The Neurobiology of Addiction
Addiction.
Is it a Disease?
The Disease Model of Addiction

*Addiction is a primary, chronic disease of the brain.

*It is a disease because drugs modify brain chemistry and the structure of cells and circuits involved with reward, motivation, learning and memory.

*In the addictive brain, drugs hijack normal learning pathways and activate reward circuits in response to drug-associated cues, which leads to cravings and compulsive drug seeking behavior, despite harmful consequences.

*The clinical significance of these brain changes is that addiction, once established, becomes a chronic illness with relapses and remissions.
The idea that addicts voluntarily chose to use drugs of addiction doesn’t make the addiction any less of a disease.

There are many chronic diseases, such as COPD, HTN, CAD, DM, that originate with voluntary lifestyle choices.

There’s a genetic component to diseases (CF, SCA, Huntington’s, BRCA1). Twin and adoption studies show a genetic component to alcoholism.

Knowing that drugs of abuse can lead to addiction doesn’t deter many from experimenting with drugs because the majority of people who use addictive drugs don’t become addicted.

While the initial choice to use drugs of abuse may have been voluntary, changes in the brain from use of these drugs make it difficult for the addict to voluntarily stop using.
The Disease Model of Addiction

Unhealthy biological structures are rightly termed diseased, regardless of the organ involved.
All known addictive drugs activate reward regions in the brain by causing sharp increases in the release of dopamine.

At the receptor level, these increases elicit a reward signal that triggers associated learning or conditioning.

In this Pavlovian-type learning, repeated rewards become associated with the environmental stimuli that precede them.

With repeated exposure to the same reward, dopamine cells stop firing in response to the reward itself and instead fire in an anticipatory response to the conditioned stimuli ("cues") that predict the delivery of the reward.

This process involves the same molecular mechanisms that strengthen synaptic connections during learning and memory formation.
Addiction involves the reward pathways of the brain.

**Reward Pathway**

- Stimulated normally by food, sex, water, etc.
- VTA (ventral tegmental area) connects to the nucleus accumbens and prefrontal cortex.
- Neurons in VTA contain dopamine, which is released in the nucleus accumbens and prefrontal cortex in response to the rewarding stimulus.
In the Disease Model of Addiction, there are **Stages of Addiction**

1.) Binge and Intoxication.

2.) Withdrawal and Negative Affect

3.) Preoccupation and Anticipation (cravings)

*Each stage is associated with the activation of specific neurobiological circuits and resultant clinical and behavioral characteristics*
Stage 1. **Intoxication**
You like the euphoric feeling, so you use it again. The more you use it, the more the brain changes and this creates negative effects when not using it, which leads to

Stage 2. **Withdrawal**
You feel distressed and to get rid of this distress, you think of using the drug again, which leads to

Stage 3. **Preoccupation and Cravings**
Cues initiate cravings for the drug and this leads to repeated use and intoxication
What causes these brain changes?

All known addictive drugs increase the release of Dopamine
Nicotine binds directly to acetylcholine receptors on dopamine cells and increases the firing frequency of dopamine neurons.
THE HIGH:
Morphine’s activation of the opioid receptor in neurons of the nucleus accumbens in the brain 1 reigns in the release of the neurotransmitter γ-aminobutyric acid (GABA) 2. This drop in GABA causes a neighboring cell to expel dopamine 3, which in turn elicits the euphoria associated with opioids.
Alcohol increases dopamine cell firing and dopamine release in axon terminal fields.
Cocaine inhibits the binding of dopamine to the transporter and increases extracellular dopamine.
All known addictive drugs increase the release of Dopamine
The release of dopamine triggers Neuroplasticity
The Concept of Neuroplasticity

Neuroplasticity = the potential of the brain to reorganize itself by creating new neural connections.

Through “axonal sprouting” axons grow new nerve endings and form new neural pathways.

These new neural pathways allow for systematic changes in the synaptic signaling, or communication, between neurons in various reward regions of the brain.

These neuroplastic changes are fundamental to learning and memory and strengthen drug-associated behaviors.
Experience-dependent learning, which occurs in repeated episodes of drug use, invokes both long term potentiation, which increases the transmission of signals between neurons and long-term depression, in which signals are decreased.

Changes in long-term potentiation and depression are in turn associated with larger or smaller synapses, respectively, and differences in the shapes of the dendritic spines in the receptive site of the receiving neuron.

Synaptic strength is controlled by the insertion or removal of receptors that are stimulated by the excitatory NT glutamate.
Neuroplastic changes triggered by drugs occur in the:

**Nucleus accumbens** (the crucial brain reward region)
**Dorsal striatum** (associated with the encoding of habits and routines),
**Amygdala** (associated with emotions, stress and desires)
**Hippocampus** (region involved in memory)
**Prefrontal cortex** (an area involved with self-regulation and the assignment of relative value).

All these regions of the brain participate in the various stages of addiction, including conditioning and craving.

These regions also regulate the firing of dopamine cells and the release of dopamine.
Dopamine Pathways

- Frontal cortex
- Striatum
  - Substantia nigra
- Functions
  - Reward (motivation)
  - Pleasure, euphoria
  - Motor function (fine-tuning)
  - Compulsion
  - Perseveration
- Nucleus accumbens
- VTA
- Hippocampus
- Raphe nucleus
Cocaine causes transcription-dependent neuroplasticity in the reward pathways. It alters the dynamics of numerous neurotransmitter systems in the mesocorticolimbic region of the brain: the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC). These areas are critical for reward, reinforcement, and higher cognitive functions.

Cocaine indirectly enhances the levels of dopamine at the interface between VTA cells and NAc cells by binding to and blocking DAT.

The activation of D1 and D2-type DA receptors stimulates intracellular signaling cascades that direct transcription factor binding to DNA. HATs and HDACs have opposing actions to push the equilibrium one way or the other. Histone acetylation (by HATs) generally allows for TF binding and gene expression while histone deacetylation (by HDACs) represses transcription.
Adapted from Nestler, McQuown and Wood (2010).
Glutamate is released by cortical and limbic terminals when exposed to drugs or drug cues.

Glutamate acts largely through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] and N-methyl-d-aspartate [NMDA] receptors.

Glutamate helps to up-regulate AMPA receptors.

The up-regulation of AMPA receptors increases the responsiveness of the nucleus accumbens to glutamate.

Specifically, the insertion of a subunit of the AMPA receptor that is highly permeable to calcium, the glutamate receptor 2 (GluR2), enhances the efficiency of transmission.

This has been shown to contribute to long-term potentiation in addiction.
Repeated exposure to dopamine leads to changes in the circuitry of the amygdala, which increases a person’s reactivity to stress and results in the emergence of negative emotions.

This “anti-reward” system is fueled by the neurotransmitters involved in the stress response, such as corticotropin-releasing factor and dynorphin.

In the addicted brain, the anti-reward system becomes overactive, giving rise to a highly dysphoric phase that ensues when the direct effects of the drug wear off.

To counter the direct and conditioned pull toward the “rewards” of drug use, there is a correspondingly intense motivational push to escape the discomfort associated with the aftereffects of use.

The addict transitions from taking drugs simply to “get high” and feel pleasure, to taking them to obtain relief from dysphoria.
Neuroplasticity effects:

Changes in the circuitry of the Amygdala increase sympathetic activation

Heroin

Noradrenaline

When heroin use stops, unopposed sympathetic noradrenaline predominates and causes withdrawal symptoms: increased HR, RR, BP, anxiety, diarrhea
Preoccupation and Anticipation:

In addition to changes in the basal forebrain that lead to stress and cravings, changes also occur in the prefrontal cortex of the brain. This is where "executive processes" such as the capacity for self-regulation, decision making, flexibility in the selection and initiation of action, attributing relative value and the monitoring of error.

Changes in the emotional circuits of prefrontal regions are disrupted by neuroplastic changes in glutamate signaling, which weakens a user’s ability to resist strong urges and to follow through on decisions to stop taking the drug.

This explains why addicts may sincerely desire to stop using a drug, but are simultaneously impulsive and unable to follow through on their resolve.
Dopamine cells stop firing with repeated exposure to natural rewards (food, sex) as satiety develops, but addictive drugs circumvent natural satiation and continue to release dopamine.

This explains why compulsive behaviors predominate with drug use and not with natural rewards.

Compulsive behaviors are also related to environmental cues and triggers. The environmental stimuli that are repeatedly paired with drug use (the place, persons and mental state involved with the process of drug use) can elicit conditioned surges of dopamine release that trigger craving for the drug, motivate drug-seeking behaviors, and lead to heavy “binge” use of the drug.

These conditioned responses become deeply ingrained and can continue to trigger strong cravings for a drug long after use has stopped.
It was previously thought that those addicted to drugs become more sensitive to the rewarding effects of drugs, resulting in higher levels of dopamine in the reward circuits of their brains, but, on the contrary, continued drug use triggers attenuated increases in dopamine levels.

This decreased release of dopamine renders the brain reward system much less sensitive to stimulation by both drug-related and non-drug-related rewards.

Those addicted to drug no longer experience the same degree of euphoria from a drug as they did when they first started using it.

They also become less motivated by everyday stimuli that was previously motivating and rewarding. Because their systems for reward and motivation become reoriented through conditioning to focus on the release of dopamine produced by the drug and its cues.

The landscape of someone who is addicted becomes restricted to the cues and triggers of drug use.

These changes become deeply ingrained and cannot be immediately reversed through the simple termination of drug use (e.g., detoxification).
Persons with addiction frequently continue to take the drug even when it no longer seems pleasurable.

Many take the drug to escape the distress they feel when they are not intoxicated.

Although the short-acting effects of increased dopamine levels triggered by drug administration temporarily relieve this distress, the result of repeated binge use is to deepen the dysphoria during withdrawal.

This produces a vicious cycle.
Feedback loop

You get high & feel better

The effect wears off, you crash

You feel terrible and want to feel good again

You seek more drug
"Just after I'd shoot up, I'd get an amazing rush. I'd be on top of the world. Once the high really set in, my mind would get slow and fuzzy. It'd feel like I was sinking into the floor. I'd forget if I was asleep or awake, and time just passed me by. I got hooked quick. After a while, I needed heroin just to get by. Too long without a fix, and...I can't even describe it. It's like I was dying in every awful way you could think of, all at once. Pain in all my bones, throwing up, chills, and I couldn't sleep for days."

“The second time I got busted, the judge decided to put me in a drug treatment program. I was so angry. I didn't want to stop using. I just wanted another fix. When I got out of jail, I decided I'd control my drug use better, and stay out of trouble. But there's no such thing as "control" when it comes to addiction. You just want more and more, and will do all kinds of crazy things to get high again.”
Only a minority of people who use drugs ultimately become addicted — just as not everyone is equally at risk for the development of other chronic diseases.

Susceptibility differs because people differ in their vulnerability to various genetic, environmental, and developmental factors and it is these factors that contribute to the determination of a person’s unique susceptibility to using drugs initially, sustaining drug use, and undergoing the progressive changes in the brain that characterize addiction.

Although long-term exposure to drugs is a necessary condition for the development of addiction, it is by no means sufficient.

In those persons where drug use progresses to addiction, the neurobiologic changes are distinct and profound.

It is estimated that the most severe phenotypic characteristics of addiction will develop in approximately 10% of persons exposed to addictive drugs.

The other 90% gives us an estimate of the magnitude of the problem.
Disease of the Brain?

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How do we treat it?