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New Theories of Addiction:
Beyond Dopamine and the Reward Center

Jennifer Buckman, PhD
Fiona Conway, PhD

Old Theory of Addiction

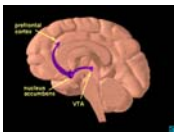
THE REWARD CENTER

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

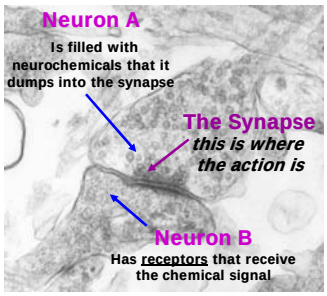
- Dopamine is a pleasure neurotransmitter.
- Drugs that increase dopamine enhance pleasurable feelings.



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

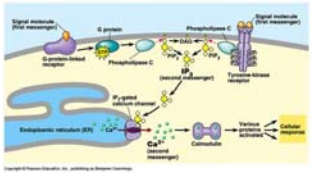
How do Drugs Work?

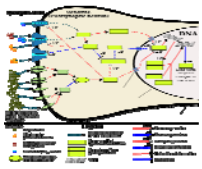
- Neurons release chemicals that are taken up by other neurons
  - Synthesis
  - Transportation to synapse
  - Release
  - Binding
  - Reuptake
  - Metabolism



How do Drugs Work?

- There are many types of **neurotransmitters**
  - Neurons usually make 1, but have receptors for many types
  - Receptor activation leads to a cascade of intracellular events





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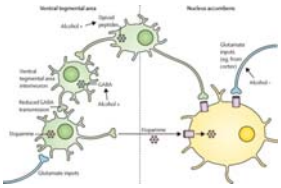
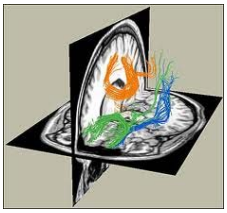
How do Drugs Work?

- No neuron is an island. Neurons form circuits.
- Information from all the receptors is "summed" to determine the next step (to continue the message to the next neuron)





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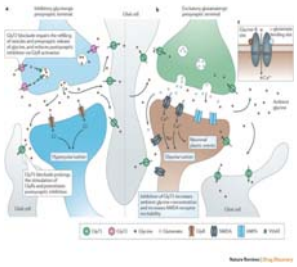
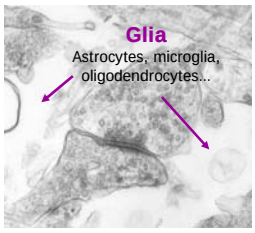
How do Drugs Work?

- Not all cells in the brain are neurons!





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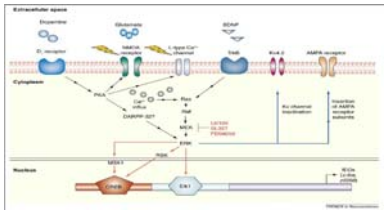
How do Drugs Work?

- Not all chemical messengers are neurotransmitters



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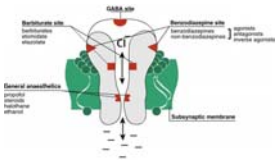
How do Drugs Work?

This is what a GABA receptor "looks" like.

- Many binding sites.
- The action of a drug depends on where it binds on a receptor …



When a person smokes or snorts cocaine, it reaches all areas of the brain, but it binds to sites in some very specific areas. These are highlighted with the yellow dots: the VTA, the nucleus accumbens, and the caudate nucleus (the largest structure). Point out that cocaine binds especially in the reward areas that you have just discussed. The binding of cocaine in other areas such as the caudate nucleus can explain other effects such as increased stereotypic (or repetitive) behaviors (pacing, nail-biting, scratching, etc..)

… and in the brain

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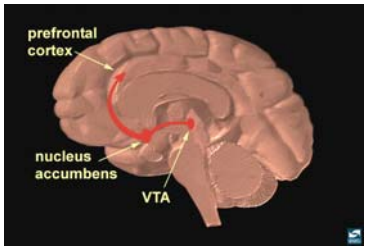
How do Drugs Work?



Common Action

↓

The Reward Center

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How do Drugs Work?

By mimicking or blocking the actions of naturally occurring brain chemicals

Drug	Brain Chemical (Neurotransmitter)
Cannabis (Marijuana)	Anandamide
Cocaine	Dopamine
Adderall	Dopamine
Sedatives (Valium, Xanax)	Gama-aminobutyric Acid (GABA)
PCP	Glutamate
Opiates (Heroin, pain killers)	Opioid
Ecstasy	Serotonin
Methamphetamine	Dopamine, serotonin, & norepinephrine

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How do Drugs Work?

Three uppers that all work on the dopamine system directly, but in different ways.

Drug	Neurotransmitter
Cocaine	Binds to the dopamine transporter, blocking the removal of dopamine from the synapse
Adderall	Binds to all monoamine transporters, disrupts vesicular storage of dopamine, allowing it to accumulate in the cytoplasm, and inhibits the degradative enzymes monoamine oxidase A and B
Methamphetamine	Releases dopamine rapidly (& serotonin)

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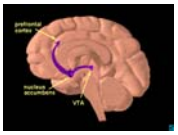
Old Theory of Addiction

THE REWARD CENTER

Is this theory *incorrect*? NO, not really.

Is this theory insufficient to explain addiction? YES.



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Inadequacy of Old Theory (1)

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.

- **Does this theory consider that drug taking itself does not constitute addiction?**

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Inadequacy of Old Theory (2)

- Are addicts actually motivated by pleasurable effects and/or avoidance of the unpleasant effects?
  - This suggests use is motivated by LIKING drugs
- At the beginning of use…
  - Drug use may emerge in pursuit of pleasure ('liking') or avoiding displeasure
  - Evidence that use becomes less pleasurable with time
    - Tolerance
    - Eventual inability to experience pleasure

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Inadequacy of Old Theory (3)

- 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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Inadequacy of Old Theory (4)

- Does this theory explain craving?

- LIKE
- WANT
- CRAVE (intense wanting?)

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Inadequacy of Old Theory (4)

- CRAVING is complicated
  - To *drug-associated* cues (pipe, syringe)
  - Even when people aren't experiencing withdrawal symptoms
  - Independent of conditioned 'highs' or memories of past pleasurable 'highs'
  - During acute 'high' (often craving is highest right after use [on 'ascending limb']!)
  - ☆ Even when negative consequences clearly and hugely outweigh the pleasure
  - Even long after drug use

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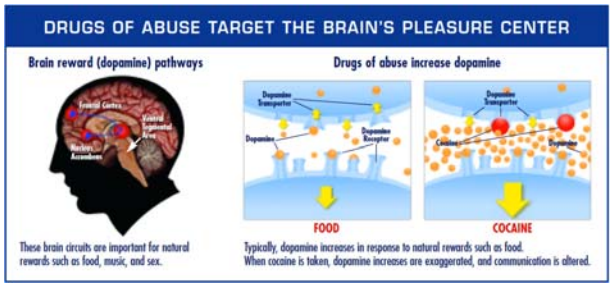
Old Theory of Addiction



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CAVEATS

Psychopharmacology (2007) 191:391–431
DOI 10.1007/s00213-006-0578-x

REVIEW

The debate over dopamine's role in reward: the case for incentive salience

[1] *Preliminary caveats*

Beyond dopamine caveat. In this paper, 'the role of dopamine in reward' is taken to be a short-hand term for the dopaminergic component of mesocorticolimbic systems. Dopamine is just one link in that chain of neuronal signals, and of course, we must go beyond dopamine neurons and synapses to understand reward function. Still, many causal manipulations powerfully affect reward by acting directly or indirectly on dopamine neurotransmission, and dopamine neural activation clearly codes reward events. Thus, dopamine deserves the special attention it has received as a crucial node of reward, and its precise role needs to be understood.

Anatomical caveat. This discussion centers on mesolimbic dopamine projections especially to nucleus accumbens, but in practice, it is often difficult to distinguish the role of mesolimbic dopamine from neostriatal, cortical, and other dopamine systems. That is because many experiments use systemic drug administration, genetic manipulations or neural sensitization to alter reward, and all are bound to impact many dopamine systems simultaneously. Dopamine might well mediate different functions in different targets, even if involving similar cellular and molecular mechanisms in each structure, but the functional dividing lines between structures cannot yet be fully drawn. For that reason, I will de-emphasize specific anatomical targets here and attempt to consider dopamine's most dominant role in reward. Still, we can, at least, surmise certain points about particular structures by a process of elimination. For example, if a reward function survives unchanged after dopamine is suppressed throughout the entire brain, then that function probably does not need dopamine in any particular brain structure.

Tonic-phasic caveat. Similarly, phasic vs tonic dopamine signals might well have consequences that differ from each other, but we cannot tell them apart in most experiments that manipulate reward. So although the distinction's importance is not denied, I will mostly focus on what we can say about the role of dopamine in reward more generally without trying to assign causal responsibility specifically to phasic or tonic signals.

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But…

Numerous studies have shown that Dopamine is neither a necessary nor sufficient cause for 'liking.'

- Taste reactivity studies found that blocking dopamine neurotransmission with medications or gene manipulation did not change 'liking' reactions to sweet tastes.
- Patients with Parkinson disease (dopamine deterioration) have normal pleasure ratings for sweet foods.

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What We Need in a New Theory of Addiction

1. The evolution of drug taking into **compulsive** drug taking.
   - CRAVING = obsession?
2. The persistence of craving & the ease of reinstatement of addiction after long periods of abstinence.
3. The fact that *wanting* a drug and *liking* a drug become differentiated with prolonged use.
   - Addicts often report liking the drug less but wanting it more.

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New Theory of Addiction - #1

Incentive Sensitization Theory of Addiction

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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New Theory of Addiction

Incentive Sensitization and Addiction

- ***Incentive****:* a reward offered; something that incites to action or greater effort.(Oxford English Dictionary, 2014)
- **Salience:** the quality or fact of being more prominent in a person's awareness. (Oxford English Dictionary, 2014)
- **Sensitization:** the process in which repeated administrations of a stimulus results in the progressive amplification of a response. (Shettleworth, 2010)
- **Incentive Salience:** the brains' attribution of prominence to a reward-related stimulus. (Robinson & Berridge, 2001)

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What is incentive motivation?

How does an incentive (something that is potentially rewarding) ***motivate*** *us to act?*

- **Incentive theories** of motivation shift the emphasis from the internal "pushes" to external "pulls." They state that motivation acts by making goal objects more attractive.

INCENTIVE THEORY in a nutshell…

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Incentive Motivation & Hunger

- Hunger makes you eat by making food more *attractive*.
  - When you are hungry, you find food more attractive and go in search of it.
- Evidence that hunger makes food more attractive:
  - When hungry, people rate a sugar solution as both very sweet and very pleasant.
  - When full, they rate the sugar solution as very sweet, but less pleasant.
  - Attractiveness of the food changes when the related motivational state changes, even though its sensory properties remain the same. Food doesn't change, perception/motivation changes.

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Incentive Attribution: How does a 'thing' become an incentive?

- Pleasure (LIKING) is experienced when a person encounters a natural incentive *(I am hungry. Look, an apple.)*
- This pleasure (LIKING) creates incentive value *(Eating the apple when I'm hungry reduces my hunger. Eating it is rewarding/pleasant)* and is linked to a 'thing' or action. *(The apple is rewarding/pleasant vs. the curbing of the hungry.)*
- Assigning pleasure to a thing comes about through learning. Then the 'thing' comes to elicit pleasure on its own. *(The apple gives me pleasure. I LIKE apples. Even when not presently hungry we can still say what we like to eat.)*
- 'WANTING' is when the 'thing' on its own becomes highly valued (incentivized), more attractive & demands attention. *(Whenever I see the apple, I get hungry and want an apple.)*

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Wanting vs. Liking

- Considering some examples:
  - Eating when you are not hungry.
    - How important is deliciousness?
  - Eating when a person is starving.
    - Food demands so much attention. It is almost impossible to resist.
    - Value placed on food is extremely high, even if food is not tasty.
  - Eating something delicious and then getting sick.
    - Liking can disappear.
  - Pica
  - Context
    - Harder to control eating at family dinners or Thanksgiving.
  - *Others?*

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Incentive Sensitization Theory

- *The incentive properties of an object are the wanting & liking. The value of each property can be different.*
- INCENTIVE VALUE = how much something is wanted.
- HEDONIC VALUE = how much something is liked.

…"Wanting" is unlike "liking" in that liking is a pleasure immediately gained from consumption or other contact with stimuli, while the "wanting" of incentive salience is a motivational magnet quality of a stimulus that makes it a desirable and attractive goal, transforming it from a mere sensory experience into something that **commands attention, induces approach, and causes it to be sought out**.

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Incentive Sensitization Theory

"If incentive salience to drug-taking… becomes pathologically amplified, then compulsive drug-seeking and drug-taking behavior may ensue"

- **Incentive Salience** – the attractiveness (wanting) that is attributed to a rewarding object.
- **Incentive Sensitization** – amplification of the incentive.
  - Liking doesn't sensitize, wanting does.
  - Wanting and liking are distinguishable at the psychological level and at the neural level.

Q: Does wanting come about from overlearning liking? Then, even when a thing is no longer liked, it is still wanted?

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Incentive Sensitization Theory

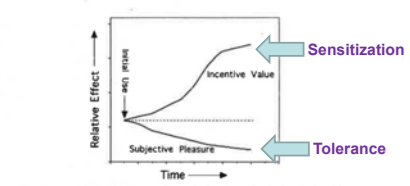

Fig. 3. A schematic illustration of the hypothetical relationship between changes in the incentive value of drugs and drug-related stimuli (drug 'wanting') vs. the subjective pleasurable effects of drugs (drug 'liking') during the development of an addiction. The development of an addiction is characterized by an increasing dissociation between the incentive properties of drugs, which gradually increase and the subjective pleasurable effects of drugs, which are shown here to slightly decrease (develop tolerance; but also see text and Note 5 in Ch. 6).

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Incentive Sensitization Theory

- The underlying neurobiology
  - All drugs of abuse share the ability to reorganize the brain and this reorganization is long-lasting.
  - Brain systems involved are linked to reward AND incentive motivation.
  - Reorganization leads to hypersensitivity to drugs and drug-associated cues. Basically, it makes 'ordinary' cues 'extraordinary' cues… labeling them as salient, attractive, 'wanted'.
  - Hypersensitivity is NOT to the pleasurable effects of drugs (liking) but rather to the salience and incentive value (wanting) of the drug.

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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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Incentive Sensitization Theory: Research

- Rodents repeatedly given amphetamine or cocaine became SENSITIZED (i.e., opposite of tolerance) to "psychomotor" effects of the drugs.
  - Psychomotor = movements that are linked to psychological processes.
  - In animals, observed as rearing behavior, repetitive behavior
  - In humans, "**Psychomotor agitation** is a series of unintentional and purposeless motions that stem from mental tension and anxiety of an individual. This includes pacing around a room, wringing one's hands, uncontrolled tongue movement, pulling off clothing and putting it back on and other similar actions."
- Same with morphine, PCP, MDMA, nicotine, alcohol, & THC
- Effects are dose-dependent
- Cross-sensitization (THC & morphine, alcohol & cocaine).

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Incentive Sensitization: Human Research

- Drug-naïve people.
- Given amphetamine 2 - 3x, 48 hrs apart.
- 2nd dose = activity/energy, mood change, rate/amount of speech, eye-blink rate increased.
- 3rd dose = activity/energy and eye-blink rate increased.

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KEY POINT

Observations of sensitization to many drugs with different underlying neural actions implies that there may be a common underlying mechanism.

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Incentive Sensitization Theory: Research

- Becomes more pronounced as time since last use increases (worse later than sooner!) *Is it permanent??*
- "Most remarkable feature of sensitization is its **persistence**"
- Most important feature of sensitization is that it's not the same for everyone.
  - Can be rapid and robust or almost nonexistent.
  - NOT an inevitable outcome of repeated drug use!
  - Individual differences in genetic, hormonal, experiential?
- It must be more than just the 'pharmacological' actions of the drug. It must be linked to other factors, but what?

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KEY POINT

Incentive sensitization theory posits that the thing(s) that determine *susceptibility to sensitization* are the same as the thing(s) that determine *susceptibility to addiction*.

* INDIVIDUAL DIFFERENCES!

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Incentive Sensitization Theory: Research

- There appears to be differences between what you see and what happens in the brain.
- Behavioral Sensitization – dependent on learning and context-dependence.
- If you give drugs in drug environment, you see sensitization. If you give it in a different environment, you do not. WHY?
  - All of the cues, context, & related 'things' also trigger reaction. In their absence, it may appear that behavior is exaggerated.
  - But wanting still exists when these things aren't there
  - Context/cues exaggerate wanting (CRAVING).
    - Craving can be TRIGGERED.

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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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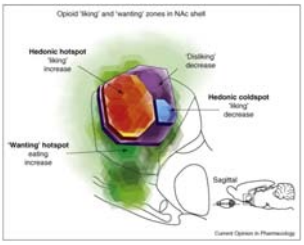
Back to neuroscience

- Where does wanting and liking reside in the brain?



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Back to neuroscience

- What neurotransmitters modulate wanting/liking?
  - **Dopamine** is not a pleasure transmitter ('liking')
  - Dopamine impacts pleasure-seeking behavior ('wanting')
    - Dopamine attributes incentive-salience to rewards
- Evidence:
  - Interrupting dopamine circuits with antagonists or brain lesions doesn't change behavioral expression of pleasure, but does change motivation to see pleasurable item
  - Drug taking happens in the absence of subjective experiences of pleasure

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Back to neuroscience

- But evidence also shows that
  - Damaging mesolimbic dopamine pathway knocks out cocaine and stimulant effects but doesn't block heroin, nicotine or alcohol self-administration (animal models).

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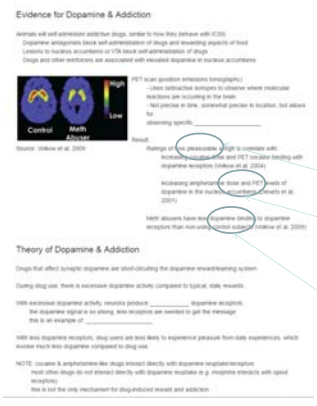

Yes, dopamine is involved.
Yes, dopamine is important.
Yes, dopamine is a central factor.

No, it isn't the only thing.
No, it doesn't explain addiction.

But liking goes down as addiction.

This is a primary drug action. Doesn't demonstrate addiction.

This is a primary drug action. Doesn't demonstrate addiction.

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Back to neuroscience

- Wanting may be implicit, NOT EXPLICIT
  - unconscious motivational process
- Under normal conditions, humans may not be able to tell the difference between wanting and liking.
  - How can I want something that I do not like?
  - "Introspection appears to interpret underlying [psychological] processes in ways that seem plausible to the person"

"Indeed, it may be because these psychological processes sometimes operate outside of conscious awareness that addicts have so little insight into why they want drugs so much. Addicts may report that they are miserable, their life is in ruins, and that even the drug is not that great anymore, and they are themselves bewildered by the intensity of their compulsive behavior."

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Incentive Sensitization: Human Research

•How do you see neural sensitization? Can't perform same studies as done in animals.
- Neuroimaging

• What behavioral measures are best to observe to quantify sensitization?
- Does eye-blink mean anything?
- Can't do study giving amphetamine 50x or more…
- Can't do study where you make person dependent, or try to get the person to self-administer!

• Do any of these drug effects predict addiction?
- Do people who get 'higher' have greater addiction liability?

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New Theory of Addiction

Addiction (2001) 96, 103-114

MECHANISMS OF ACTION OF ADDICTIVE STIMULI

Incentive-sensitization and addiction

TERRY E. ROBINSON & KENT C. BERRIDGE

Department of Psychology (Biopsychology Program), The University of Michigan, Ann Arbor, MI, USA

IS THIS THEORY SUFFICIENT TO EXPLAIN ADDICTION?

WHAT ELEMENTS OF ADDICTION HAS IT MISSED?

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