Addicted Brain, Derailed Mind, Self-Defeating Behavior: Neurobiologic Mechanisms of the Addict's Inability to Learn from Past Bad Outcomes

Jacob Sperber
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NUMC Psychiatry Grand Rounds

Addiction: Behavioral Definition

- Addiction to a substance is compulsive use of the substance despite adverse consequences, often accompanied by denial and tolerance.

Shifts in Scientific Paradigms

Harvard physicist Thomas Kuhn, in his *Structure of Scientific Revolutions* (1962) theorized about how scientific paradigms change:

- Older generation of scientists
  - attached to prevailing theory as ideology
  - New observational technologies
    - higher resolution -> new data which contradict the accepted scientific paradigm
- Younger generation of scientists
  - more open to noticing accumulating data which conflict with the accepted model.
    - see new patterns in the new data -> new model
    - new view crystallizes as accepted belief.
  - Repeats in each generation.

Paradigm Shifts in the Scientific Understanding of Addiction:

1. 1950s - prevailing paradigms – a neurosis
   - psychoanalytic ideas of personality predisposition by oral fixation
   - Complicated by fear of physical withdrawal
2. 1960s – mid 80s new paradigm – a conditioned response
   - operant conditioning
   - based on the neurophysiologic data about a midbrain "reward center" in lab animals
3. late 1980s and 1990s – a brain disease
   - New data from real-time human neuroimaging, a more complex paradigm of operant conditioning (basal ganglia/limbic system) interacting with impaired regulatory cortical functions for impulse inhibition (brain)
4. 2000s – a disorder of learning & memory
   - Disturbed connectivity among neurocircuits for impulse saliency, memory, learning, and prediction (mind)

How scientific paradigms change:

- Addiction, just a brain disease, or is there a mental miss-step in every instance of addictive over-use of the substance?
- If there is a mental miss-step, how does it work and where is it transacted in the brain?
Paradigm I: Clinical Observations of Compulsive Use to Avoid Withdrawal; and Oral Fixation

- In general, mid-20th century clinical theories of addiction placed too heavy an emphasis on relapse being driven by the negative reinforcement of relieving the dysphoria of withdrawal states.
  - The desperation of the alcoholic in impending DTs
  - and the psychoanalytic model of a personality ruled by early traumas and “oral fixation” (unconscious mind)
- psychoanalytic model of addiction blames the personality
  - the alcoholic is fixated at an infantile stage of mental development. The psychological repair is psychoanalysis.
  - This model is mental, but just wrong (Vaillant).
  - And the treatment failed.

Paradigm II: The Era of Behaviorist Addiction Research

- At McGill, James Olds, Donald Hebb, and two graduate students working in Hebb’s lab, Roy Wise and Eliot Gardner, developed animal models of addiction, correlating learned drug self-administration behavior with neurophysiology.
  - Working with laboratory mice, they defined a mammalian stimulation/reward center in the midbrain, the study of which redefined addiction as
    - a process of operant conditioning transacted by the stimulating impact of addictive substances on the “reward” dopamine neurons of the medial forebrain bundle and related structures in the VTA, n. accumbens, etc.

The Beginning: James Olds discovers ICSS

- Intra-Cranial Self Stimulation is an electrical technique to explore the electrophysiology of the central nervous system
- At McGill in the 1950s, James Olds developed this technique to demonstrate the function of a mid-brain stimulation-reward center, which seemed to be the site of reward reinforcement, consistent with Skinner's operant conditioning behavioral paradigm.
  - See http://www.youtube.com/watch?v=Ez4nX9MjOo at 17:57

James Olds invents ICSS

- Olds showed that he could induce a sensation of “pleasure” in a rat by placing an electrode in its brain and applying a mild electric stimulus. The intensity of the pleasure seemed to depend on the precise position of the electrode.
- Drawing on the work of the legendary Harvard psychologist B.F. Skinner, Olds developed a system in which rats could administer their own stimuli by pushing a lever, and they would do so as many as 6,000 times an hour if the electrode was placed "to their liking.”

James Olds
May 30, 1922–August 21, 1976
Schultz reviews Olds’ work

http://www.youtube.com/watch?v=Ez4nX9Mf0s

- Schultz on Olds 17:55

Animal Behavioral Models of Addiction

- some strains of laboratory mice quickly “learn” to self-administer addictive substances compulsively despite severe adverse consequences.
- This animal learned drug self-administration behavior seemed strikingly similar to human addictive behavior.

2 major pioneers trained by Hebb: Eliot Gardner & Roy Wise

Behavioral Characteristics of Animal Drug Self Administration

- Compulsiveness
- Conditioned Environmental Cues

Roy Wise and Eliot Gardner pioneered drug self-administration by lab animals

- While Olds was at work with electrical stimulation, experimental psychologists in Hebb’s lab like Wise and Gardner were using similar systems to characterize the pharmacology and phenomenology of drug abuse.

- In their laboratories, rats and monkeys learned to push levers to get intravenous amphetamines, cocaine or opiates.
Figure 3: (Bozarth & Wise, JAMA, 1985) **COMPULSIVENESS:** Cumulative number of fatalities from intravenous cocaine hydrochloride and heroin hydrochloride self-administration during unlimited access to drug. Percentage of animals lost are depicted as function of days of continuous testing. Solid circles indicate deaths in cocaine group; solid squares, deaths in heroin group.

**Animal Alcohol Self-Administration**

The Neurobiology of Addiction

An Overview,


Animal Model of Relapse Triggers: Place Conditioning

The Neurobiology of Addiction


Schematic of Reward Circuitry

- Gardner's 1988 schematic diagram of the brain-reward circuitry of the mammalian (laboratory rat) brain, with sites at which various abusable substances appear to act to enhance brain-reward and thus to induce drug-taking behavior and possibly drug-craving.
- This neurotransmitter receptor map provides a basis for pharmacologic interventions in the addictive process.
Addictive Drugs

Eliot Gardner noted that of the 10 million chemicals listed in the ACS compendium of all chemicals, fewer than 100 happen to fit, in a lock-and-key relationship, with the neuroreceptors of the the mammalian stimulation-reward center. It is this stereochemical similarity to the neurotransmitters of the reward center that make them addictive drugs.

Paradigm III: of the Neurophysiology of Addiction: addresses new evidence of cortical activation during intoxication and craving

But what about cortex and consciousness?

- "reward center"/operant conditioning model of Gardner & Wise based on rodents with little cortex or consciousness.
- Implies that addiction is acquired and driven entirely in deep mid-brain, outside of consciousness -> the addict’s conscious experience of pleasure is an epiphenomenon, irrelevant to compulsion, coming after the unconscious reinforcement.
- Addictionologists in the 1980s talked about the addict as the passive servant of a “rewired” brain.
- Bill Moyers, in his 1990s TV special on addiction, used as his title NIDA Director Alan Leschner’s phrase “the hijacked brain.”

Cortex and Consciousness In Addiction

- But this is counter intuitive. After pleasurable drug experiences, there is a wide variety of conscious choices and addictive outcomes among new users.
- Also, some new users just stop on their own. Other recreational users impose control on their use patterns.
- Only 1 out of 6 adolescents who try drugs become addicted. What protects the other 5 out of 6?????
- Also, conscious craving often precedes relapse.
- This all suggests cortical involvement.

Volkow lab shows that addiction involves more than the mid-brain “reward center”:

Drug Addiction and Its Underlying Neurobiological Basis: Neuroimaging Evidence for the Involvement of the Frontal Cortex

Rita Z. Goldstein, Ph.D., and Nora D. Volkow, M.D.

Weakened cortical functions in addiction (Goldstein & Volkow, 2002)

“If the frontal cortex and its supervisory functions are indeed down-regulated in human drug addiction, the relevance of motivational, higher cognitive, and self-monitoring processes to this affliction cannot be overstated.”

- Therefore the mind has a key role in addictive behavior and its treatment.
The Dynamics of Cortical Activity During Intoxication, Craving, & Withdrawal

Enter PET and other real time Brain Scans
- What is PET?
- Live humans
- Performing behavioral experiments, e.g. anticipating intoxication, self-administering drugs, being intoxicated, enduring withdrawal.

Pioneers of PET in Addiction: Volkow & Goldstein

Dr. Volkow prepares subject for a PET scan.

PET SCANNER

Craving lights up cortex
Protracted Withdrawal

- Glucose metabolism was higher in orbitofrontal cortex and striatum of cocaine abusers within 1 week of past use than in controls, but
- lower than in controls after 2 weeks since last use
- There have been similar time-course findings with alcohol.
- These findings suggest **worse cortical functioning during withdrawal**

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“Reward-Center” neurons are also under active during withdrawal.

**FIGURE 3. Lower Relative Glucose Metabolism in the Prefrontal Cortex and Anterior Cingulate Gyrus of a Cocaine Abuser more than 2 wks after last use than in a Normal Comparison Subject**

"Reward-Center" neurons are also under active during withdrawal.

**FIGURE 4. Lower Striatal Dopamine D2 Receptor Binding in Drug Users During Withdrawal From Cocaine, Methamphetamine, and Alcohol Than in Normal Comparison Subjects**

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**Effects of Damaged (Cortical) Neurocognitive Mechanisms: Misjudgment of Benefit/Risk**

1. Intensely positive reinforcement by repeated drug intoxication may hinder positive association formation from non-drug reinforcers, which are weaker.
2. Expectations of drug effect are distorted, exaggerated: Reward deficiency (less DA activity), the anhedonia of withdrawal and abstinence, exaggerates the perception of the value of the drug to restore “rewardability,” increasing the tendency to relapse in abstinence/withdrawal.

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**The Accelerator/Brakes Analogy**

- The mesolimbic, reward center circuit, is the “accelerator” of compulsive drug use, driven by operant conditioning.
- But higher, prefrontal and cingulate cortical functions can serve to inhibit impulses which have had bad outcomes in the past, the “brakes” to slow down the drug use when dangerous.
- Cortical volume and DA activity studies demonstrate that in addicts, the addictive substances not only overdrive the “accelerator” but also damage the “brakes.”
- Normally, both accelerator and brakes are “on” all the time, in continuous balance, permitting reward while maintaining judgment. (like Freud’s “pleasure & reality principles.”)
Volkow’s error

- Volkow forgot to consider DA release in response to pain.
- Animals withdrawing from experimental foot shock release midbrain dopamine in the same way as animals approaching opportunities for experimental drug reward.
- So mesolimbic DA release is not reward but rather the connection of affect to action, both action to withdraw from pain and to approach opportunities for pleasure.

Paradigm IV: New sub-Paradigms

- Incentive salience: enactment, not pleasure, is increased - Berridge & Robinson
- Prediction-signal error, that shapes behavior by learning to most efficiently obtain rewards – Schultz
- Deconsolidation/reconsolidation instability of long-term memories during recall – Alberini
- Ego depletion by social stressors which predispose to relapse – Baumeister

Current Paradigm Shift: Refinements of the Model to Integrate Neuroimaging and Intracellular Molecular Data that reveal complex component processes in addiction.


Reconsideration of Mesolimbic Dopamine as the Neuremediator of Reward:

A 4th paradigm shift in the neurophysiology of addiction is forced by the new contradictory data that:

1. “DA does not, in and of itself, induce “pleasure”;
   “mesolimbic DA efflux increases not only in response to a reward, but also in anticipation of a potential reward and during aversive states, including foot shock, restraint stress, and the administration of anxiogenic drugs. 17,24,34” (Adinoff, 2004)
Current Paradigm Shift: Dopamine is not “reward juice"

“Advances in functional neuroimaging revealed new data which contradict this relatively simple model of addiction:

- Although the mesolimbic dopaminergic efflux associated with drug reward was previously considered the biologic equivalent of pleasure, dopaminergic activation occurs more generally in the presence of all unexpected and novel stimuli (either pleasurable or aversive) and
- appears to determine the motivational state of wanting or expectation, including, but not limited to, the wanting or expectation of pleasure.”

- These data have forced a revision of the understanding of the mesolimbic axis, no longer as “reward center,” but more as a “wanting center.”

Salience

- A measure of the tendency to enact the impulse

Publication title: Pleasures of the Brain
Authors: Morten Kringelbach and Kent Berridge
Publication date: 01 October 2009

Reward: Feeling it vs. Wanting it

“Thus, the initial assumptions regarding the role of electrical brain stimulation in defining “reward” pathways were apparently overly simplistic:

- It appeared that the “pleasure” pathway, identified primarily from studies of animals . . . may have been mislabeled. Instead, Berridge and colleagues . . . and others—have suggested that the mesolimbic pathway determines the incentive salience, or wanting, of a prospective reward—not the pleasurable experience of the reward itself.”

- “Wanting,” separated from “liking,” measures the tendency to act on the impulse.

Liking vs. Wanting

- Berridge’s term “incentive salience” refers to the linking of the memory of a cue predicting a rewarding object, or the memory of the rewarding object itself, to the motivation to take complex, difficult, sustained action routines to obtain and consume it.
November 2001
Former Harvard Medical School professor of psychiatry Steven Hyman was tapped as the University’s new provost. He has spent the previous six years as director of the National Institute of Mental Health.

Steven E. Hyman, M.D., Addiction: A Disease of Learning and Memory, Am J Psychiatry 2005; 162:1414–1422

- Why affect evolved: so we have emotional vectors connected to memories of past action outcomes to learn what is useful and adaptive to survival and what is dangerous: If it turned out badly last time, I will avoid it. If it turned out well last time, I will approach it.

- “Evidence . . . is converging to suggest the view that addiction represents a pathological usurpation of the neural mechanisms of learning and memory that under normal circumstances serve to shape survival behaviors related to the pursuit of rewards and the cues that predict them.”

Hijacking complex survival routines
- Hyman (2005) restates that this mesocorticolimbic DA release connects the memory of rewarding (and painful) outcomes to actions useful for survival. Specifically, it links reward memory to the Darwinian determination to have one’s offspring survive by taking complex, persistent, contextually strategic action routines to get food and shelter for one’s young, the sense of importance to act despite obstacles, intense “wanting” to obtain the goal, now attached to the seeking and ingestion of drugs.

Hyman (2005 pp 1417-8) is saying that addiction hijacks an integrated web of DA and glutamate neurons which evolved to trigger inherited action routines for high-risk foraging and hunting to promote the feeding/survival of offspring, and for reproduction.

DA is the messenger for a continuous feedback process of error reduction in behaviors seeking repeated reward:

- “Overall, it can be concluded that dopamine release is not the internal representation of an object’s hedonic properties; the experiments by Schultz et al. suggest instead that dopamine serves as a prediction-error signal that shapes behavior to most efficiently obtain rewards.”

To Enact or Not To Enact (the impulse), that is the question
Schultz’s Prediction Signal Error

- An impulse (to acquire and ingest drugs) arises in the amygdala/mesolimbic system.
- The impulse undergoes a cortical (Ucs/Cx) review comparing it to past affective memories of the outcomes of enacting similar impulses (Did it turn out good or bad last time?) This mental review step is missing from Skinner/behaviorism.
- According to Schultz, based on the memory of feeling of previous outcome (good vs. bad), a prediction signal is made about the current impulse, resulting in an emotional go/no-go decision for enactment of the impulse (permission or inhibition of enactment).
- The affective reaction to the outcome of the new enactment is compared to the prediction, a calculation of prediction signal error, which then changes the record for next time, making enactment of a similar impulse in the future more or less likely, a process of LEARNING.

Schultz’s prediction signal error

- Addictive drugs force a miscalculation of action outcome compared to prediction, thus short-circuiting learning from bad outcomes.
- The next time there is an impulse, nothing having been learned from the previous wrong prediction, enactment is repeated, addiction.

Do dopamine neurons report an error in the prediction of reward?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reward Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prediction</td>
<td>No reward occurs</td>
</tr>
<tr>
<td>Reward predicted</td>
<td>Reward occurs</td>
</tr>
<tr>
<td>No reward occurs</td>
<td>Reward predicted</td>
</tr>
</tbody>
</table>

CS = conditioned, reward-predicting stimulus.
R = primary reward.

RESULTS

Drugs disrupt tracking of prediction error and the learning from bad outcomes that depends on it.

**RESULTS**

**FIGURE 1: Decision Making on a Modified Iowa Gambling Task**

*Net gain* = number of positive outcomes (good decks) minus number of negative outcomes (bad decks). The graph shows improvement over time in net score in the comparison group but not in the substance-dependent group.

**Results:**

Compared with healthy subjects, substance-dependent patients were less sensitive to loss compared with gain, made less consistent choices, and performed worse on the modified Iowa Gambling Task. The ventral striatum and medial orbitofrontal cortex did not track prediction error as strongly in patients as in healthy subjects.

**Conclusions:**

Weaker tracking of prediction error in substance-dependent relative to healthy individuals suggests that altered fronto-oral and basal ganglia error learning signals may underlie decision-making impairments in drug abusers. Computational fMRI may help bridge the knowledge gap between physiology and behavior to inform research aimed at substance abuse treatment.
Addictive drugs are molecules which

- hijack the recording of the emotional memories associated with the outcome of the addictive enactment, forcing a false record of a better than predicted signal error.
- No matter how terrible the consequences of the drug use (sickness, jail, rejection, embarrassment, car accident, etc.) the drug forces an affective memory of a good outcome
- Drugs cause an affective amnesia for the feeling of bad outcomes during subsequent impulses, making learning impossible.

Addictive mental process

<table>
<thead>
<tr>
<th>Step</th>
<th>Required</th>
<th>Optimal</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Cue/stimulus associated with past use, Priming, Craving, or Stress</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Impulse to use (Cx or Ucx)</td>
<td></td>
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<tr>
<td>3</td>
<td>Unconscious review reference emotional memories of past enactments</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Prediction signal</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Go/no-go signal to enact ➔ Impulse becomes conscious</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Conscious review of the go signal to enact. CBT can intervene here.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Enactment/inhibition of the impulse</td>
<td></td>
</tr>
</tbody>
</table>

If Addiction Involves false and disrupted memories, can they be erased?

- Alberini’s “eraser”

Alberini’s Eraser: Erasing Addictive & Traumatic Memories?

Taubenfeld, S M, Muravieva, E V, Garcia-Ostaa, Ana, and Alberini, C M, Disrupting the memory of places induced by drugs of abuse weakens motivational withdrawal in a context-dependent manner, PNAS, July 6, 2010, vol. 107, no. 27.

Alberini’s eraser: Disrupting Contextual Memories Induced by Drugs of Abuse Alleviates Motivational Withdrawal

Memory plays a major role in the development of addiction. Places where drugs are experienced become associated with the effect of the drugs, and re-encountering those places brings back the memory of being high, precipitating craving and relapse.

At the time of recall, long-term memories are fragile

- And must be “reconsolidated” in order to continue to be remembered
- In lab rats, Alberini “erases” these LTP memories by chemically blocking “reconsolidation”
- She proposes to try this in addiction by blocking reward memories and in PTSD by blocking trauma memories.
Part VI: Social Causation of Diminished Impulse Control

It is very difficult — perhaps literally impossible — to resist continuously persisting desires (no matter what the source). The evidence comes from social psychology, specifically studies on ego depletion (Baumeister et al. 1998; Baumeister 2002).

In ego depletion paradigms, subjects are divided into two groups. One group performs a self-control task (e.g., watching a humorous film without smiling), the other performs another task that is equally demanding but that does not require self-control (e.g., performing a series of three-digit multiplications using pencil and paper).

Then, the two groups are given a common self-control task to perform (e.g., keeping one’s hand immersed in icy water or persisting at an unsolvable anagram task). Subjects who have recently engaged in a task requiring self-control persist for a significantly shorter period of time than subjects who have engaged in a task that does not require self-control.

These studies appear to demonstrate that self-control is a depletable resource. When we engage in self-control, we draw down our reserves of this resource. Sooner or later, we exhaust it, and we then give in to prepotent urges.


Social variables in addiction, continued

- Ego depletion has significant implications for our understanding of addictive behavior.
- Whether an addict gives in depends not only on his traits for self-control, but also on how often and for how long the addict’s life stressors have exhausted his resources for exerting control.
- Addicts struggling with poverty and homelessness have less strength left to cope with relapse impulses.

Summary

- Addictive chemicals disorganize evolved brain systems which normally serve to learn from action outcomes, causing a kind of amnesia for learning from the distress experienced during bad outcomes of drug use. New impulses are met with false predictions of good outcomes, and compulsive enactment persists.
- Under conditions of life stress, already-compromised mental functions of impulse monitoring and review are exhausted and enactment of wrong-minded addictive impulses persists.
- Treatment based on this model of addiction can:
  - Intervene by training the addict to delay enactment and use techniques to recall the feelings of past bad outcomes (AA), moving from external monitoring to supported internal monitoring.
  - Erase false reward memories pharmacologically during their fragile state during recall, before reconsolidation occurs (experimental).

Why addiction is a disease

Nestler and Kandel

http://www.youtube.com/watch?v=Ez4nX9MfJoQ

35:00

Other addictions?

http://www.youtube.com/watch?v=Ez4nX9MfJoQ

Schultz on Other addictions in striatum

43:00

Genetics of addiction

48:30
Memories can be temporarily fragile when recalled or reactivated, and the reconsolidation process offers an opportunity to block the reconsolidation process and thereby prevent relapse in drug addicts. Taubenfeld et al. thus suggest that disrupting drug-induced memories may provide a method for mitigating drug relapse impulses and context-specific emotional withdrawal and thereby preventing relapse in drug addicts.

DA neurons code for error between predicted & actual reward
- . . . dopamine neurons do not simply report the occurrence of appetitive events. Rather, their outputs appear to code for a deviation or error between the actual reward received and predictions of the time and magnitude of reward.
- These neurons are activated only if the time of the reward is uncertain, that is, unpredicted by any preceding cues. Dopamine neurons are therefore excellent feature detectors of the "goodness" of environmental events relative to learned predictions about those events.
- They emit
  - a positive signal (increased spike production) if an appetitive event is better than predicted,
  - no signal (no change in spike production) if an appetitive event occurs as predicted, and
  - a negative signal (decreased spike production) if an appetitive event is worse than predicted (Fig. 1).

The Adinoff addiction mental cascade, potential places to intervene:
- Drug experience ➔
  - Liking (feeling the reward) (n. accumbens shell)
  - Remembering pleasure and cues (LTP) (amygdala, hippocampus)
  - Wanting, incentive salience (mesolimbic DA) "accelerator"
  - Inhibiting, suppressing (OFC & ant. cingulate) "brakes"
  - Behavioral ACTION “seeking” routines (dorsal striatum, motor areas)