive stimulus (eg, negative emotional state of drug withdrawal) increases the probability of a response (eg, dependence-induced drug intake).
Automaticity	Defined as behaviors that occur without conscious awareness of intentionality.
Motivation	Defined as a 'tendency of the whole animal to produce organized activity' (Hebb, 1972).
Intracranial self-administration	A procedure whereby drugs injected directly into the brain in minute amounts serve as positive reinforcers.
place conditioning	A procedure whereby drugs directed into the brain are paired with a specific environment and vehicle with another environment. Subsequently, the animal is tested for its preference for the paired environment or the nonpreferred environment.
Second-order schedule of reinforcement	A procedure in which an animal is trained to work for a drug under conditions of two components. In the first component, a previously neutral stimulus such as a light or tone is delivered under certain requirements (eg, each stimulus is delivered after 10 lever presses). In the second component, the drug is delivered after the last 10th response after 15 min has elapsed (Arroyo *et al.* 1998).

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Motivation & the transition from use to abuse

- May begin with initial use in vulnerable individuals
- May begin in vulnerable developmental periods
- (After acute trauma?)

Neuroplasticity = **"**the potential that the brain has to reorganize by creating new neural pathways to adapt, as it needs. Think of the neurological changes being made in the brain as the brain's way of tuning itself to meet your needs."

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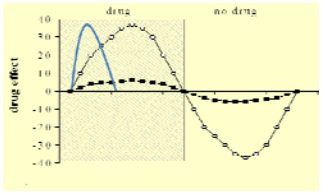
Opponent Process Theory

- Motivation (drive states) linked to hedonic, affective, or emotional states



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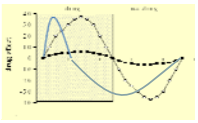
Opponent Process Theory



- Opponent process is more sluggish in onset, slower to build to an asymptote, slow to decay, and get larger with repeated exposure.

Opponent process begins early in drug use
- Reflects changes in brain (reward/stress)
- Becomes a major motivator for compulsivity

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Motivation & the transition from use to abuse

- Also described by
  - Conditioned reinforcement
  - Incentive motivation
  - Behavioral sensitization
  - Maladaptive Stimulus-Response learning

This theory "narrows the focus to drug-seeking at the expense of natural rewards.

Incentive Salience
Drugs are hypothesized to hijack brain systems responsible for directing an person to salient cues for survival

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Incentive Salience (not to be confused with Robinson & Berridge's Incentive Sensitization!)

- "Many have argued that by means of associative learning, the enhanced incentive salience state becomes oriented specifically toward drug-related stimuli, leading to the escalating compulsion for seeking and taking drugs."

- It's the persistence of the neural changes that make a drug user so vulnerable (to addiction?) to long-term relapse.

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Incentive Sensitization (acknowledged!)

- Provides foundation for exploring the neurocircuitry of addiction and a model of neuroplasticity that shifts from 'liking' to 'wanting'

Does liking/wanting map onto positive/negative reinforcement?

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Neuroadapations

- Unique to each drug
  - Opiates
    - tolerance & withdrawal that lead to escalation in use or profound dysphoria, physical discomfort and somatic withdrawal during abstinence.
    - Intense preoccupation
  - Stimulants – more binge/intoxication state
  - Nicotine/Cannabis – less binge/intoxication, more withdrawal/negative affect & preoccupation

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Side note: Animal models

- Koob's research again raises the question whether addiction is a purely human condition.
  - Animals sometimes self-administer
  - Those that do often escalate in use (if they are made dependent)
  - Faster drug reinstatement after extinction
  - Increased resistance to punishment and will sustain more punishment to obtain drug.

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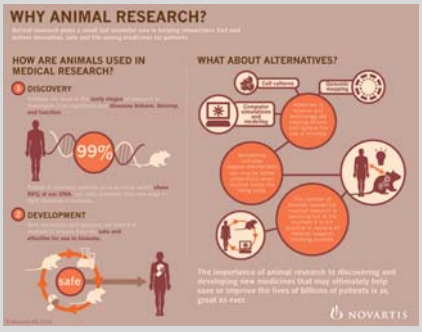
Side note: Animal models



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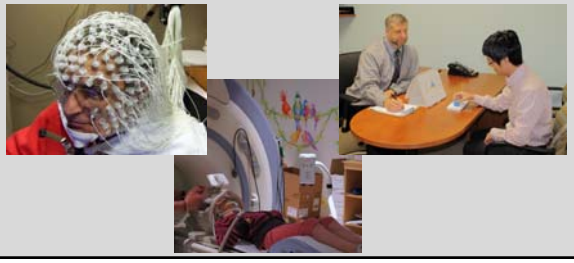
Side note: Animal models

- Koob's research again raises the question whether addiction is a purely human condition.
  - Even if so, are our technologies sufficient?



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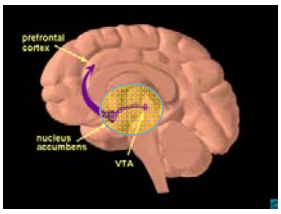
Stage 1: Binge/Intoxication

- Olds & Milner 1954



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Dopamine again

- New hypothesis
  - Faster signaling = role in reward and valuation of prediction outcomes of a behavior
  - Steady signaling = enabling specific behavior systems.

?

DA - Part of the **acute** effects of stimulants/uppers, but not all drugs.
DA – Involved somehow in all drugs of abuse but there is a lot of evidence that other neural pathways/structures/transmitters support reinforcement.

THERE ARE A LOT OF INPUTS INTO THIS PATHWAY.

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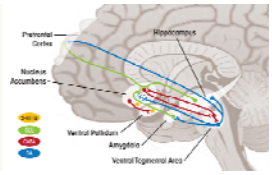
Beyond dopamine

- There are many things that modulate this one 'mesolimbic' pathway.



Other neurotransmitters!

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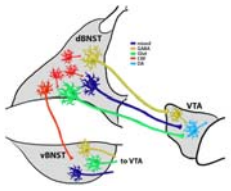
Beyond dopamine

- There are many things that modulate this one 'mesolimbic' pathway.



- **Inputs** – BNST involved in stress, relapse
- **Interneurons**
- **Other outputs**: amygdala, cingulate, hippocampus, olfactory bulb, prefrontal cortex

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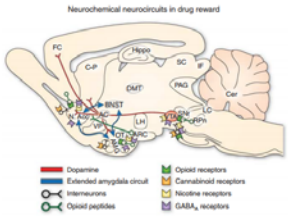
This is a neuroCIRCUITRY theory

- And it's not just reward.
- Drug-seeking is a motivation
- Transition from use to compulsive use
  - striatum

This is a mouse brain



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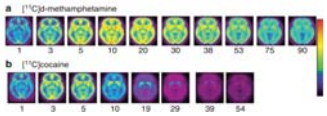
Evidence from humans

- Use comes about from
  - Hedonic value
  - Reinforcement from peer groups (conforming) – *motivational transfer to reinforcement for use*
  - Therapeutic use
    - Opiates, benzodiazepines, stimulants for ADHD?
  - Addiction potential linked to speed of delivery to brain and duration of action
  - Don't discount role of expectation



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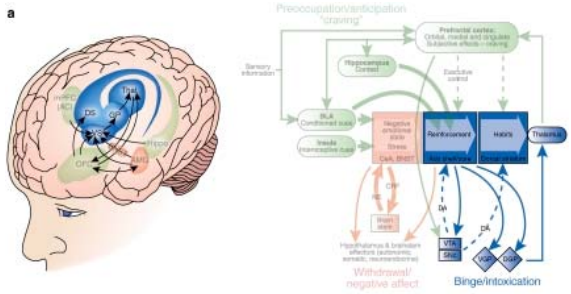
Stage 1: Binge/Intoxication



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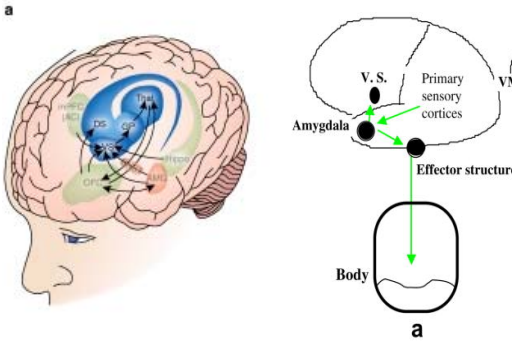
Binge State - Impulsive ?



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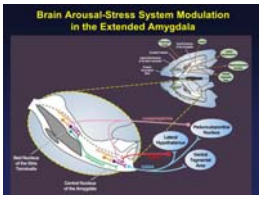
Stage 2: Withdrawal/Negative Affect

- **Within-system** neuroadaptations to drugs: Dopamine
- Seen behavioral as decreased motivations for non-drug cues and increased sensitivity to drug cues.
  - In humans (stimulants):
    - Fatigue
    - Decreased mood
    - Psychomotor retardation
  - In animals
    - Less motivation to work for natural reinforcers
    - Less locomotor activity



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Stage 2: Withdrawal/Negative Affect

- AND **between-system** neuroadaptations
  - Systems that modulate stress become engaged in an attempt to overcome the chronic presence of drugs
  - Goal → restore normal functioning despite drug presence.
- Acute withdrawal is a stress state
  - Withdrawal from all drugs with abuse potential leads to:
    - Elevated stress hormones (ACTH, corticosterone)
    - Elevated CRF in amygdala
      - Withdrawal from cocaine induces anxiety, reversed by CRF antagonists
    - Other stress-related systems (noradrenergic pathways)
      - Injection of NA into BNST blocked opioid withdrawal-induced place preference
      - Substance P, vasopressin, neuropeptide Y, endocannabinoids, nociceptin

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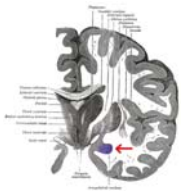
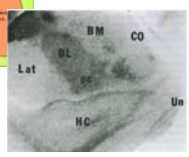
Withdrawal/Negative Affect

- Brain arousal & stress system



Amygdala → Extended Amygdala



CRF-stress system & HPA axis

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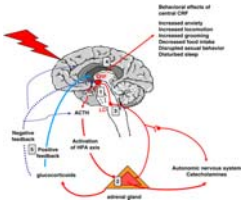
Withdrawal = Stress, CRF



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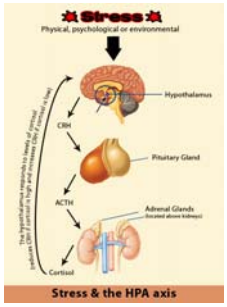
Withdrawal = Stress, HPA Axis



Stress & the HPA axis

HPA axis: A complex set of direct influence and feedback interactions among 3 endocrine glands: hypothalamus, pituitary gland, and the adrenal glands.

HPA axis integrates physical and psychosocial influences in order to allow an organism to adapt effectively to its environment, use resources, and optimize survival.

Increased production of cortisol during stress results in an increased availability of glucose in order to facilitate fighting or fleeing. Cortisol also suppresses the highly demanding metabolic processes of the immune system to further increase glucose availability.

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Evidence from humans

- Different for each drug based on chronicity and frequency of use
  - Withdrawal from different drugs impacts different NT systems & brain structures based on primary actions.
- Acute physical withdrawal can be fatal
- All show *motivational withdrawal*
  - Dysphoria, irritability, emotional distress, sleep disturbances that persist
  - Chronic hypofunctionality of DA pathway
- Abstinence sensitizes cue reactivity*

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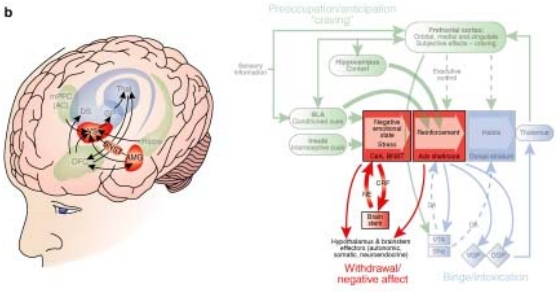
Stage 2: Withdrawal/Negative Affect



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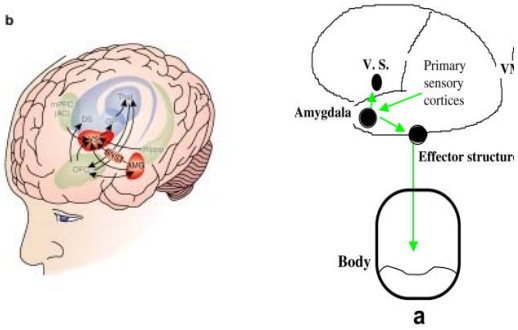
Withdrawal – Impulsive?



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Stage 3: Preoccupation/Anticipation

- Key element in craving
  - Craving is difficult to measure clinically
  - Often doesn't correlate with relapse
  - It's not just experiencing craving, it's acting upon it
- Key element in relapse
  - This stage is what it makes it a chronic relapsing disorder
  - Perhaps the most difficult element of the condition to understand scientifically

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Relapse

Secondary inducer/reflective system?

- Cued by drug or drug-related stimuli
  - Drug itself → MPFC, striatum
  - Drug cues → amygdala, feedforward to PFC
    - GABA, glutamate, dopamine
- Cued by acute stress or residual negative emotion
  - Extended amygdala
    - Glutamate, CRF & NE

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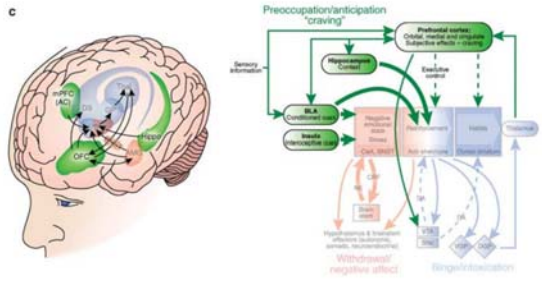
Stage 3: Preoccupation



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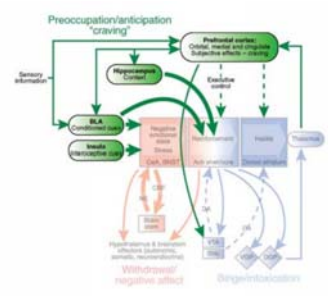
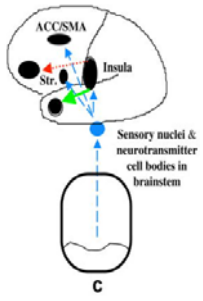
Stage 3: Preoccupation vs. Somatic Marker





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Reprogramming in the brain

- Behavioral reprogramming
  - Reward and motivation
  - Memory, conditioning, and habituation
  - Executive function and inhibitory control
  - Interoception and self-awareness
  - Stress reactivity

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Reprogramming in the brain

- Neurocircuit reprogramming
  - Mesolimbic dopamine system
  - Ventral striatum
  - Ventral striatum/dorsal striatum/thalamus circuit
  - DLPFC/inferior FC/hippocampus circuit
  - Extended amygdala

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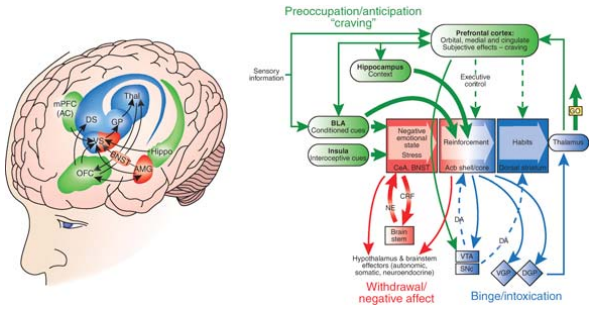
Neurocircuitry of Addiction



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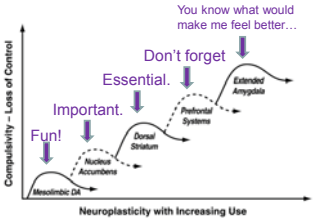
Progressive neuroplasticity



- Dopaminergic synapses are highly flexible but once drug-related changes are initiated, may become difficult to reverse
- Excitatory synapses in Nacc are then changed and salience is assigned.
- Dorsal to ventral shift moves from choice to compulsion.
- Memory, impulse control, delayed gratification then malfunction…

Thus, one can envision the development of a change in firing in mesolimbic dopamine neurons that begins with one administration of the drug, develops into LTP… [then].. via feedback loops, subsequently engages the dorsal striatum. …Long term changes in the amygdala cortex may follow, and combined with dysregulation of the brain stress systems, may provide a powerful drive for drug seeking behavior even months after drug withdrawal.

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How do theories stack up

Behavioral Elements	Incentive Sensitization	Somatic Marker	3 Stages of Change
Reward	X	X	X
Memory		X	X
Executive		X	X
Interoception		X	
Stress			X

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How do theories stack up

Neural structures	Incentive Sensitization	Somatic Marker	3 Stages of Change
Mesolimbic DA	X	X	XX
Brain stem		XXX	X
Primary SSC		X	
Hypothalamus		XXX	
Thalamus		XXX	X
Hippocampus		X	X
Amygdala		X	X
Extended amygdala			XX
Ventral striatum (Nacc)		X	X
Dorsal striatum		X	X
Primary SSC		X	

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How do theories stack up

Neural structures	Incentive Sensitization	Somatic Marker	3 Stages of Change
Mesolimbic DA	X	X	X
VMPFC		X	X
DLPFC		X	
OFC		X	X
IFC			X
Posterior Cingulate		X	X
Anterior Cingulate		X	
Insula		XX	X

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The authors

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Cognitive Deficits

- Attention
  - Sustained attention
- Working memory
- Cognitive flexibility
- Delayed reward discounting
- Spatial, verbal, recognition memory

All predict poorer treatment outcomes