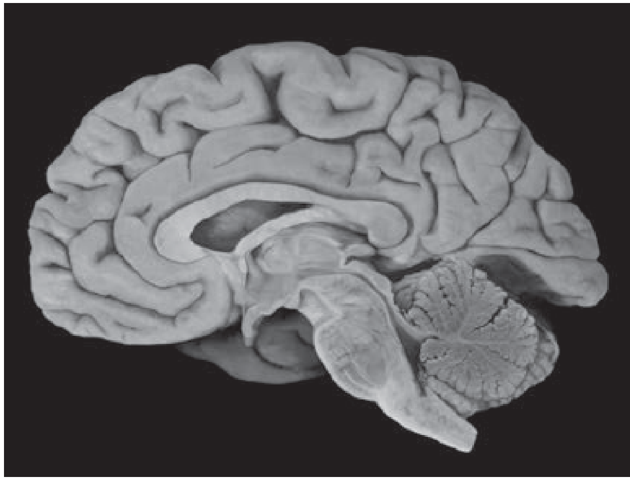
Addiction and the Brain

Part 1

Why the brain?



There is an assumption that the brain is responsible for everything we are and everything we do.

So isn't it reasonable to focus on understanding the neural mechanisms underlying our experience, such as impulsive behavior and craving?

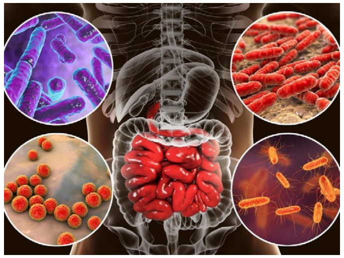
That is what many of us neuroscientists still think.

Why not just the brain?

Because data show otherwise.

Everything that has influences our experience affects our behavior.

The brain is the stage in which these influences interact and are marked.



What does the Central Nervous System (CNS) do?

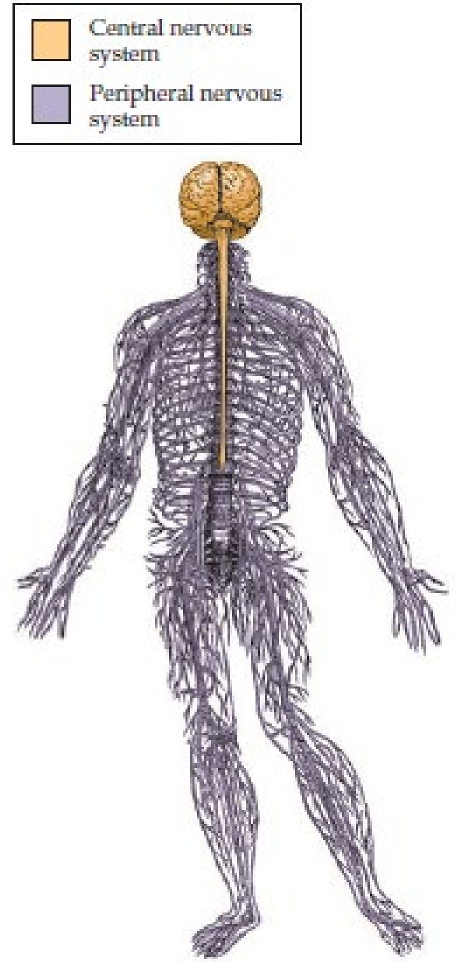
The CNS (brain and spinal cord) is extremely complex.

But we can say with some certainty that the CNS does two basic functions:

1. Responding to the environment.
2. Adapting to the environment.

These two basic functions are essential in how drugs work.

It is the brain adapting to the influence of drugs that results in addiction.

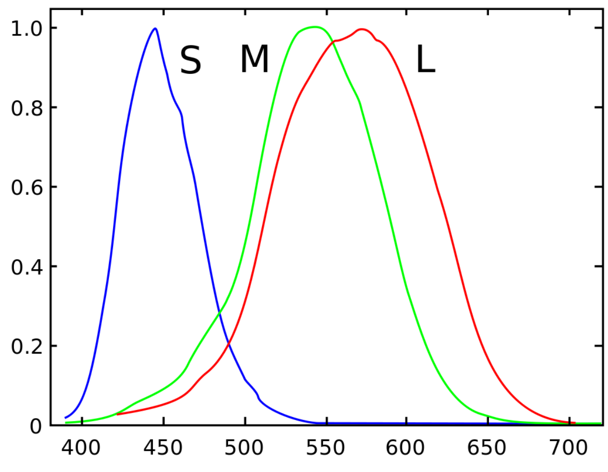


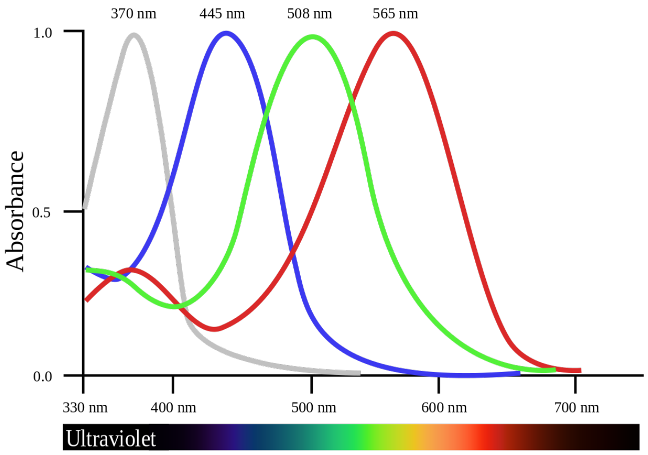
What does the Central Nervous System (CNS) do?

The CNS is how we interact with the environment.

Most of the CNS is involved in sensing, perceiving, and reacting.

But we are limited in our experience of the environment.





How does the Central Nervous System (CNS) do its job?

The CNS converts environmental stimuli into electrical and chemical signals.

All drugs change this activity.

But then so does every experience: every single experience changes the structure and function of the brain.

The brain changes. For us to experience anything at all, our brain needs to be changed by the experience.

Signal to noise ratio

For any experience to register with the CNS, the stimulus should produce a perceptible impact on the background activity of neurons.

So the signal must be greater than the background “noise”.

As such, the brain acts as a contrast detector. Experience is distinguished from monotonous activity.

The brain baseline activity must be stable

For any brain system to function, it is critically important that the baseline activity is maintained at a stable level.

Maintaining the stable baseline activity is an example of biological homeostasis.

Homeostasis

Homeostasis requires

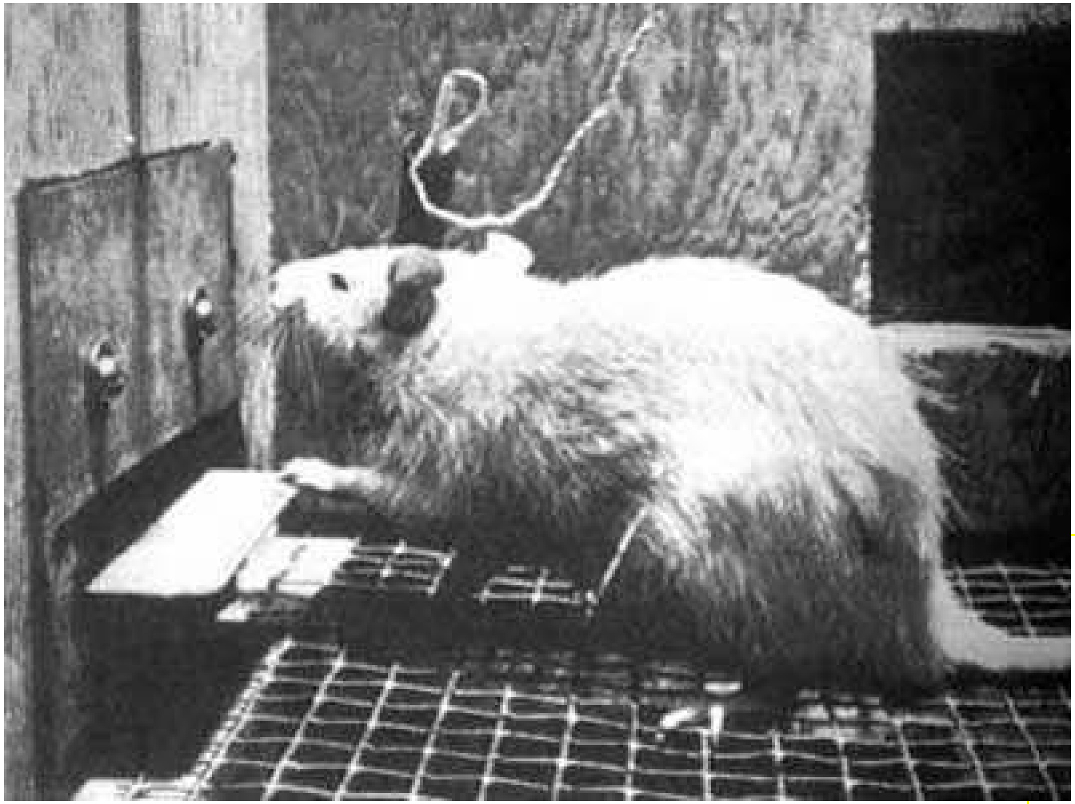
- A set point
- A comparator
- A mechanism of adjustment

Example: Maintaining the body temperature at ~37 °C.

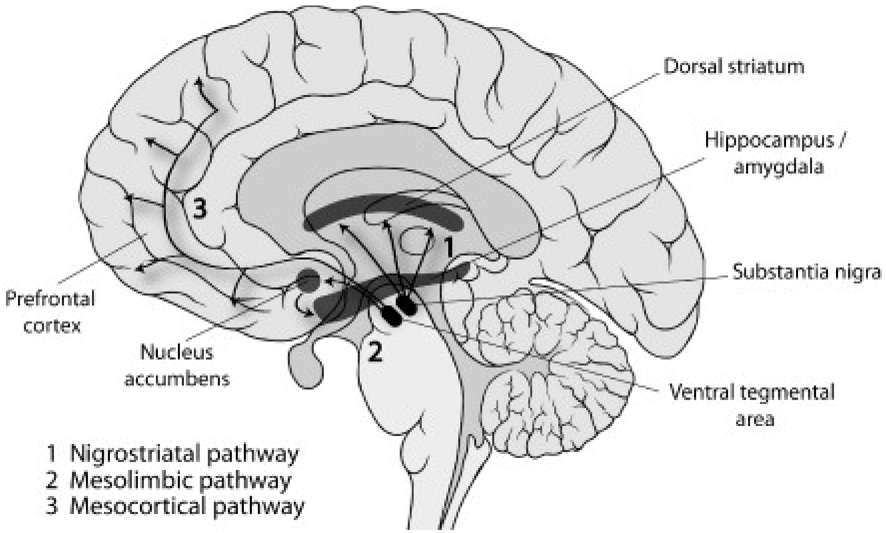
Feelings (emotions) are also tightly constrained under normal conditions. We can only detect good and bad feelings if there is a baseline OKness.

Drugs commandeer the brain's contrast detection mechanisms for pleasure.

The Olds and Milner Experiment:



The mesolimbic pathway



Drugs affect multiple brain circuits, and variation in their sites of neural action accounts for their different effects.

However, all addictive drugs are addictive because they share the ability to stimulate the mesolimbic dopamine system.

The mesolimbic dopamine pathway

A

When activity in the mesolimbic pathway is—either physically by severing neurons or pharmacologically with drugs that block dopamine—the subject is unable to experience pleasure. (*Anhedonia*)

This might seem like a cure, but it is ethically problematic. Such an intervention would prevent pleasure from all sources, including things like food and sex.

B

However, it doesn't work all that well for seasoned addicts who use mainly to avoid unpleasant symptoms associated with withdrawal rather than seeking a high.

Without dopamine in the nucleus accumbens, nothing would alleviate a persistently bleak existence.

The mesolimbic dopamine pathway

The mesolimbic system evolved to promote behaviors such as eating and sex.

But in general, the mesolimbic pathway conveys a transient good time, not a stable sense of hopefulness that would truly serve as an antidote to depression.

New evidence has shown that dopamine in the mesolimbic pathway works not by signaling pleasure but by signaling the anticipation of pleasure.

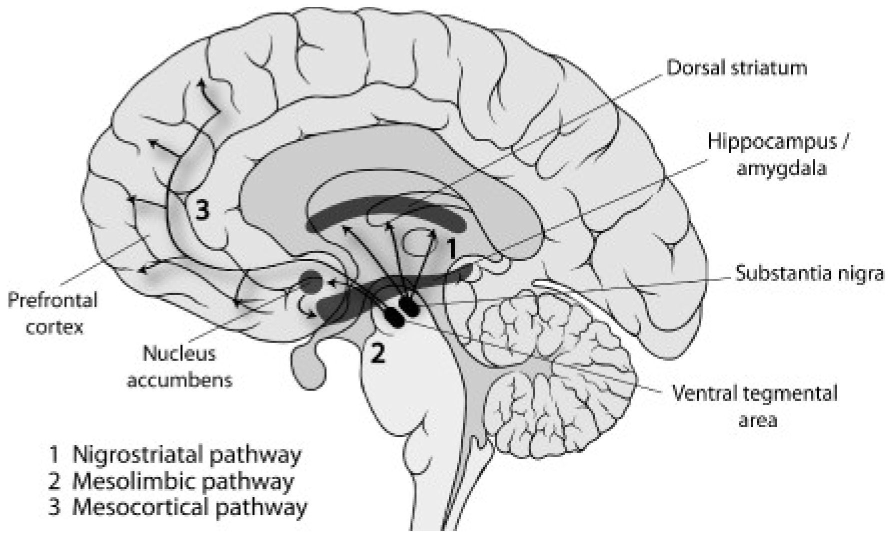
The nigrostriatal dopamine pathway

This is a second dopamine circuit that is involved in addiction.

It connects the substantia nigra dopaminergic neurons to the striatum.

The nigrostriatal pathway is essential for initiating movement.

Deficits of dopamine in this pathway leads to Parknison’s disease.



Biological actions of dopamine pathways

Many stimuli are natural reinforcers by acting on dopamine in both pathways.

Some are strong and obvious, such as food and sex.

Some are subtle, such as music and play.

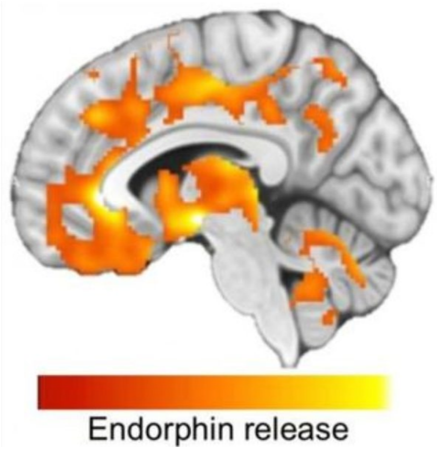
The effects of these stimuli are most often to release small transient dopamine in target regions.

Drug actions on dopamine pathways: Potency

Natural stimuli pale in comparison to the potency of drugs on dopamine pathways. (Why?)

Endorphins, e.g., stimulate dopamine release, in response to a variety of natural stimuli such as exercise or sweets.

Endorphin effects are nowhere near the sledgehammer effect of opiates derived from the extract of the poppy plant *Papaver somniferum*.



Drug actions on dopamine pathways: Timing

Natural stimuli produce a sequence of changes in neural pathways resulting in effects that are gradual and typically moderate and slow.

In contrast drugs act rapidly and directly to produce instantaneous changes in neurotransmitters, including dopamine.

Also the timing of exposure to drugs is unnatural in that the user controls the delivery timing of a drug.

The more frequent and predictable the delivery, the more addictive the drug.

The 3 laws of psychopharmacology

1. Drugs act by changing the rate of natural brain processes.
2. All drugs have side effects.
3. The brain adapts to a drug by counteracting the drug's effects.

1. Drugs act by changing the rate of natural brain processes.

Drugs can't do anything other than interacting with existing brain structures and function.

Therefore, drugs either speed up or slow down ongoing neural activity.

Every drug's chemical structure is complementary to the structure of some molecule(s) in the brain. The interaction of the drug with these molecules leads to its effects.

E.g. Δ-9-THC, nicotine and heroin respectively substitute for natural neurotransmitters anadamide, acetylcholine and endorphin and act with their receptors.

2. All drugs have side effects.

Unlike natural neurotransmitters, drugs are not precisely targeted to cells or circuits. They flood the system and act on all accessible targets.

E.g. serotonin (5HT) is involved in many behaviors (waking, aggression, sex, eating, mood). 5HT is naturally released at precise times and targets precise CNS structures.

But a drug that enhances or reduces 5HT acts in all places at once. Thus its effect on say enhancing mood also affects sleep and sexual function.

3. The brain adapts to and counteracts the drug's effect.

This concerns how the brain (dynamically) responds to drugs, rather than drugs acting on the (passive) brain.

Thus drugs and the brain have a bi-directional relationship.

Repeated administration of a drug that affects the brain leads the brain to adapt and compensate for the changes produced by the drug.

This change in behavior reflects the states of tolerance (we need more of the drug to achieve its effects) and dependence (without the drug we feel symptoms of withdrawal).

The brain's response to a drug is to promote the opposite state.

The only way for a regular user to feel normal is to take the drug.

Getting high becomes more and more short-lived and the purpose of using is to avoid withdrawal.