The Neurophysiology of Addiction
Moving Beyond the “Reward Center”

Three types of addiction research
1. Modern addiction research began with the discovery of the pleasure center (Olds & Milner, 1954). This research focused on acute changes to the brain when exposed to abusable substances.
   - Era: 1960s to 1990s
   - Suggested that addiction may be a brain disease
2. Changes in the brain’s neural responsivity that occur when someone transitions from intermittent use or abuse to addiction—much more recent.
   - Determines the changes that occur when transitioning from abuse to addiction.
   - Important for medication development.
   - Increases our understanding of how addiction changes brain-behavioral functioning, guiding non-pharmacological treatment.

My Bias and Interest
- My belief is that the medications that are currently available are an important, but small small part of effective treatment.
- I spent my 30 years working in treatment programs asking myself:
  - “Can we improve current or create new treatment interventions based upon brain science?”
  - “Why does this intervention not work?”
  - “Why does this intervention work?”
- The concept of AddictBrain and RecoveryMind® arose out of this neurophysiological study.
- The book: RecoveryMind Training is in press and will be released late in 2016.

Addicted rats act like addicted humans...

The Mesolimbic Reward Circuit
Addiction Neurophysiology: Beyond the “Reward Center”
Olds and Milner

- Discovered the reward center in 1954, quite by accident. Electrical stimulation to a few selected areas of the brain proved to be deeply rewarding.
- Animals would continue to seek the stimulation, enduring electrical shocks or learning a complex series of behaviors to obtain electrical stimulation.
- They discovered that this effect would not satiate unlike natural rewards such as water, food and sex.

Addiction confused with Physiological Dependence

- Prior to the 1970s, addiction was thought to be defined by:
  - The development of tolerance
  - The presence of withdrawal symptoms
- This led to blunders of diagnosis: In the 1970s, the leading textbook of psychiatry stated that cocaine was not addicting!

Dopamine Reward Circuit

Ventral Tegmental Area

Nucleus Accumbens

History

- Dopamine / Reward Model (1980s)
  - In the 1980s, clinicians move away from the dependence model differentiating physical tolerance (a universal quality of certain drugs) from addiction (a vulnerability of certain individuals).
  - The dopamine depletion model of addiction, developed in animal research, was introduced to the clinical world by Drs. Dackis and Gold.

Dackis, C.A. & Gold, M.S. New concepts in cocaine addiction: the dopamine depletion hypothesis. 
Dopamine / Reward Model

- Dopamine neurons in the Ventral Tegmental Area (VTA) project to shell of the Nucleus Accumbens (NAc).
- All drugs of abuse seem to activate this circuit, albeit through a variety of neurotransmitter substrates. In fact, all human behaviors that are driven by reward originate in this brain circuit.
- In the 1980s, Dopamine discharge in this complex was felt to produce pleasure and reward.

The Model was Incomplete

- Drug reward was considered the biological equivalent of pleasure, however dopaminergic activation occurs in the presence of unexpected and novel stimuli. This suggested that the model was incomplete or even inaccurate.

<table>
<thead>
<tr>
<th>The Dopamine Model explains...</th>
<th>But fails to explain...</th>
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<tbody>
<tr>
<td>Addiction is a brain disease</td>
<td>The lack of pleasure with continued use</td>
</tr>
<tr>
<td>That addiction hijacks life-sustaining primitive drives (food, water, sex, procreation, child rearing).</td>
<td>Why people relapse after long periods of abstinence</td>
</tr>
<tr>
<td>That addiction is not drug specific, any drug that activates the VTA-NAc complex can and does trigger the illness</td>
<td>The phenomenon of euphoric recall</td>
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</table>

Incentive Salience

- Patients who had deep brain stimulation electrodes placed in the 1970s noted more compulsion than pleasure from the electrical stimulation.
- Berridge, after destroying the VTA in rats, noted they continue to enjoy food but do not work for it.
- This seminal study along with years of supporting research led to the conclusion that the VTA→NAc produces “wanting” rather than “reward.”
- “This may explain why life’s intense pleasures are less frequent and sustained than intense desires.”

Dorsolateral Striatum

Decoupling Reward

The incentive salience theory decouples wanting from liking in addiction.

Reward and Signal Salience

Drug Use ➔ Pleasure
Memory Consolidation Of Event ➔ Signal Salience ➔ Increase in Motivation

Subtleties in Dopamine Firing

- Dopamine neurotransmission in the area of the VTA mediates acute reinforcing effects of abused drugs.
- This reinforcement comes from "phasic" firing (sub second bursts) and short-lived escalations in dopamine level.
- Sustained changes in dopamine level was not related to animal models of addiction.

Subtleties in Dopamine Firing

- Recent research (Willuhn, Brown) suggests that:
  - Shortly after initial use, ventral medial striatum (VMS) signaling drops off and the rate of this drop directly relates to drug escalation.
  - During protracted use, changes in signaling in the dorsolateral striatum (DLS) drive compulsive use and continued drug seeking behaviors.
  - This dopamine signaling is phasic, tonic state changes do not appear to correlate with animal addiction behaviors.
  - Administration of the dopamine precursor L-DOPA decreased the intensity of dose escalation but did not change the neuroadaptation noted in these studies.

Three models for addiction drivers

- Opponent Process Model (Koob & LeMoal)
  - Initial drug use is driven by the rewarding effects of a drug or addicting behavior, but that continued use decreases the proper functioning of the brain's reward system which drives accelerated use.
- Incentive Salience Model (Berridge & Robinson)
  - Dopamine motivates the pursuit of rewards by attributing incentive salience to reward-related stimuli.
- Aberrant Learning Model (Robbins & Torregrossa)
  - Drug use enhances positive learning and memory about the drug while inhibiting learning about the negative consequences.

Changes are Lasting

Addiction Neurophysiology: Beyond the "Reward Center"
Mechanism of Tolerance

ΔFosB is an inducible gene which is increasingly expressed in the nucleus accumbens following high doses of an addictive drug or overexposure to other addictive stimuli.

- ΔFosB is thought to increase sensitization to the negative aspects of addictive substance use.
- ΔFosB levels remain high for extended periods and may account for the chronic nature of addiction.
- It may also be responsible for the priming effect of small doses of the same or any other drug or behavior in stimulating relapse.

Mechanism of Sensitization

Neural Adaptation to Drug use

After extended drug exposure, these structural changes along with the previously mentioned accumulation of ΔFosB appear to be partly responsible for priming: a low dose of an addictive substance triggers a full-blown relapse.

Moving Beyond the Reward Center

Addiction modulates other Brain Centers

- Inhibition of executive control centers
- Activating motivation and attention circuits
- Drug cues that command attention by activating the amygdala
- Memory circuits
  - Entrainment of Procedural Memory
  - Haunt & trigger some addicts when PTSD-like memories appear intrusively
- Brain centers that activate stress and modulate emotions
- Higher cortical areas that:
  - Make judgement as to cause and effect
  - Generate self-concept
  - Regulate the conscious sense of self
Addiction derails Inhibitory Controls

- The dorsolateral (DLPC) and orbitofrontal (OFC) prefrontal cortices are involved in inhibitory decisions, immediate versus delayed responses and weighing the importance of various goal-related behaviors.
- Addiction produces decreased sensitivity to non-drug reinforcers and decreased ability to inhibit maladaptive or disadvantageous behaviors.
- Inhibitory control problems may be picked up on neurophysiological tests such as the Stroop.

Addiction hijacks Attention and Motivation

- Under non-addicted conditions:
  - The Prefrontal Cortex (PFC) creates a representation of goals, assigns a value to them and selects actions to attain goals.
  - The Anterior Cingulate Cortex focuses attention and monitors performance.

Addiction hijacks Attention and Motivation

- When addicted, addiction-related stimuli initiate a supraphysiological glutamatergic response sent to the nucleus accumbens which stimulates drug seeking.
  - Pathways from the OFC activate well learned drug foraging behaviors.
  - Activity in the ACC focuses sustained attention on drug procurement behaviors.
- At the same time, changes in this circuit reduces the capacity of the prefrontal cortex to initiate responses to healthy goals.

Addiction & Memory

- Addiction shares striking similarities with neural plasticity associated with natural reward-based learning and memory.
- Addiction affects memory in many ways. We will discuss three of them here:
  - Addiction entrains the brain to respond to drug cues.
  - Addiction entrains drug or alcohol foraging into Procedural Memory.
  - Addiction Flashbacks: PTSD-like recall of substance related events.

Types of Memory

<table>
<thead>
<tr>
<th>Immediate recall (aka Sensory memory) - up to 1 second</th>
<th>Short-term memory - minutes</th>
<th>Long-term memory - days, months, years</th>
</tr>
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<tbody>
<tr>
<td>Retention of 7 “chunks” of information (repetition)</td>
<td></td>
<td>Retention of and abstraction of learned information transferred from short-term memory (recall)</td>
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Addiction Neurophysiology:
Beyond the Reward Center

Types of Long-term Memory

- **Declarative memory**
  - Semantic memory
  - Episodic memory
  - Facts & figures
  - Events & times

- **Non-declarative memory**

  - Procedural memory
  - Priming
  - Emotional responses
  - Muscle Memory

  - Medial Temporal Lobe of Cortex

  - Cerebellum, putamen, caudate nucleus, motor cortex, amygdala

  - Neocortex

  - Emotional Responses

  - Muscle Memory

Cue-based Craving

- The brain embeds the experience of substance use, adding environmental stimuli to produce an "addiction memory."
- Building credence to the aphorism to "change playmates, playgrounds, and playthings."
- A strong cue remains embedded in the amygdala awaiting reactivation.
- The Amygdala signals the VTA through glutaminergic circuits that establish the hunger and urgency associated with a cue-based craving.
- Memory stored in the hippocampus and eventually becomes episodic memory located in the temporal lobe.


Brain structures in Procedural Learning

- Striatum and basal ganglia: two parallel information processing pathways diverge from the striatum, both acting in opposition to each other in the control of movement. The striatum is comprised predominately of GABA neurons. The system is activated by dopamine.
- Supplementary Motor Area: participate in the development of skills requiring internal elaboration of motor behavior.
- Cerebellum: Records the movement component of memory. Fine tunes procedural skills, increasing their efficacy. The automation of unconscious behavior occurs here.
- Amygdala: attaches emotional qualities and intensity to a memory.

Addiction and Procedural Learning

- The basal ganglia are involved with behavioral learning
- Attentional circuits (Anterior Cingulate) and dopamine-mediated incentive salience (VTA and NAc) direct the basal ganglia to record behaviors that result in drug procurement.
- Repeated use over time perfects and automates alcohol and drug procurement (basal ganglia and cerebellum).
- When stimulated by related cues (amygdala), automatic and partially automatic relapse behaviors ensue.
- Like all procedural learning, the knowledge is automated, rigid, life-long and partially unconscious.

Addiction Flashbacks

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Acute Fear – Normal Processing

- A traumatic event occurs
- The amygdala sounds an alarm through the "short loop." More malleable and slower responses to the event occur through the thalamocortical (long) loop.
- The pituitary gland secretes Corticotropin-releasing Factor (CRF)
- The cerebellum is mobilized for movement
- The medulla oblongata activates the cardiovascular system and shuts down digestion. The pons increases respiration.

- The locus coeruleus secretes norepinephrine and the nucleus accumbens and surrounding structures secrete dopamine to rivet attention.
- The visual cortex, in concert with the hippocampus, creates a visual recording of the event.
- When the acute situation subsides, the cortex revisits the images, reprocessing the event into semantic and episodic memory. This deactivates the amygdala-driven memory circuits.
- Dreams further process the meaning of the fear-event, providing behavioral alternatives to avoid or deflect the trauma and improve survivability. Dreaming encodes complex behavioral responses (procedural memory) and draws associations between the current fear event and past fear memories.

What happens with PTSD?

- The acute trauma is either too overwhelming or is repeated, preventing the individual from reprocessing the trauma
- The trauma "tape" becomes stuck in visual memory
- The victim numbs to avoid emotionally experiencing the trauma
- Dreams and further meaning-extraction does not occur, rendering the organism susceptible to recurrence
- The victim may engage in "trauma re-enactment" to reactivate the release of endorphins and dopamine

Addiction Flashbacks

- Intrusions have sensory properties (mental images, i.e. not just verbal thoughts).
- Come to mind unbidden (i.e. not those deliberately recalled).
- Most likely shares the same circuitry with PTSD

Brain Centers & Addiction
The Brain’s “Default Mode”

Gazzaniga’s Interpreter

Sperry’s Split Brain Experiments

Each hemisphere was presented a picture that related to one of four pictures placed in front of the split-brain subject.

The left and right hemispheres easily picked the right card. The left hand pointed to the right hemisphere’s choice, and the right hand pointed to the left hemisphere’s choice.

The patient was then asked why the left hand was pointing to the shovel. Only the left hemisphere can talk, and it did not know the answer because the decision to point to the shovel was made in the right hemisphere.

Immediately the left hemisphere made up a story about what it could see—the chicken. It said the right hemisphere chose the shovel to clean out a chicken shed.


The Interpreter

1. Consciousness does not constitute a single generalized process. It is an emergent property that arises locally out of hundreds if not thousands of widely distributed specialized systems or modules.

2. From moment to moment different modules or systems compete for attention. The winner serves as the neural system underlying that moment of conscious experience.

3. We do not experience a thousand chattering voices but a unified experience. Consciousness flows easily and naturally from one moment to the next with a single, unified and coherent narrative.

4. The narrative story of who we are comes from the left parietal cortex. It creates a coherent whole out of conflicting information.

5. The psychological unity we experience emerges out of a particular specialized system called the interpreter.

6. The interpreter appears to be uniquely human and specialized to the left hemisphere. It is the trigger for human beliefs which constrain our brain.

Gazzaniga: The Gifford Lectures (2009)

The Interpreter in Addiction

- The concepts of cause and effect are produced by the Interpreter. They are colored by cultural and intellectual history.

- Rational and conscious thought has a limited relationship with deeper drives.

- Addiction introduces a potent and foreign driver into our brain, confusing our internal narrative.

- This produces the thick denial that typifies the addicted state.

AddictBrain / RecoveryMind

AddictBrain

The sum of all brain responses, maladaptive associations and learning caused by addiction.

RecoveryMind

The sum of the all cognitive, emotional and spiritual retraining that the mind must undergo to attain recovery.
We seek to put more heart and soul back into addiction medicine. We are all passionate in our belief that psychosocial and spiritual interventions are always important and that medication management alone is not adequate.

We also believe that prescribing medication for opioid addiction without providing and/or prescribing other psychosocial and spiritual interventions falls far short of "best practice" for an addiction medicine specialist.

We are believers in the great benefits of 12 step recovery modalities in facilitating long-term recovery.

www.LikeMindedDocs.com

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Education and Consultation

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