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New Theories of Addiction:
Beyond Dopamine and the Reward Center

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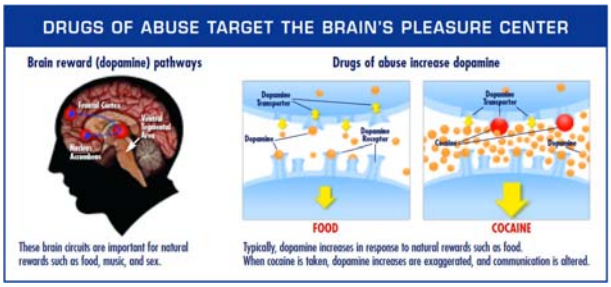
Old Theory of Addiction



Old Theory of Addiction

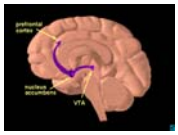
THE REWARD CENTER

Two motivations for substance use

1. Pleasure-seeking – social, "expansion", high
2. Avoidance of unpleasant effects - withdrawal, emotional dysregulation, avoidance

Dopamine and the Reward Center

- Dopamine is a pleasure neurotransmitter.
- Drugs that increase dopamine enhance pleasurable feelings.



Is this theory *incorrect*? NO, not really.
Is this theory insufficient to explain addiction? YES.

Inadequacy of Old Theory

- Does pleasure (or LIKING) perpetuate use?
  - Maybe liking motivates sometimes, but is that what sustains use, especially as negative consequences build?
  - Pleasure seeking does not explain the persistence of addictive tendencies.
  - Pleasure seeking does not explain the progressive, gradual nature of drug use.

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Incentive Sensitization Theory

New Theory of Addiction - #1

1. Potentially addictive substances have the ability to produce long-lasting changes in the brains' systems. *(persistence)*
2. These systems include those involved in the process of incentive-salience and reward. *(focus on drug and related cues)*
3. The changes render the brains' reward systems hypersensitive ("sensitized") to addictive substances (and substance-associated stimuli). *(regular to compulsive transition)*
4. The sensitized brain systems produce compulsive patterns of substance-seeking behavior *('wanting')*.

(Robinson & Berridge, 2001)

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Incentive Sensitization Theory

- By increasing the *incentive value*, you increase the **motivation** to use, until it becomes an all-encompassing experience. Nothing else captures your **attention**. Nothing else is 'tagged' by the brain as having **value**. Nothing else triggers **action** to the same degree.
- Hypersensitivity in incentive circuits (**obsessive**) drive actions to relieve obsession (**compulsive** behaviors).
- All of this is made 'worse' by **learning**.
- Incentive value and motivation become more and more focused on the drug and related stimuli.
- The addict learns that drug use provides relief from wanting/craving.

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KEY POINT

- **There are 2 types of sensitization:**
  - **Behavioral sensitization**
  - **Neural sensitization**
- Being sensitized vs. showing that you are sensitized.
- Things can happen in the brain even if we don't see them behaviorally.
  - Evidence: a slice of brain tissue kept alive in a Petri dish shows evidence of neural 'sensitization'
  - Evidence: In drug context → sensitization, then in non-drug context → no sensitization, then in drug context again → sensitization.

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Somatic Marker Theory

New Theory of Addiction - #2

DECISION-MAKING IS A PROCESS GUIDED BY EMOTIONS

Negative Marker + Future outcome = ***Alarm Bell***

Postive Marker + Future outcome = ***Incentive***

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Somatic Marker Theory

New Theory of Addiction - #2

Somatic markers:

Emotional signals (feelings generated from emotions) that have been connected by learning to anticipated future outcomes.

SOMATIC (soma = body, Greek): Collection of body-related responses that are hallmarks of emotions.

- Includes internal milieu and viscera
- May or may not be observable
  - Hormone release
  - Heart rate*
  - Smooth muscle contraction
  - Posture
  - Facial expression*
  - Fight or flight/freezing

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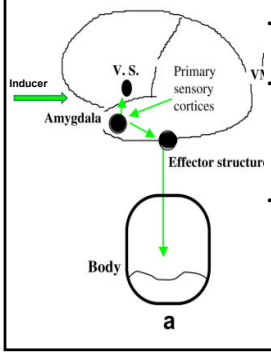
Limbic = Impulsive System



- Amygdala is a trigger structure for emotional (somatic) states from primary inducers.
- It couples the features of primary inducers, which can be processed subliminally (e.g., via the thalamus) or explicitly (e.g., via primary sensory cortices), with effector structures that trigger the motional/somatic response.
- However, the amygdala is also directly connected to the ventral striatum (V.S.) and its trigger can also activate classical motivational systems associated with approach of drug related cues.

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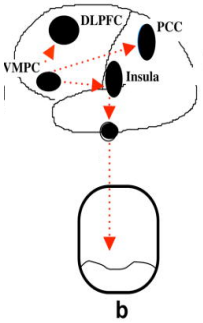
Cortical structures = Reflective System



- Functionally intact reflective system is critical for making decisions that are advantageous in the long run.
- Impairment in any of components of this system disrupts entire reflective system.
- As you deliberate on several options and scenarios (which are held being held in your working memory), somatic states bias weightings to promote some options and reject others before any option are translated into action.
- Impairments are well characterized in long-term substance users and adolescent substance users.

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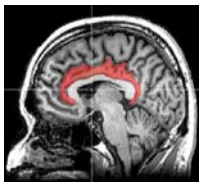
3rd part of the 2 system model…

The anterior cingulate cortex



Possible role in subjective feeling and craving.

- More likely a conflict monitoring center.
- Participates in motor response selection and generating plans for action.

Important because craving is a feeling connected to actions of seeking, obtaining, and consuming the drug. Maybe ACC isn't associated with craving, but with the tendency to act on the feeling.

- Biases response selection based on conscious/ explicit information.
- "Action with awareness of what is right or wrong".
- The decisions are 'voluntary' or 'willful' and guided by knowledge, awareness, and premeditation.

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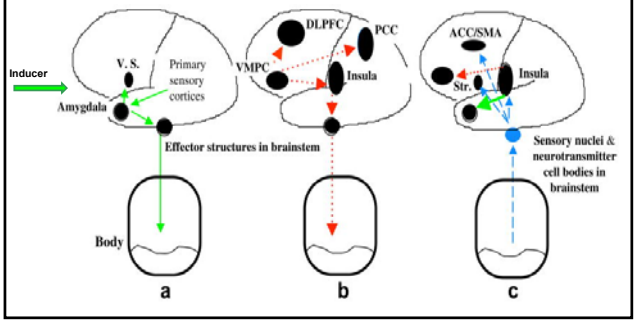
Somatic Marker Theory

Decisions are determined by impulsive vs. reflective inputs,
but somatic markers stack the deck.



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Somatic markers Bias Behavioral Decisions

- For somatic signals to influence decisions, they must act on other neural systems that generate action.
  - Sensory comes into brain. (INSULA)
  - Motor goes out of brain. (IMPULSIVE/REFLECTIVE)
- Addiction is viewed as a condition in which a person becomes unable to choose according to long-term consequences.
- This is important because if the pain signals triggered by thoughts of future negative consequences DO NOT dominate those triggered by the immediate rewarding consequences then consuming the drug continues.
- Bottom-up somatic bias can modulate top-down cognitive mechanisms. It can interfere or hijack the top-down mechanisms that help orient decisions towards future outcomes.

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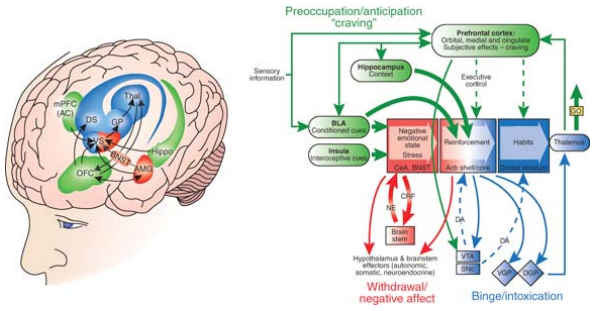
Three Stages of Change Theory
Neurocircuitry of Addiction
New Theory of Addiction - #3



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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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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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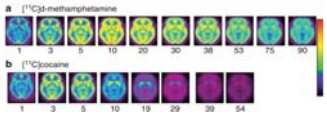
Stage 1: Binge/Intoxication

- Use comes about from
  - Hedonic value (dopamine again)
  - 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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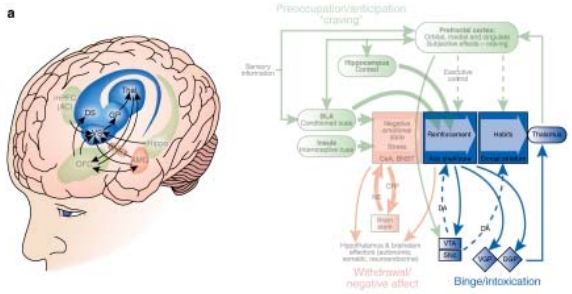
Stage 1: Binge/Intoxication



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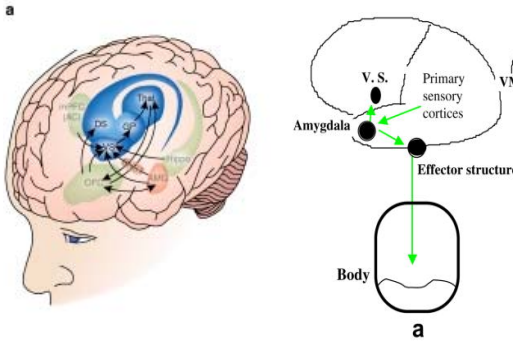
Binge State - Impulsive ?



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Stage 2: Withdrawal/Negative Affect

- 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

- 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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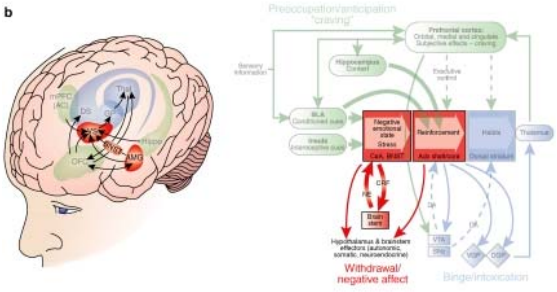
Stage 2: Withdrawal/Negative Affect



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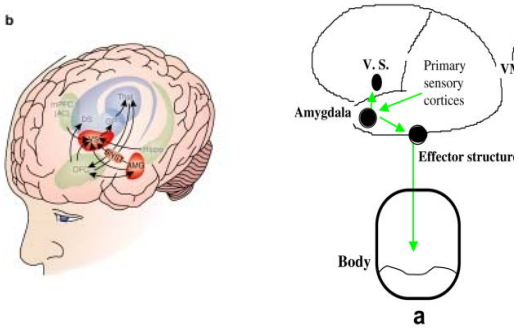
Withdrawal – Impulsive?



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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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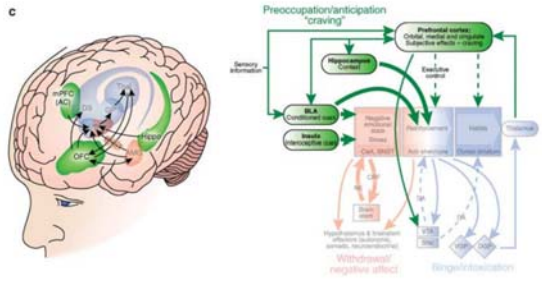
Stage 3: Preoccupation



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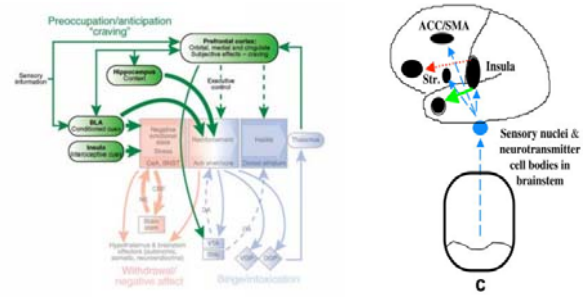
Stage 3: Preoccupation vs. Somatic Marker



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Three Stages of Change Theory

New Theory of Addiction - #3

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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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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Video Resources

- The Rat Park
- Do our current treatments work? Tom McLellan
- Incentive Theory
- Nora Volkow
- George Koob