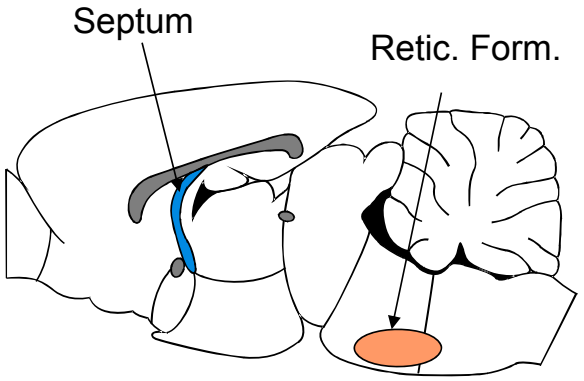
Reward Circuits and Drug Addiction (I) Ch.4

- Reward Circuits in the Brain
  - Intracranial Self Stimulation
  - The Mesolimbic Dopamine System
- Basic Principles of Drug Action
  - Tolerance, Withdrawal

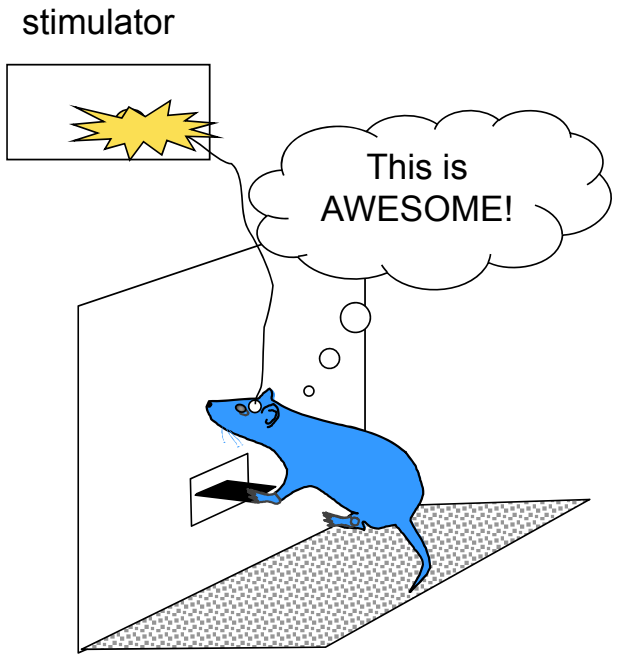
- Relevant parts of the textbook:
  - Ch. 4 pg 114-142 (From Section 4.3 on) and
  - Ch. 15, pg 502-503 (“Electrical stimulation of the brain…”)

A History of Reward Circuits



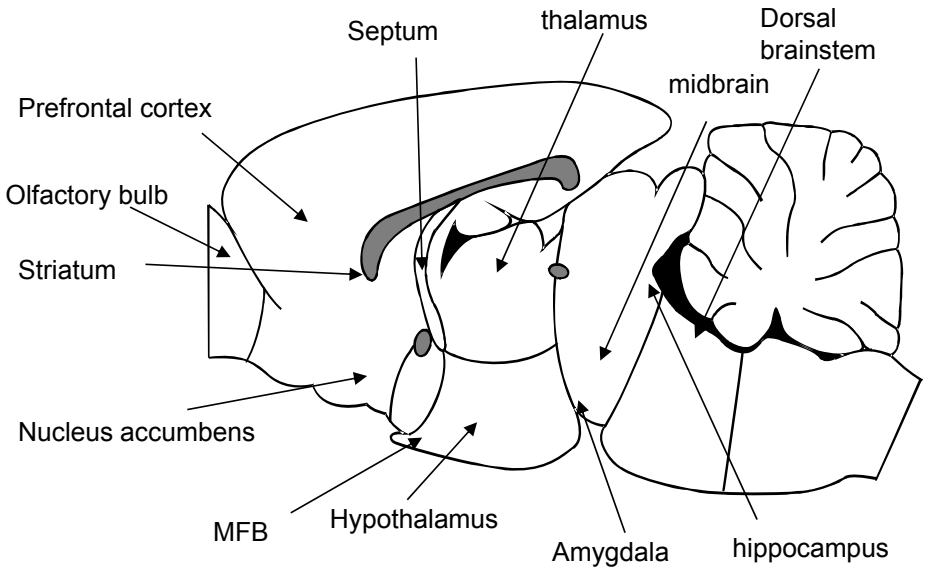
- Olds and Milner (1954) wanted to look at how stimulation of reticular formation could affect learning
- In a test to see if stimulation was aversive, one rat appeared to find it pleasurable
- Dozens of other rats did not show this effect
- Milner was trained as a social psychologist and was a bad surgeon: electrode was in the septum (more than half a brain away)
- Other rats with septal electrode implants (but **not reticular formation**) also appeared to find stimulation of that area rewarding

Intracranial Self Stimulation (I)



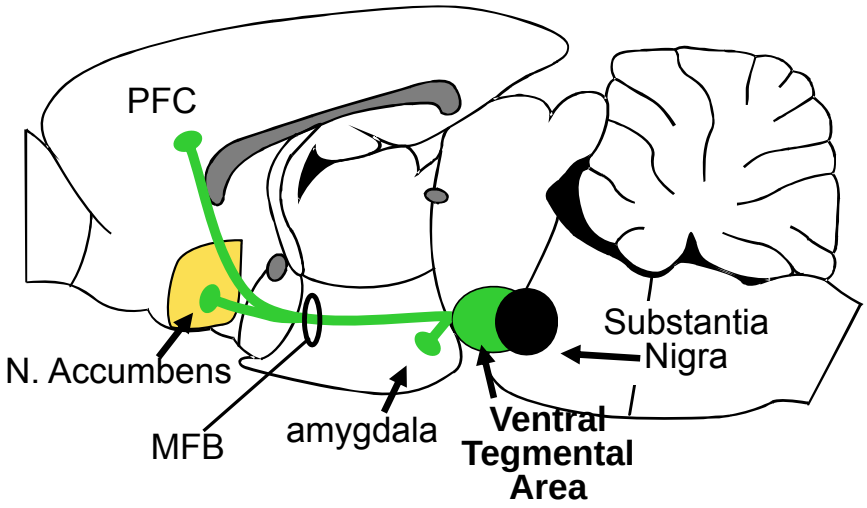
- This form of instrumental learning is acquired quickly and rats respond at very high rates (higher than for food)
- Rats will self stimulate until exhaustion- ignoring food/water to near death
- Will risk harm to obtain access to self stimulation

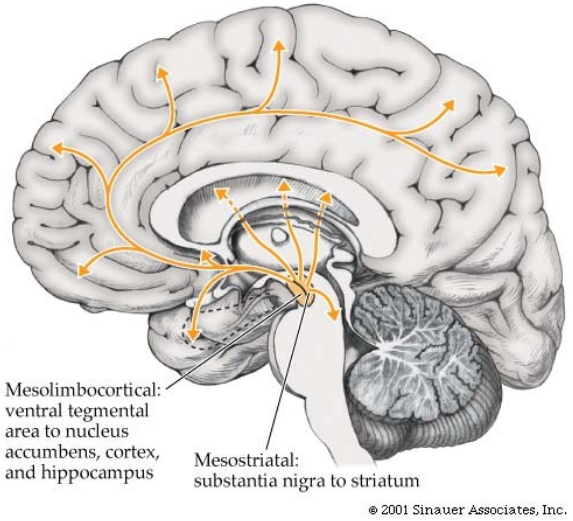
Intracranial Self Stimulation (II)



- Multiple brain sites found to support self-stimulation
- Not a ubiquitous phenomenon; some sites do not support self stim, and stimulation of some sites is aversive
- All brain regions that support self stimulation are directly/indirectly connected to the **mesolimbic dopamine system**

The Mesolimbic Dopamine (DA) System





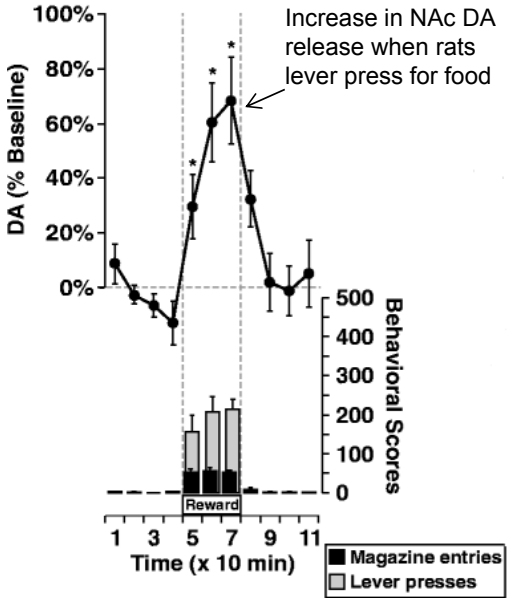
- DA neurons are **projection neurons**: all cell bodies located in midbrain, send axons to many brain regions. Substantia nigra sends DA axons to striatum, involved in motor functions
- **Ventral Tegmental Area (VTA)** is the heart of the mesolimbic DA system, sends DA axons via medial forebrain bundle to limbic regions such as prefrontal cortex, amygdala and **nucleus accumbens (NAc)** region of the ventral striatum

Mesolimbic DA and Reward

- Self stimulation **increases** DA release in the limbic system, particularly the accumbens,
- Reducing DA transmission **reduce** self stimulation
- Similarly, animals will work to have DA agonists infused directly into accumbens
- **Natural rewards, or conditioned stimuli associated with rewards** increased accumbens DA release

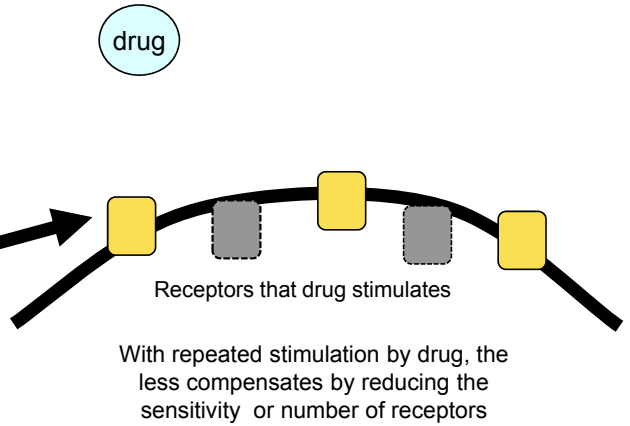
➢ **These and other findings suggest DA plays an important role in reward-related approach behaviors**

- ALL DRUGS OF ABUSE with high-addiction potential (opioids, psychostimulants, nicotine, alcohol) increase DA release in the nucleus accumbens (through different mechanisms)



Principles of Drug Action (I)

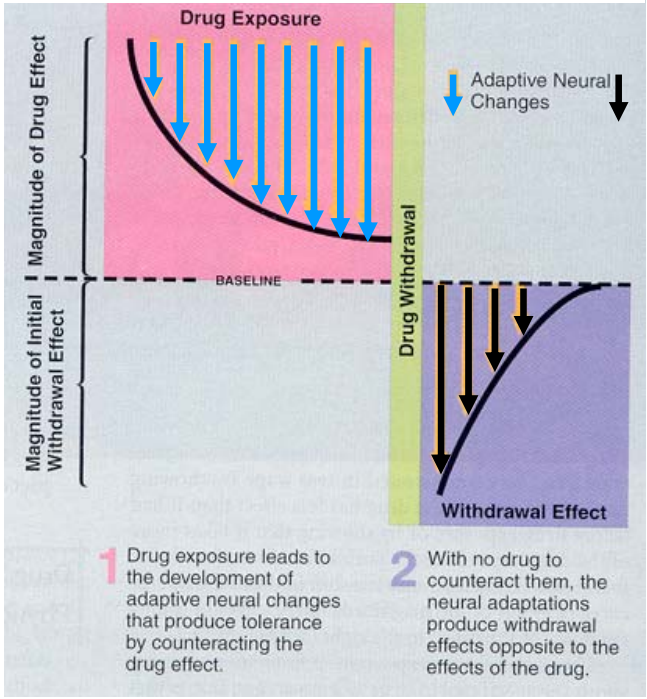
- **Tolerance**: Decreased sensitivity to effects of drug after repeated use. Two types:
  - ***Metabolic***: Body (liver) becomes more efficient at metabolizing drug, less drug gets to sites of action
  - ***Functional*** (Pharmacodynamic): occurs at site in brain/body where drug exerts its effects (eg; receptor # decreases)



- Tolerance develops to some effect of drugs, not others, and can develop at different rates for different effects
  - eg: heroin causes euphoria and can suppress respiration.
  - Tolerance to pleasurable effects develops faster than to respiratory effects. Heavy users increase dose to obtain a better high, but this can lead to overdose by over-inhibiting respiratory centers.

Principles of Drug Action (II)

- **Withdrawal:** Rebound reaction to elimination of drug from system after repeated exposure.
- Typically opposite of the drugs action.
  - e.g.: after prolonged exposure to sleeping pills, withdrawal causes insomnia
- May be viewed as body's attempt to maintain homeostasis.
  - Drugs cause body/brain to initiate compensatory changes to counteract the effects of the drug (i.e.; **tolerance).**
  - When drugs have been eliminated from system, these changes can linger for sometime after = [withdrawal symptoms]



➢ **Additional drug taking can alleviate withdrawal**

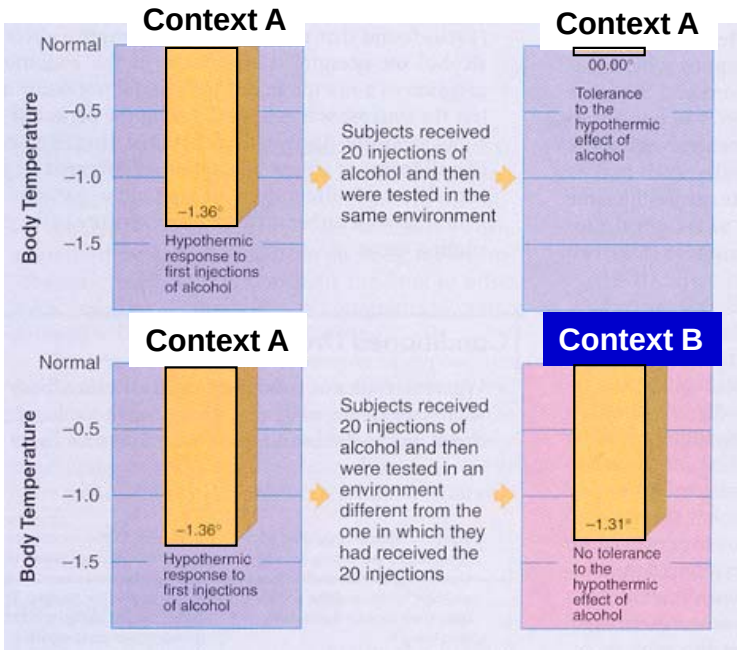
•Individuals suffering from withdrawal symptoms are said to be **physically dependent**

— severity of symptoms depends, but usually longer/greater exposure = greater withdrawal symptoms.

Principles of Drug Action (III)

- Pavlovian conditioning can heavily influence tolerance/withdrawal
  - Drug effects can serve as conditioned stimuli. Brain will make associations between the drug effects and the context where they occurred

- **Conditioned tolerance**: Tolerance is maximal when drug is administered in environments similar to those where drug effects were experienced previously.

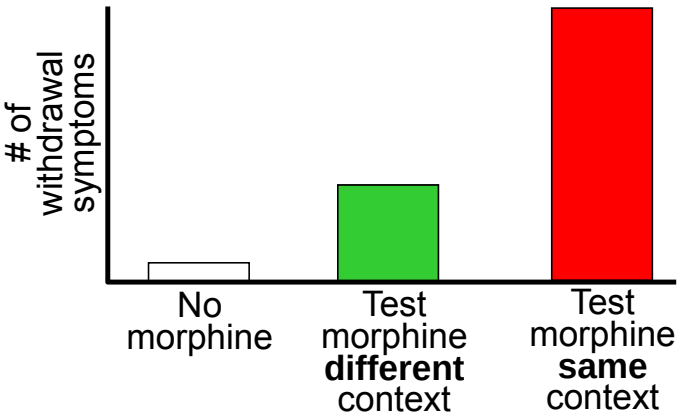


- ***Study***: Alcohol causes hypothermia. Give rats 20 shots of alcohol in one environment (over 20 days). On test day, one group gets alcohol in same context, other group gets it in different context.

➢ Rats receiving test day in same context displayed tolerance, those in different context did not

Principles of Drug Action (IV)

- **Conditioned withdrawal:** Withdrawal elicited by the drug environment or drug associated cues.



Study: looked at morphine withdrawal. 3 groups of rats

1) never received morphine
2) Received repeated injections of morphine in one context, withdrawal test assessed in **different** context
3) Received repeated morphine in one context, withdrawal test assessed in **same** context

- Withdrawal was maximal when animals were in same context where drug effects were previously experienced
- Suggest that exposure to drug-related cues can induce conditioned compensatory responses