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## New Theories of Addiction: Beyond Dopamine and the Reward Center


Jennifer Buckman, PhD  
Fiona Conway, PhD

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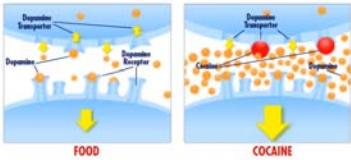
## Old Theory of Addiction

### DRUGS OF ABUSE TARGET THE BRAIN'S PLEASURE CENTER

**Brain reward (dopamine) pathways**



**Drugs of abuse increase dopamine**



These brain circuits are important for natural rewards such as food, music, and sex.

Typically, dopamine increases in response to natural rewards such as food. When cocaine is taken, dopamine increases are exaggerated, and communication is altered.

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## 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

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## 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

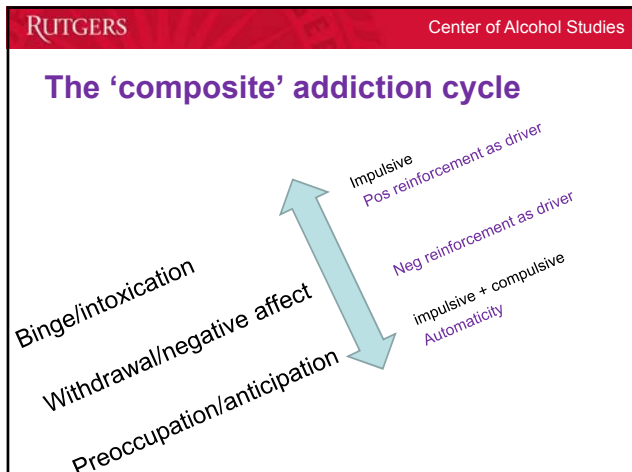
- Addiction is
  - An impulse control disorder
    - ❖ *increasing tension/arousal before committing an act*
    - ❖ *pleasure/gratification/relief upon committing the act*
    - Associated with **positive reinforcement**.
  - A compulsive disorder
    - ❖ *characterized by anxiety and stress before/without 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 ultimately lead to “pathological condition known as addiction”



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Table 1 Definitions

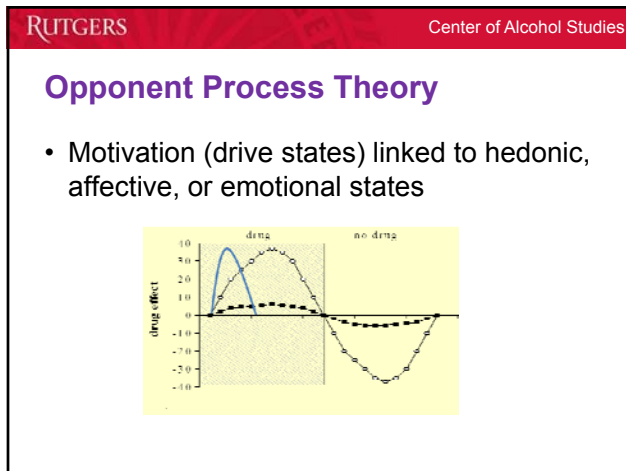
<b>Addiction</b>	Assumed to be identical to the syndrome of Substance Dependence (as currently defined by the Diagnostic and Statistical Manual of Mental Disorders; American Psychiatric Association, 1994), and Substance Dependence on Alcohol is assumed to be identical to alcoholism. In this paper, we 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.
<b>Impulsivity</b>	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' (Poelker et al. 2001). Impulsivity is often measured in two domains: the choice of a smaller, immediate reward over a larger, delayed reward (Nackles 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., 1977). Impulsivity is a core deficit in substance abuse disorders (Allen et al. 1998).
<b>Compulsivity</b>	Defined as elements of behavior that result in perseveration in responding in the face of adverse consequences, perseveration in responding in the face of aversive responses in choice situations, or persistent repetition of habitual acts (Elliott 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).
<b>Positive reinforcement</b>	Defined as the process by which presentation of a stimulus, usually pleasant (eg, the drug itself), increases the probability of a response.
<b>Negative reinforcement</b>	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).
<b>Automaticity</b>	Defined as behaviors that occur without conscious awareness of intentions.
<b>Motivation</b>	Defined as a 'tendency of the whole animal to produce organized activity' (Holtz, 1972).
<b>Intracranial self-administration</b>	A procedure whereby drugs injected directly into the brain in minute amounts serve as positive reinforcers.
<b>place conditioning</b>	A procedure whereby drugs injected directly 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 nonpaired environment.
<b>Second-order schedule of reinforcement</b>	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?)

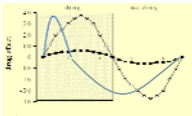
**Neuroplasticity** = "the potential that the brain has to reorganize by creating new neural pathways to adapt, as it needs. Think of the neurological changes being made in the brain as the brain's way of tuning itself to meet your needs."



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### Opponent Process Theory

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



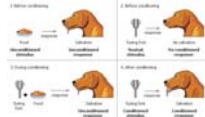
Opponent process begins early in drug use

- 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



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

Hijack R Rigidity ADAPT

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

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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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## Neuroadaptations

- 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

**WHY ANIMAL RESEARCH?**  
Animal research is essential to understanding how and why diseases occur, and the safety and efficacy of medicines.

**HOW ARE ANIMALS USED IN MEDICAL RESEARCH?**

**DISCOVERY**  
99% of new drugs are discovered in animals. (Source: National Institutes of Health)

**DEVELOPMENT**  
99% of drugs that make it to the clinic are tested in animals. (Source: National Institutes of Health)

**WHAT ABOUT ALTERNATIVES?**  
In vitro (cell and tissue) research and in silico (computer) modeling are important tools, but they cannot fully replace animal research. Animal research is essential to understanding how and why diseases occur, and the safety and efficacy of medicines.

The importance of animal research to discovering and developing new medicines that may ultimately help save or improve the lives of billions of patients is as great as ever.

NOVARTIS

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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.

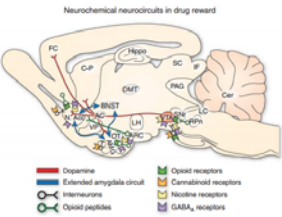
- **Inputs** – BNST involved in stress, relapse
- **Interneurons**
- **Other outputs:** amygdala, cingulate, hippocampus, olfactory bulb, prefrontal cortex

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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 →

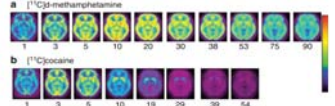


Neurochemical neurocircuits in drug reward

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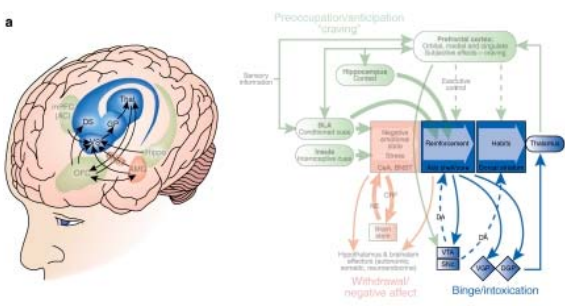
### Evidence from humans

- 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



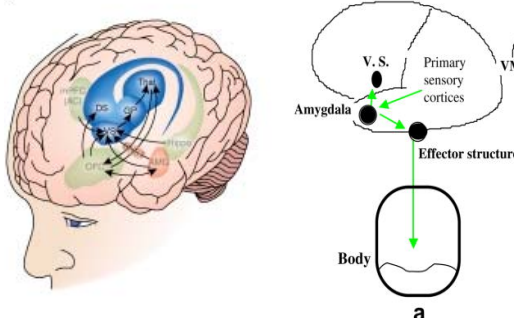
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### Stage 1: Binge/Intoxication



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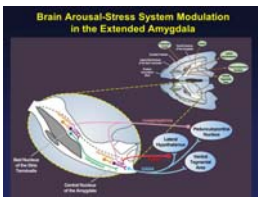
### Binge State - Impulsive ?



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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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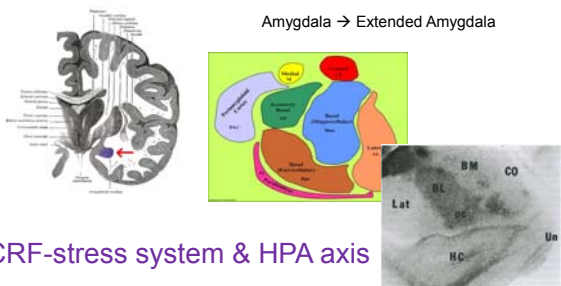
## Stage 2: Withdrawal/Negative Affect

- **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

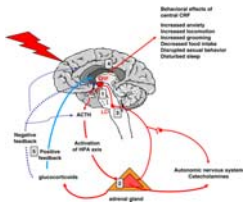


Amigdala → Extended Amygdala

CRF-stress system & HPA axis

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## Withdrawal = Stress, CRF



**Behavioral effects of acute CRF:**  
 Increased anxiety  
 Increased grooming  
 Decreased food intake  
 Disrupted sexual behavior  
 Disrupted sleep

**Regulatory pathways:**  
 Hypothalamus → ACTH → Adrenal gland → Corticosterone

**Neuroendocrine pathways:**  
 Hypothalamus → CRF → Amygdala → HPA axis

**Autonomic nervous system:**  
 Hypothalamus → Sympathetic nervous system → Adrenal gland

**Stressors:**  
 Trauma? → Hypothalamus → ACTH → Adrenal gland → Corticosterone

**CRF-stress system & HPA axis:**  
 Hypothalamus → CRF → Amygdala → HPA axis → Corticosterone

**Severe stress switches CRF action in the nucleus accumbens from appetitive to aversive**

Julia C. Lemos, Matthew J. Wood, Jeffrey S. Smith, Beverly A. S. Reyes, Nick G. Halpin, Elizabeth J. Van Bockstaele, Charles Chavkin & Paul E. M. Phillips  
 Affiliations | Contributions | Corresponding author

Nature 485, 402–406 (18 October 2012) | doi:10.1038/nature11436  
 Received 11 May 2011 | Accepted 23 July 2012 | Published online 10 September 2012  
 | Corrected online 17 October 2012

Stressors activate an array of adaptive responses ranging from 'fight or flight' to an internal vigilance signal facilitating long-term goals<sup>1</sup>. However, traumatic or chronic uncontrollable stress promotes the onset of major depressive disorder, in which acute stressors lose their motivational properties and are perceived as insurmountable impediments<sup>2</sup>. Consequently, stress-induced depression is a debilitating human condition characterized by an affective shift from interest of the environment to withdrawal<sup>3</sup>. An emerging neurobiological substrate of depression and depressive pathways in the nucleus accumbens, a region with the capacity to mediate a diverse range of stress responses by interacting limbic, cognitive and motor circuitry<sup>4</sup>, we report that corticotropin-releasing factor (CRF), a neuropeptide released in response to acute stressors<sup>5</sup> and other aversive environmental stimuli<sup>6</sup>, acts in the nucleus accumbens of mice to increase dopamine release through coactivation of the receptors CRF1R and CRF2R. Remarkably, severe-stress exposure completely abolished this effect without recovery for at least 50 days. This loss of CRF's capacity to regulate dopamine release in the nucleus accumbens is accompanied by a switch in the reaction to CRF from appetitive to aversive, indicating a dramatic change in the emotional response to acute stressors. Thus, the current findings offer a biological substrate for the switch in affect which is central to stress-induced depressive disorders.



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### Withdrawal = Stress, HPA Axis

**Stress**  
Physical, psychological or environmental

Hypothalamus  
Pituitary Gland  
Adrenal Glands (Adrenal cortex & medulla)  
Cortisol

CRH  
ACTH

The hypothalamus secretes CRH, which stimulates the pituitary gland to secrete ACTH, which stimulates the adrenal glands to secrete cortisol.

**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

**b**

Sensory input

Preoccupation/anticipation "craving"

Prefrontal cortex: Critical neural and cognitive subjective effects - craving

Hypothalamus: CRH

HPA: ACTH

Adrenal glands: Cortisol

Conditioned cues

Negative emotional state (Craving, Irritability, Anxiety)

Reinforcement

Withdrawal/negative affect

Binge intoxication

Withdrawal/negative affect

Binge intoxication

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### Withdrawal – Impulsive?

**b**

V.S.

Primary sensory cortices

Amygdala

Effector structure

Body

**a**

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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

c

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### Stage 3: Preoccupation vs. Somatic Marker

c

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## Reprogramming in the brain

- Behavioral reprogramming
  - Reward and motivation
  - Memory, conditioning, and habituation
  - Executive function and inhibitory control
  - Interception 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

The diagram illustrates the neurocircuitry of addiction, showing the following components and interactions:

- Sensory information** enters from the left.
- Prefrontal cortex** (Orbitofrontal, medial and orbital) provides **Executive control** and is involved in **Preoccupation/anticipation "craving"**.
- Hippocampus** is involved in **Conditioned cues**.
- BLA (Basolateral Amygdala)** and **Insula (somatosensory cortex)** are involved in **Negative emotional state** and **Stress**.
- DA (Dopamine)** is released from the **VTA (Ventral Tegmental Area)** and **SNc (Substantia nigra pars compacta)**.
- Reinforcement** occurs in the **Nucleus Accumbens** and **Habits** circuitry.
- Withdrawal/negative affect** is associated with **Hypothalamus & brainstem effectors** (autonomic, somatic, neuroendocrine).
- Binge/intoxication** is associated with **SNc** and **DA**.

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## Progressive neuroplasticity

The graph plots **Compulsivity - Loss of Control** on the y-axis against **Neuroplasticity with Increasing Use** on the x-axis. The curve shows a progression from **Fun!** (low compulsivity) to **Important!** (moderate compulsivity) to **Essential!** (high compulsivity) to **Don't forget!** (very high compulsivity) to **Compulsion!** (extreme compulsivity).

Key brain regions and systems involved in this progression are:

- Mesolimbic DA** (Dopamine)
- Nucleus Accumbens**
- Dorsal Striatum**
- Prefrontal Systems**
- Extended Amygdala**

Text annotations include: "You know what would make me feel better..." and "Don't forget!"

- 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	<b>X</b>	<b>X</b>	<b>X</b>
Memory		<b>X</b>	<b>X</b>
Executive		<b>X</b>	<b>X</b>
Interoception		<b>X</b>	
Stress			<b>X</b>

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### How do theories stack up

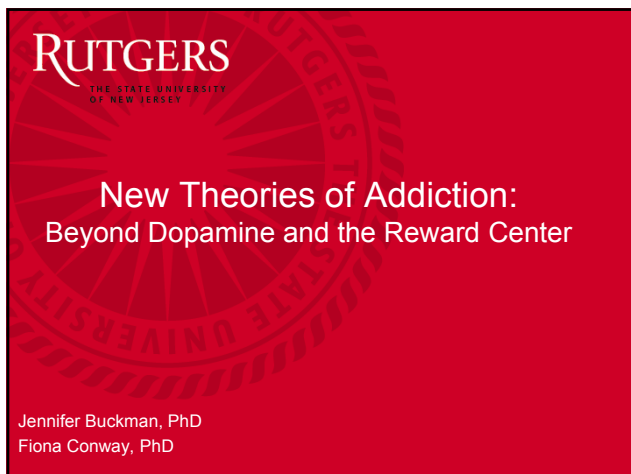
Neural structures	Incentive Sensitization	Somatic Marker	3 Stages of Change
Mesolimbic DA	X	X	XX
Brain stem		XXX	X
Primary SSC		X	
Hypothalamus		XXX	
Thalamus		XXX	X
Hippocampus		X	X
Amygdala		X	X
Extended amygdala			XX
Ventral striatum (Nacc)		X	X
Dorsal striatum		X	X
Primary SSC		X	

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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	
Anterior Cingulate		X	X
Insula		XX	X

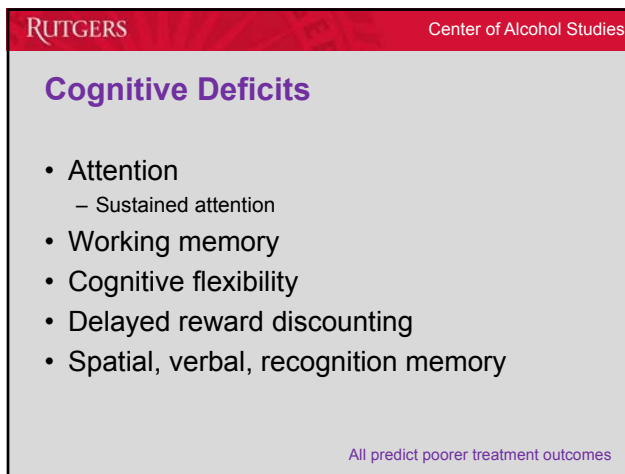
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- ### The authors
- [Nora Volkow](#)
  - [George Koob](#)



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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