How Opioids Work on the Brain

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How Opioids Work on the Brain

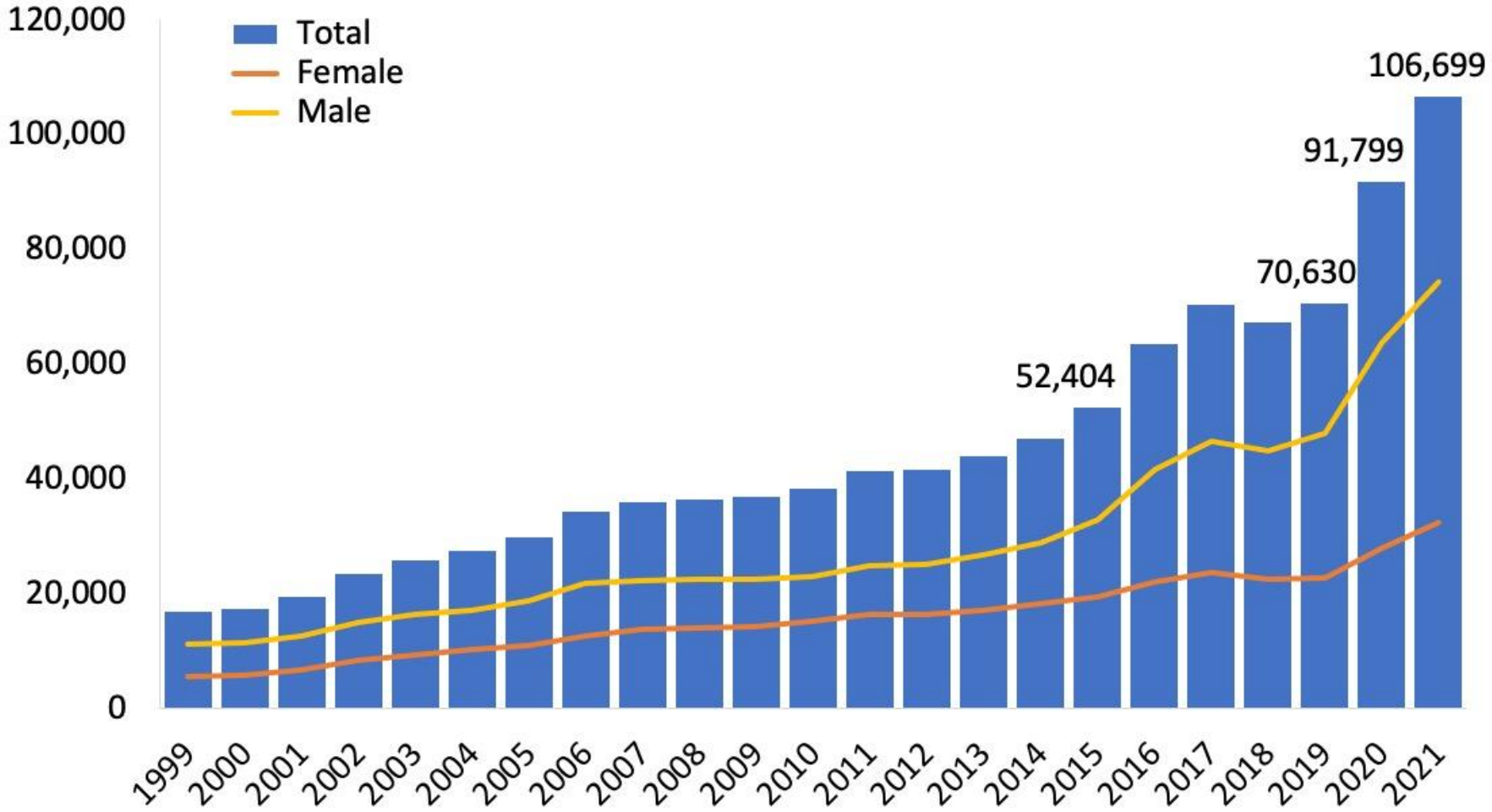
- Overview:
  - Brief review of the current opioid epidemic
  - Basic review of neuroanatomy, with a focus on key brain structures affected by opioids
  - Discussion on how opioids are absorbed by the body, used by the brain, and eliminated from the body

Human Side

Motor Vehicle Accidents

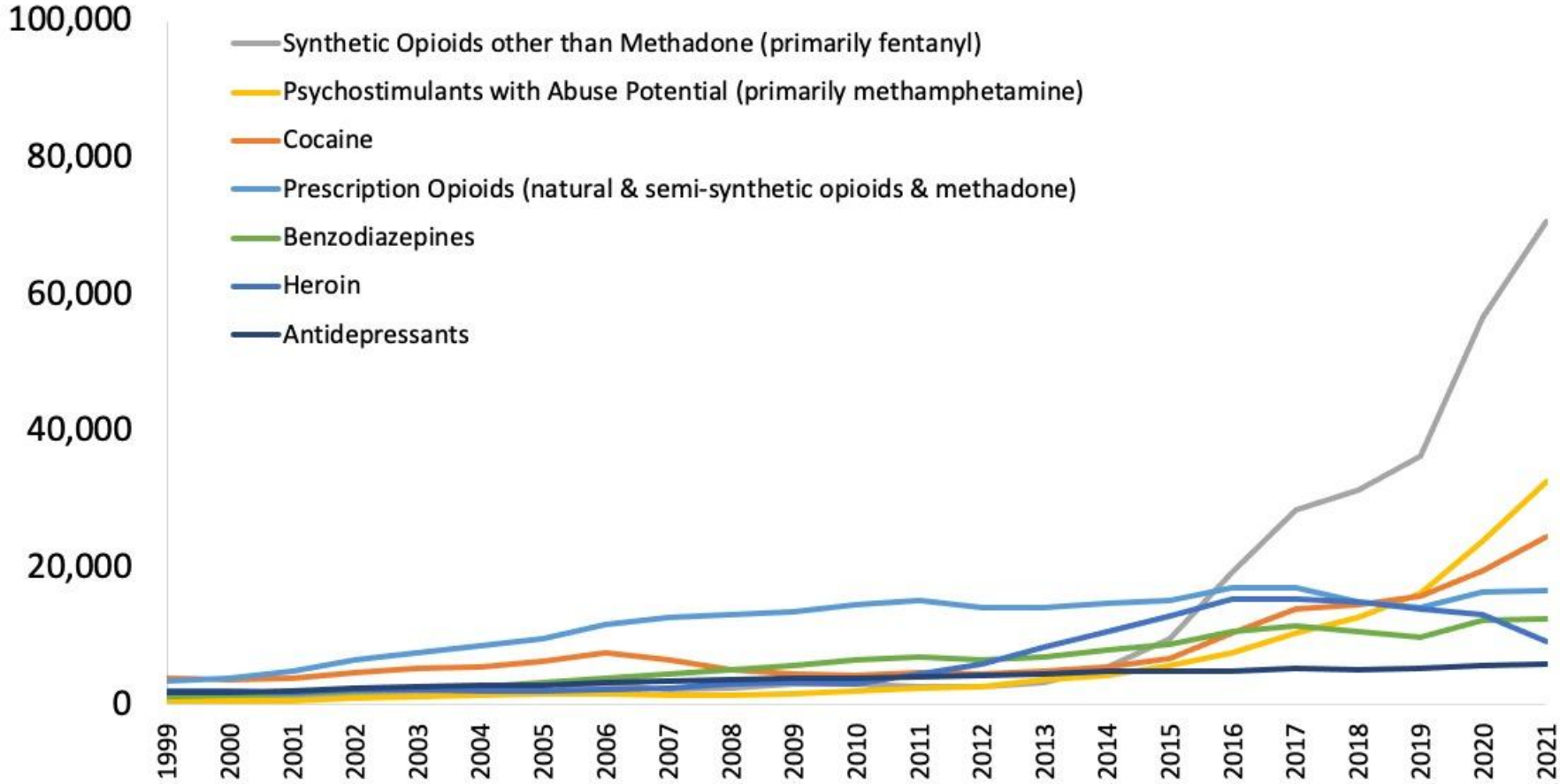
- U.S. population: ~330 million
- How many people do you think die in a car accident in the U.S. each year?

Figure 1. National Drug-Involved Overdose Deaths*, Number Among All Ages, by Gender, 1999-2021



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2021



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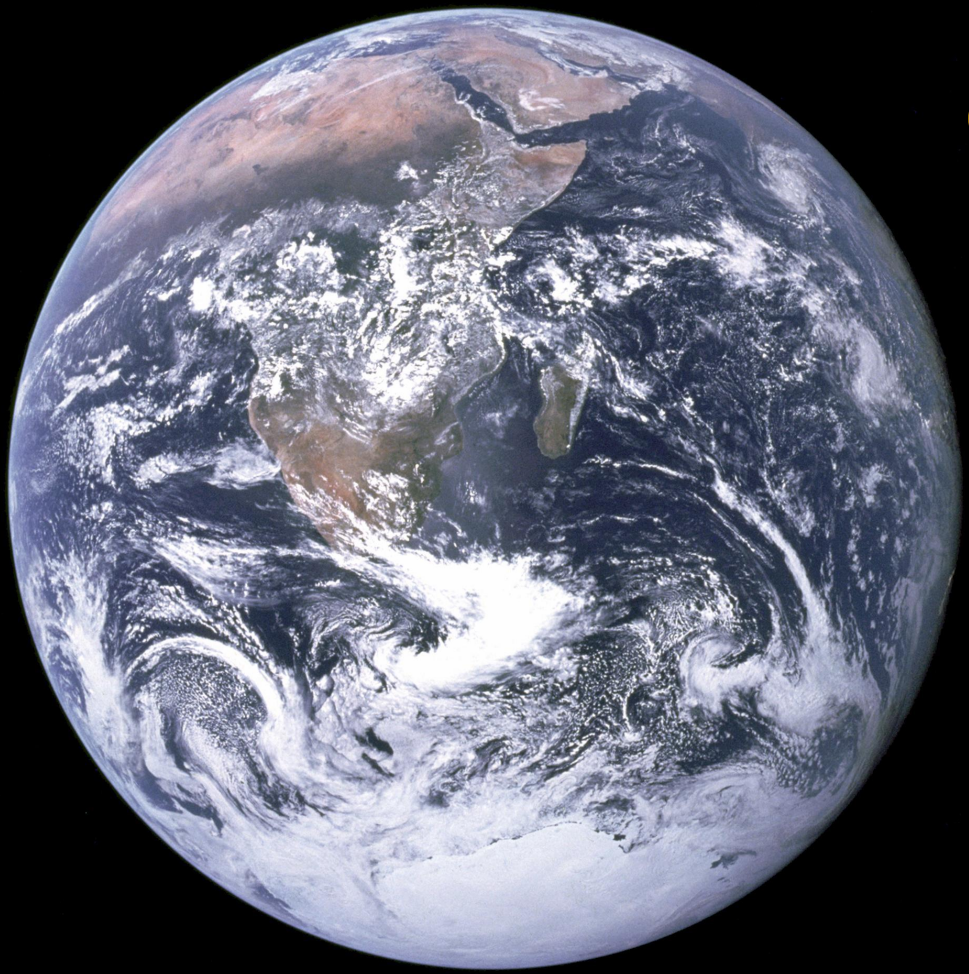
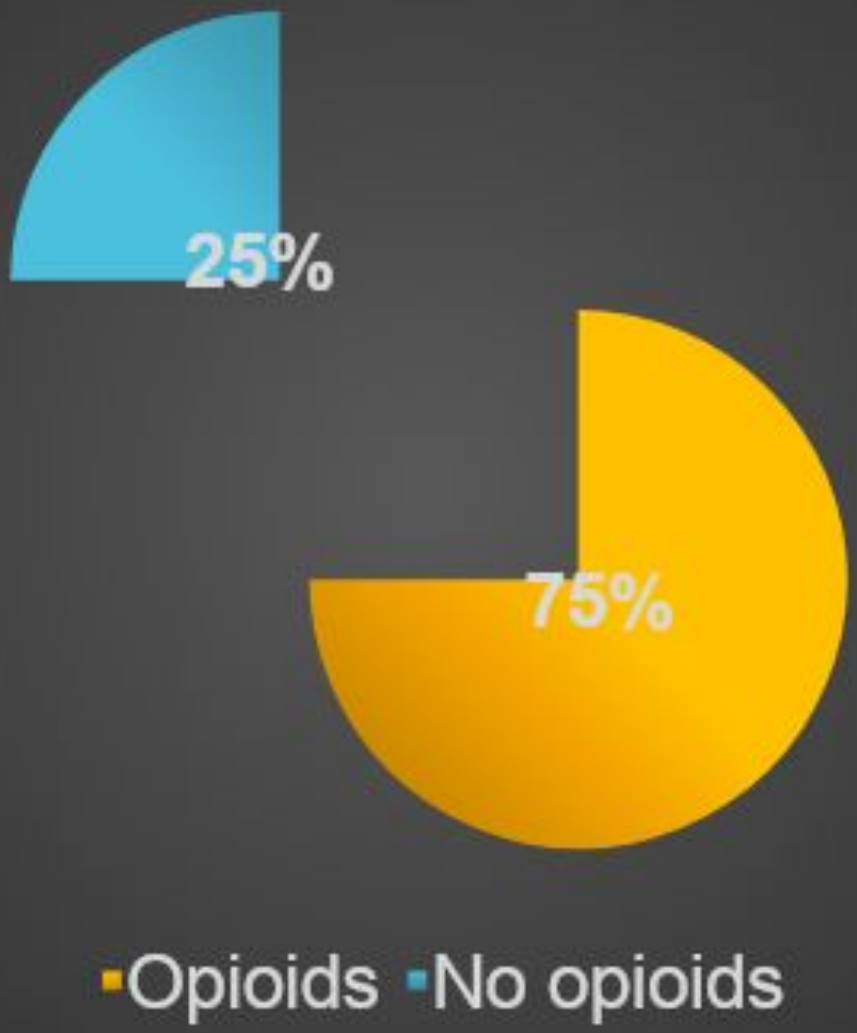
Overdose Deaths vs. Homicide



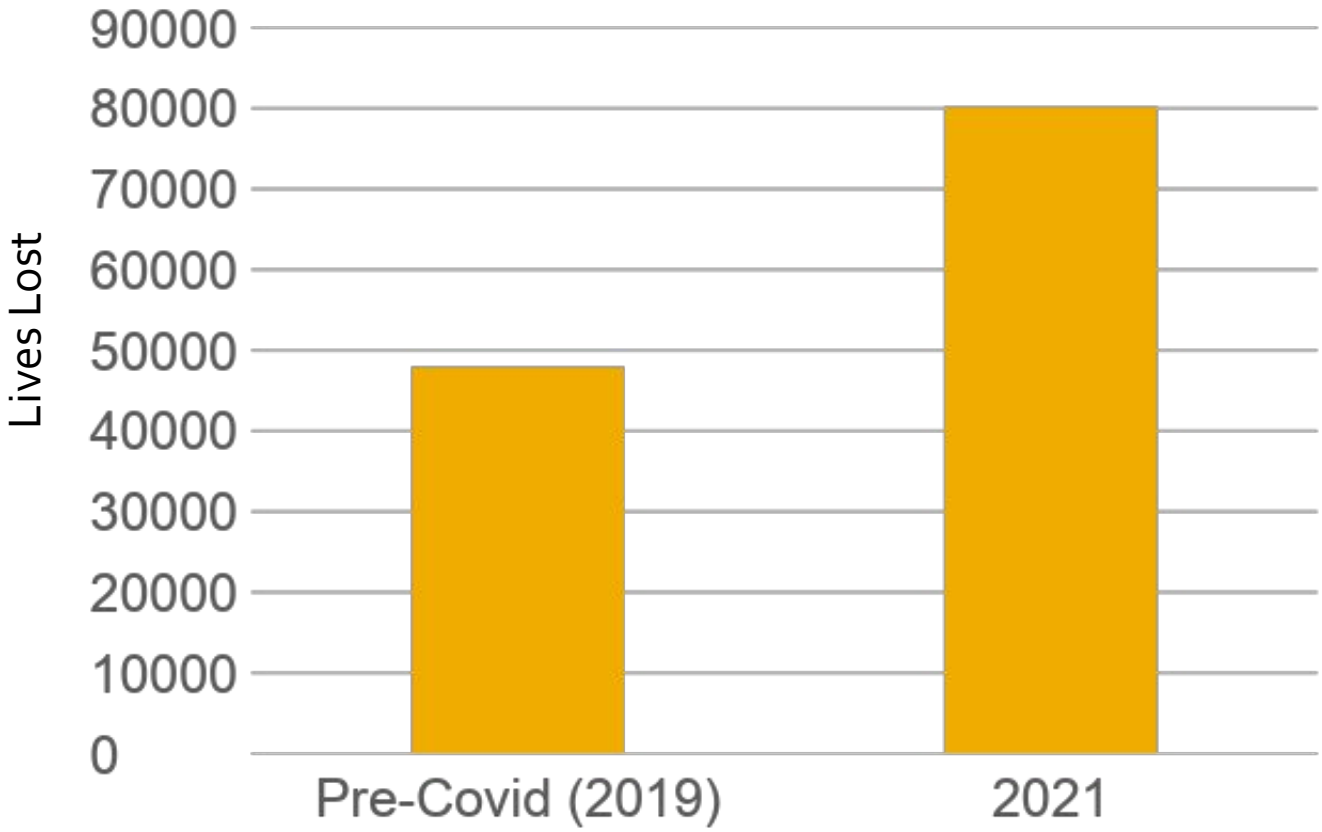
Overdose = ~107,000

Homicide = ~26,000

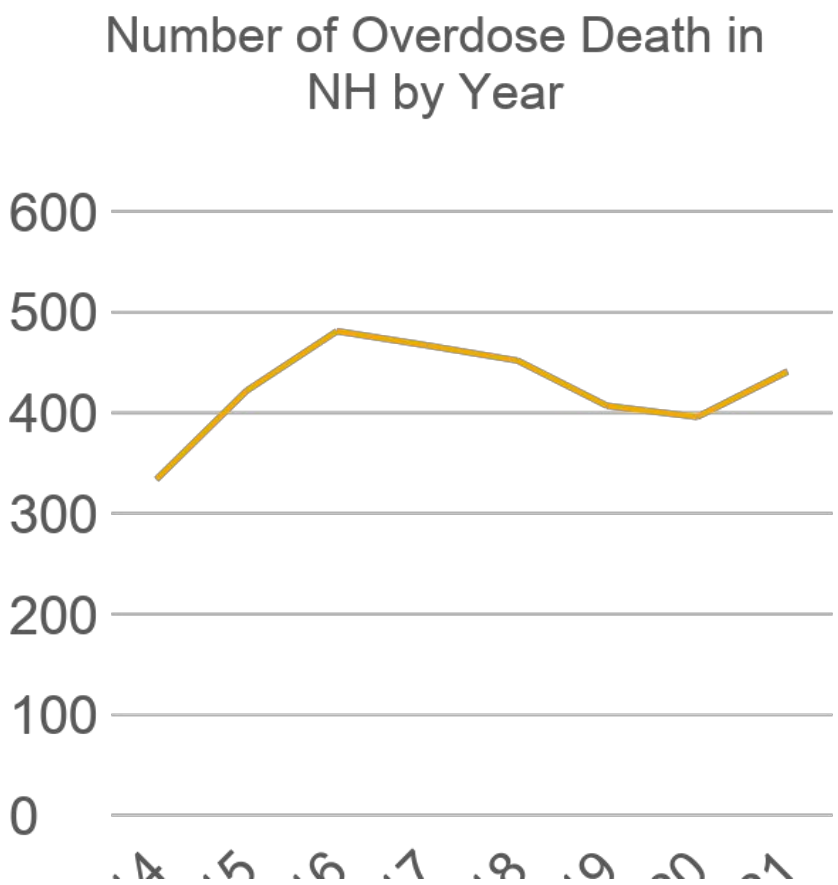
Majority of Overdose Deaths Involve Opioids



Opioid Deaths in U.S

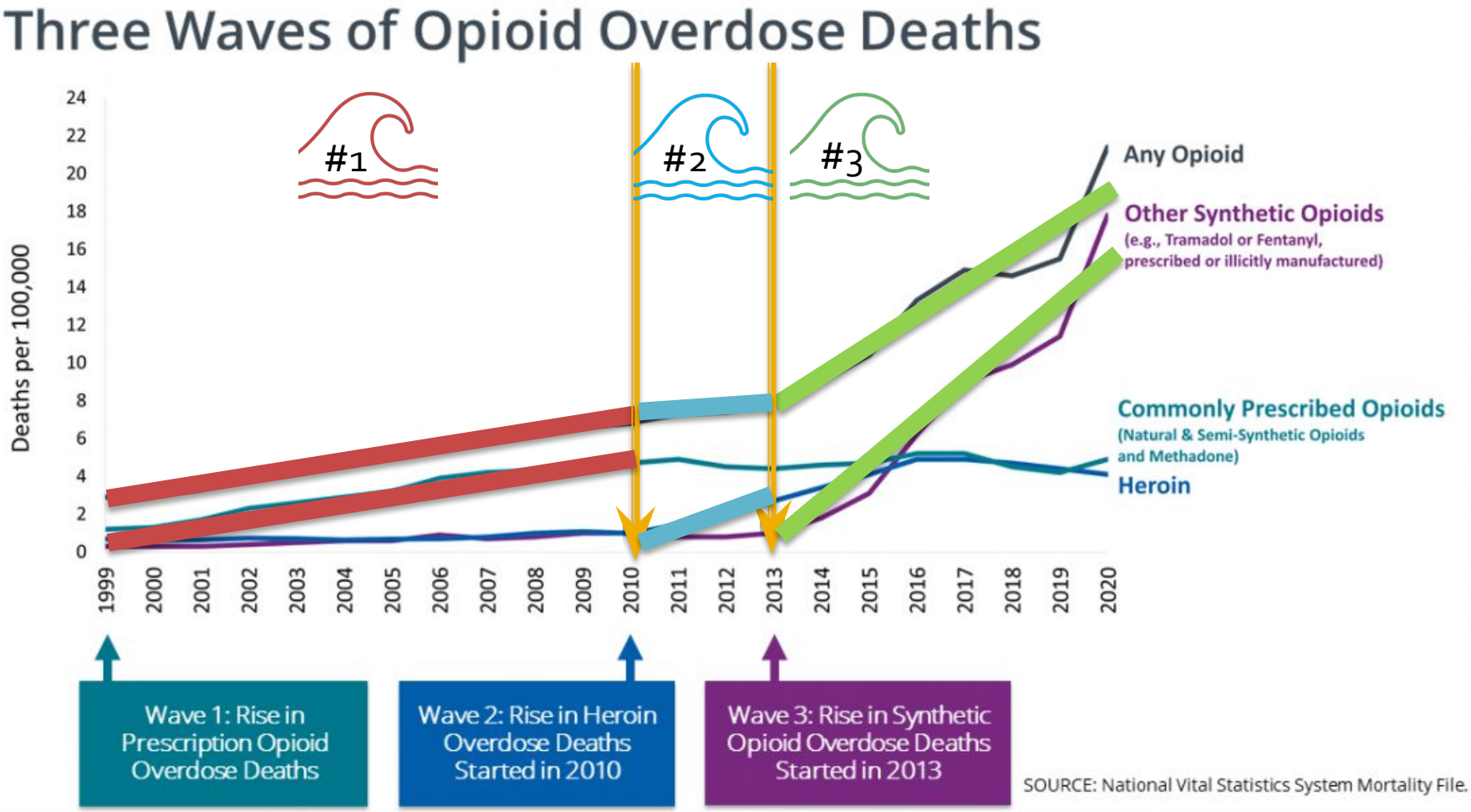


Overdose Deaths NH



Year	State Ranking Rate per 100,000
2014	3rd most
2015	2nd most
2016	3rd most
2017	5th most
2018	6th most
2019	9th most
2020	22nd
2021	23rd

Types of Opioids Causing these Deaths



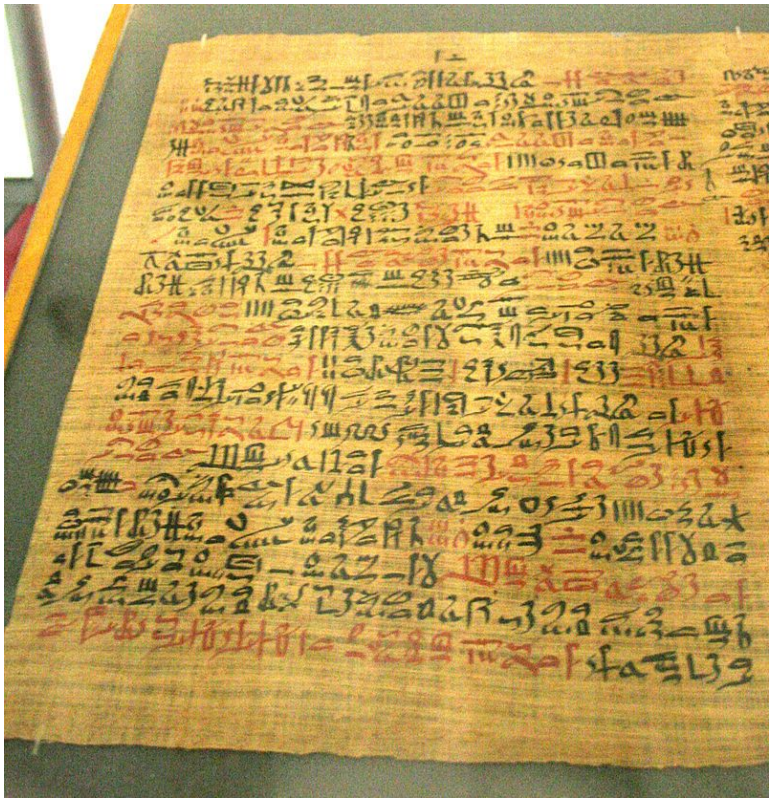
Opioids Originally Came from the Poppy Plant

The “milk” is gathered

Turned into heroin & other drugs

Brief Opioid History

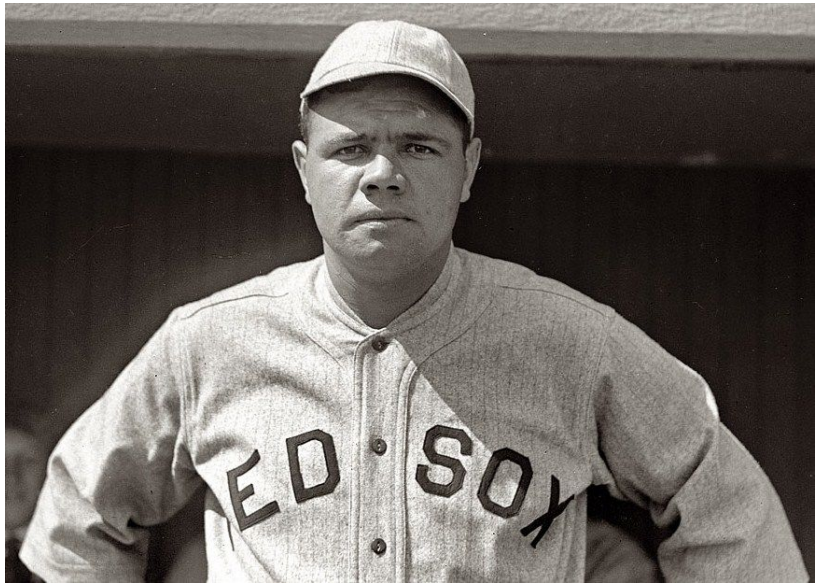
- Opium was listed in the Ebers Papyrus, which was written about 3,500 years ago in ancient Egypt.
- In the 1800's, opium became a major recreational drug in Europe and the United States. Available by mail order.
- The discovery of morphine in 1803 as the principal active ingredient in opium revolutionized medical treatment of pain and chronic diseases.



Ebers Papyrus

Major opioid laws in the 1900s

- Prior to the 1900's opioids were widely available and were not regulated in the U.S.
- In 1906 the Pure Food and Drug Act was passed, which stated that addictive drugs must be accurately listed on the product's label.
- In 1914 the Harrison Act was passed, which regulated and taxed the opiates and products made from coca leaves.
- The Comprehensive Drug Abuse Prevention and Control Act of 1970, set up the five schedules of drugs that we still use today.



Historical context: Babe Ruth make his major league debut with the Boston Red Sox in 1914

There are many opioids

- A few common opioids include:
  - Codeine
  - Fentanyl
  - Heroin
  - Hydrocodone (Vicodin)
  - Morphine
  - Oxycodone (OxyContin, Percocet)
  - Subutex
  - Tramadol

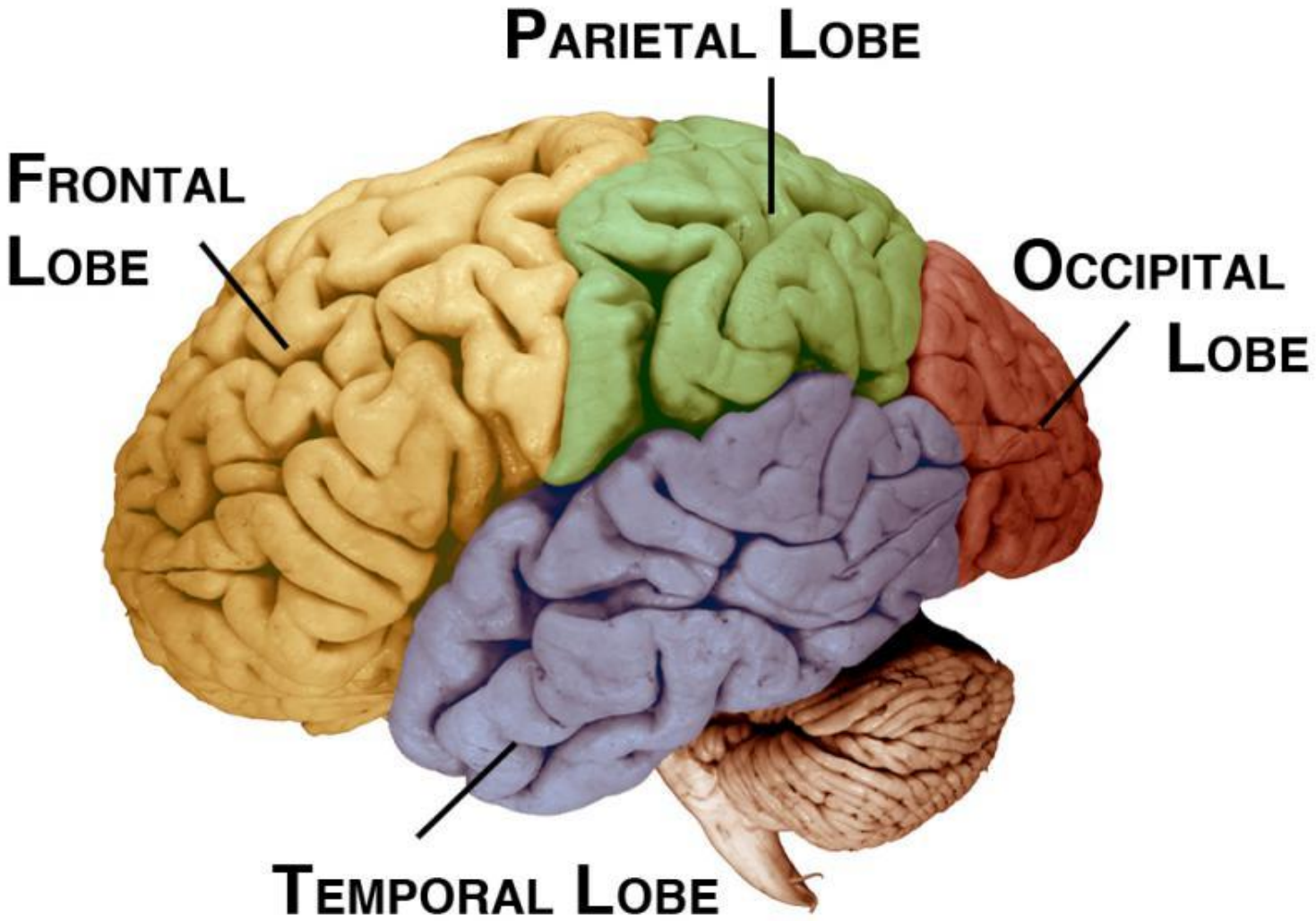
U.S. opioid laws after 1970

- The Comprehensive Drug Abuse and Prevention Act of 1970, set up the five schedules of controlled substances we use today. Importantly, drug enforcement shifted from the Treasury Department to the Justice Department.
  - Schedule I: Heroin
  - Schedule II: Vicodin
  - Schedule III: Subutex
  - Schedule IV: Tramadol
  - Schedule V: Low doses of codeine in cough syrup

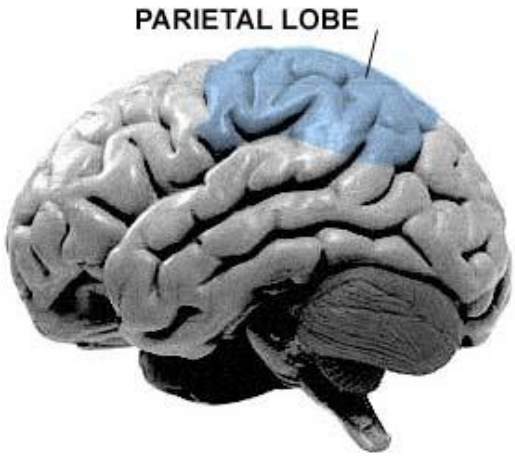
Primary effects of opioids

- Pain relief
- Euphoria
- Constipation
- Respiratory depression
- Decreased sex drive
- Skin flushed and warm
- Cough suppression

Major Regions of the Brain

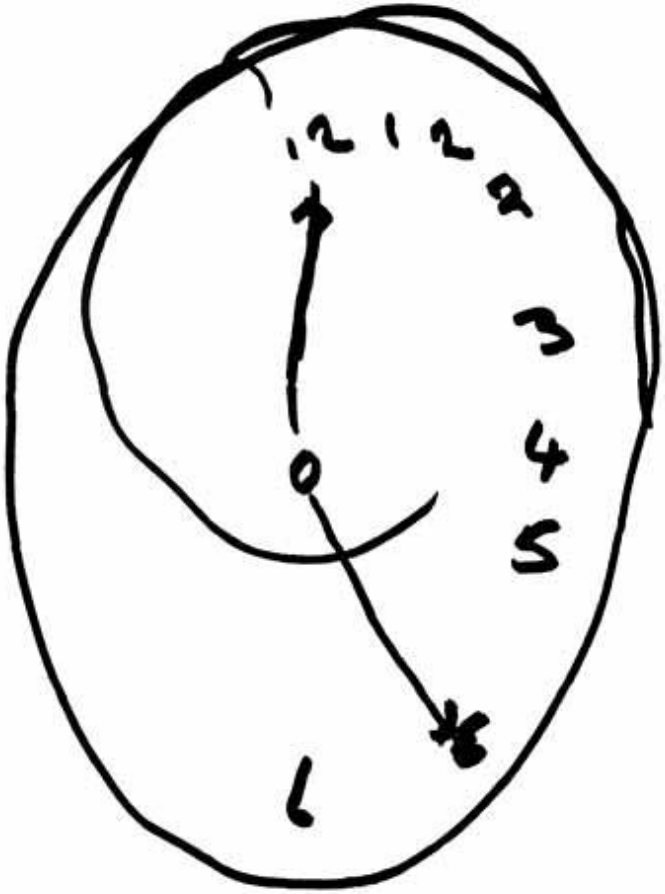


Parietal Lobe



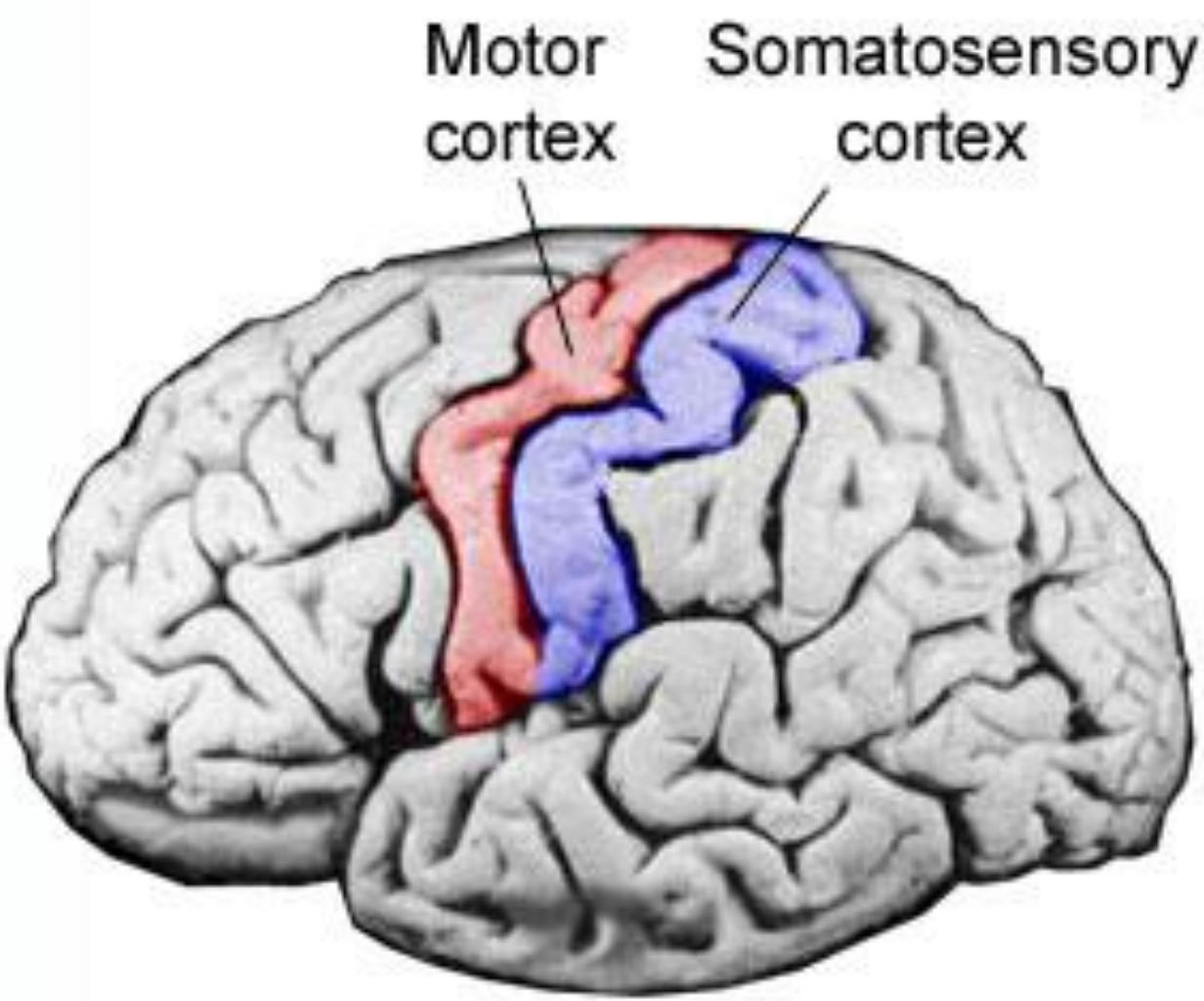
- Located behind the central sulcus
- Sense of touch and pain
  - Primary somatosensory cortex
  - Pain is inhibited due to the disruption of neurons in this area.
- Also controls visual attention

Visuospatial Neglect



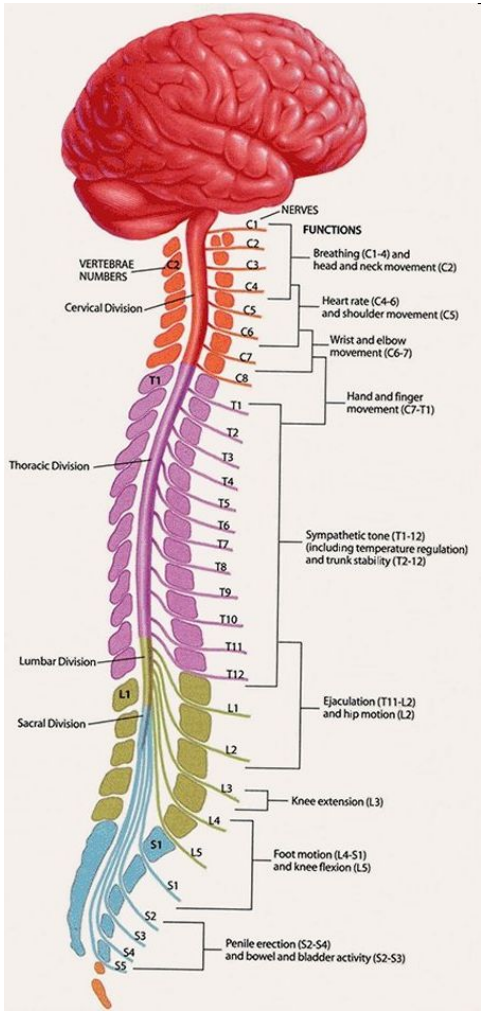
Somatosensory Cortex

Location where the pain signal is processed



Ascending Spinothalamic tract

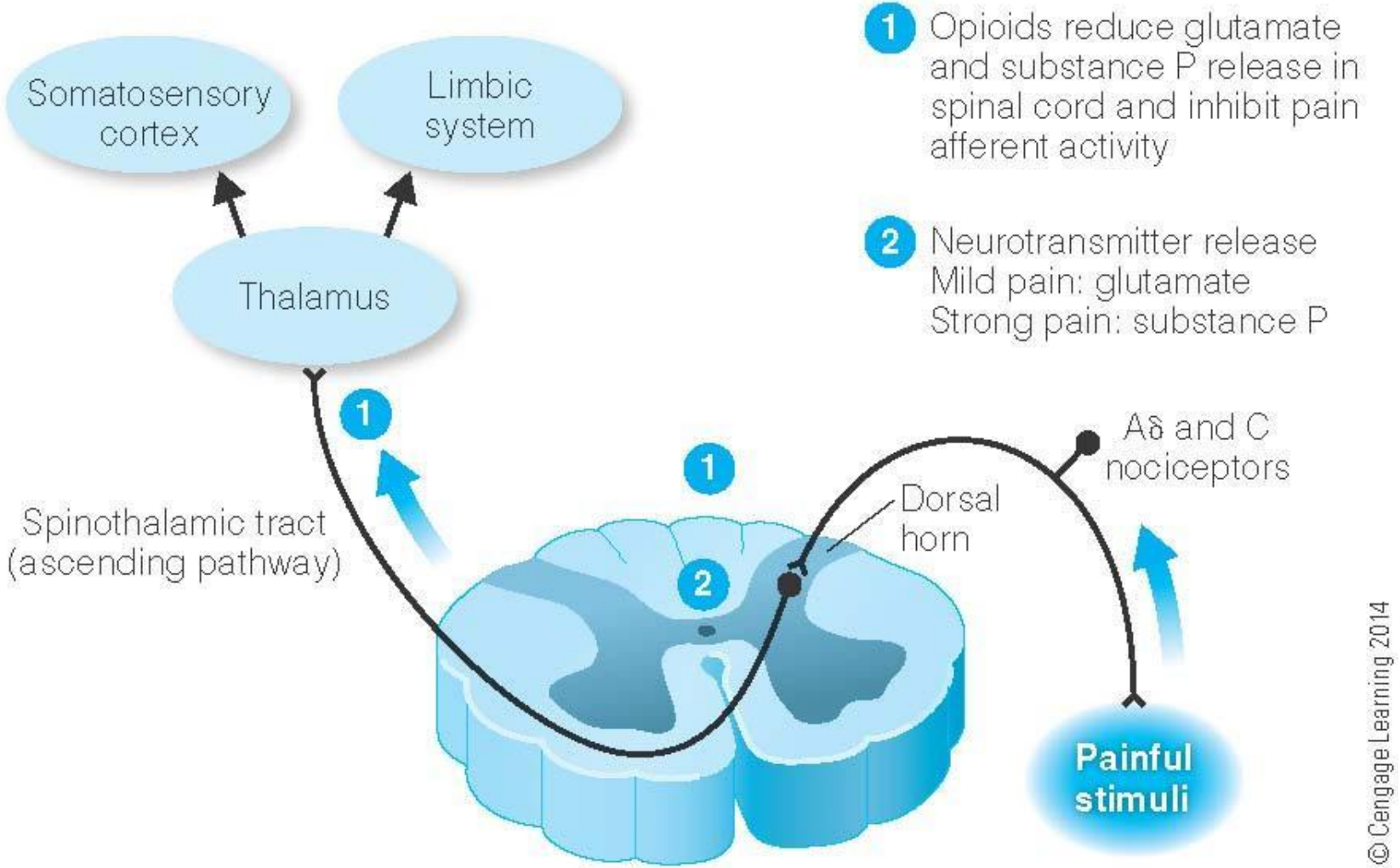
- Somatosensory receptors synapse with neurons into <u>two primary pathways</u> that transmit information from the spinal cord to the thalamus and then the cortex.
- In both pathways information travels to the contralateral hemisphere.
- The two system carry different information to the brain



Ascending Spinothalamic tract

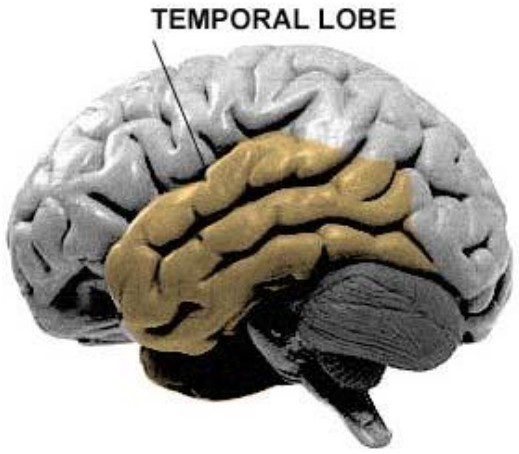
- Ascending spinal-thalamic tract – carries information related to pain and temperature.
  - Information crosses to the contralateral side at the spinal cord
  - Travels parallel to the spinal cord
  - Pathway: Pain or temperature is felt travels up the spinal cord to the thalamus primary somatosensory cortex

Ascending Spinothalamic tract



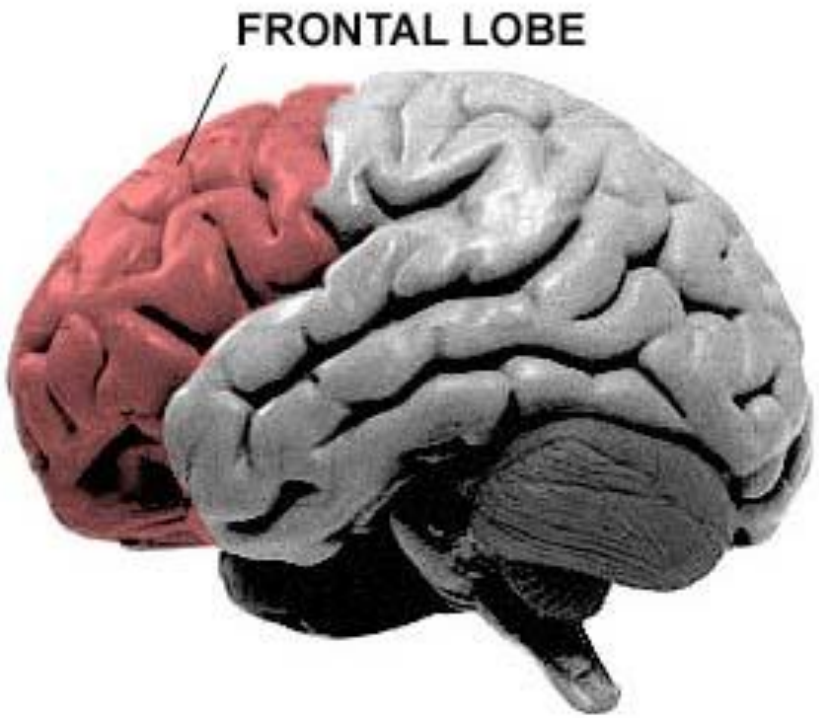
Temporal Lobe

- Involved in hearing, language comprehension
- The hippocampus is buried deep in the temporal lobe and plays a vital role in learning and memory
  - Memory is often impaired while on opioids



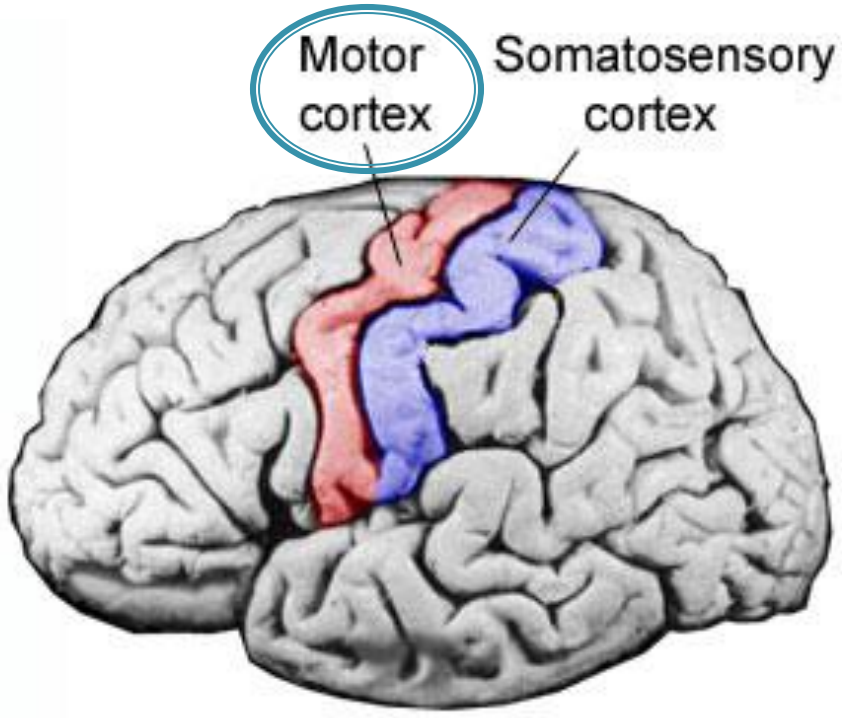
Frontal Lobe: General Functions

- Emotional control
- Executive functions
- Higher-order intellectual functions
- Personality
- Processing emotional memories
- Voluntary movement
- Verbal Fluency
- Working memory



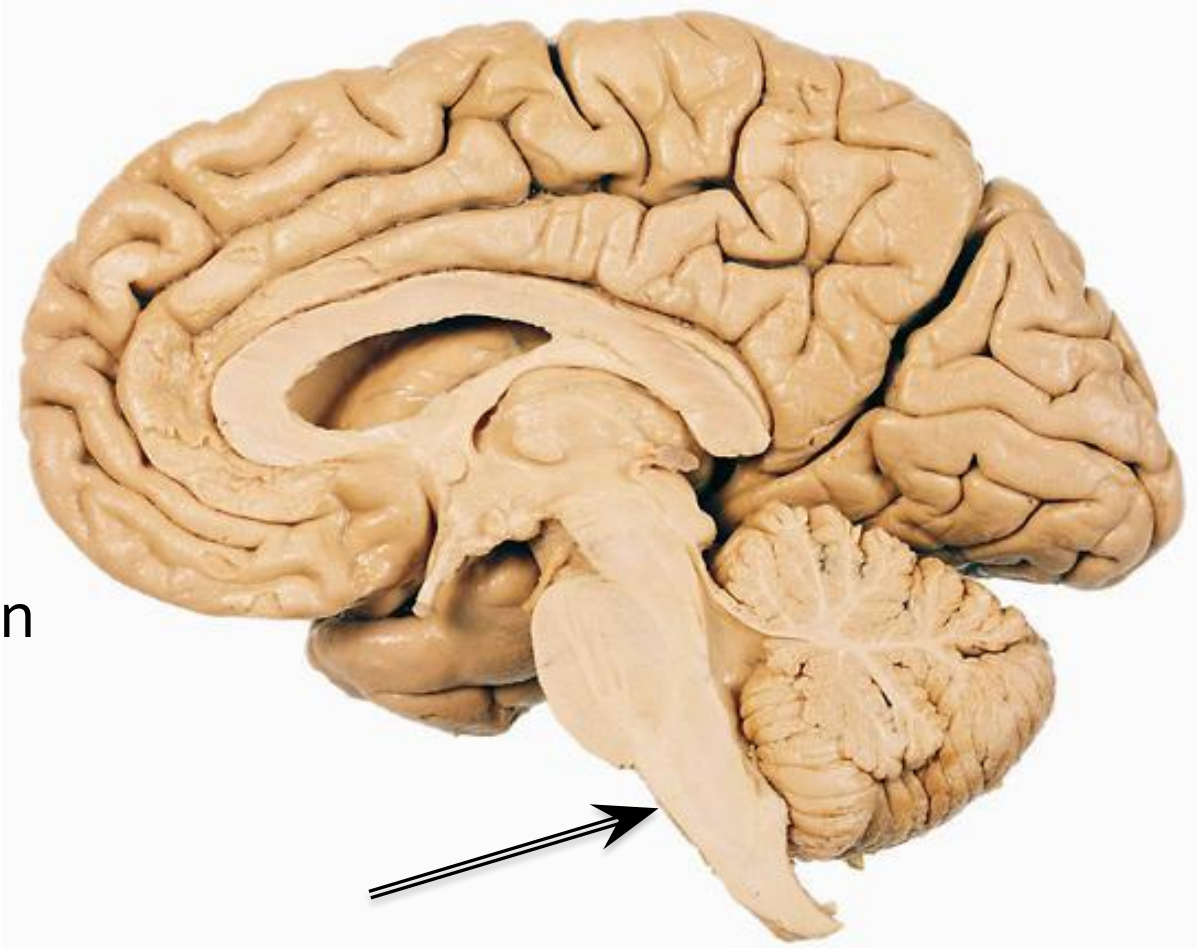
Frontal Lobe: General Functions

- Origin of descending motor pathways
- Involved in the initiation of voluntary movement



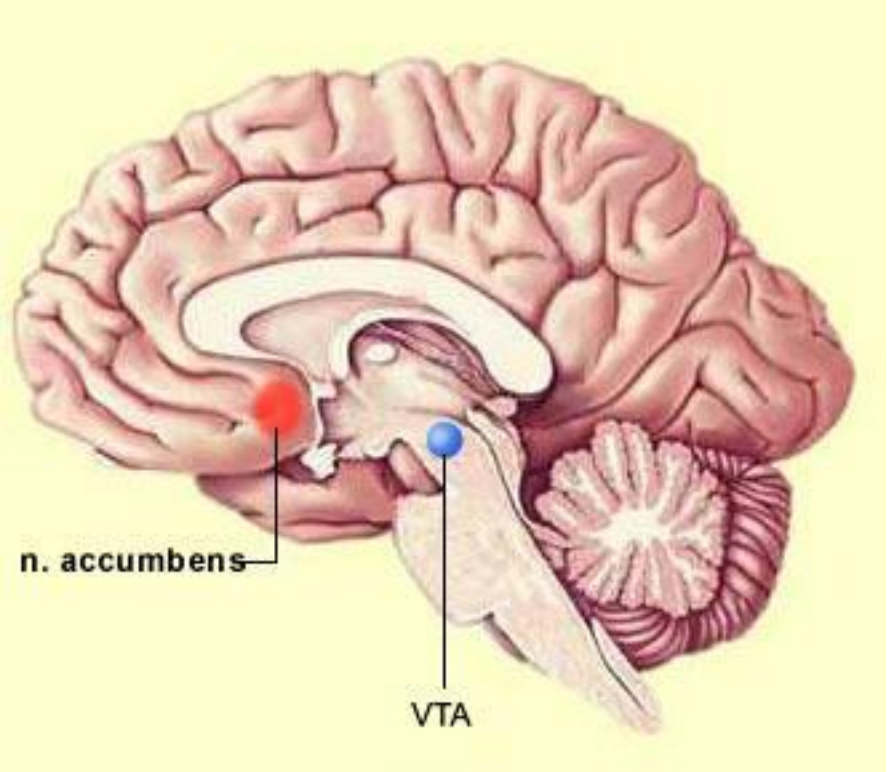
Medulla Oblongata

- Function: Vitals
  - Respiration
  - Blood pressure
  - Heart rate
  - Vomiting
- Damage or inhibition of neurons
  - Life-threatening

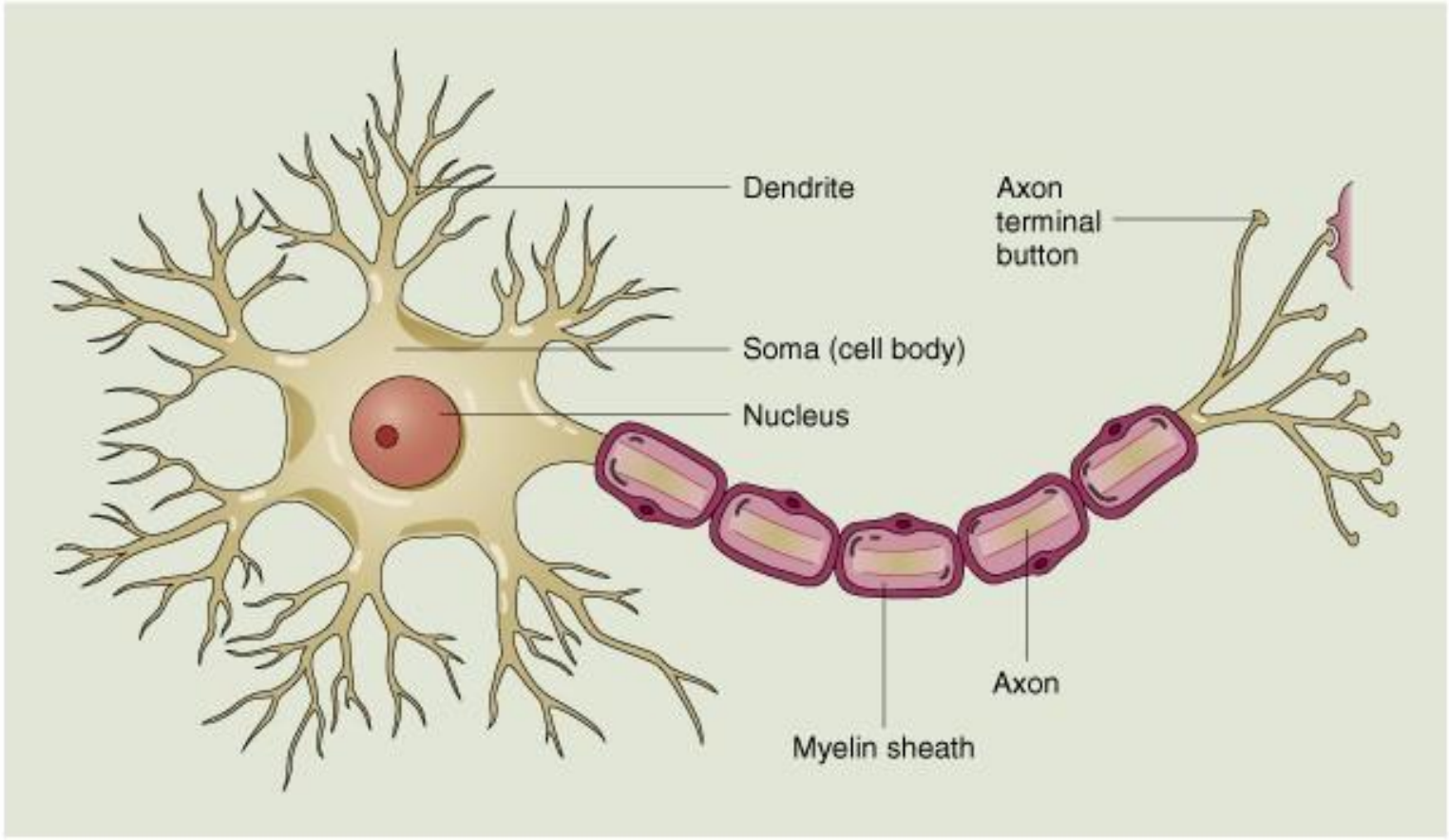


Ventral Tegmental Area & Nucleus Accumbens

- Implicated in addiction
- Is the "reward circuitry" of the brain.
- The ventral tegmental area (VTA) is in the midbrain.
- The VTA projects to several areas of the brain, including the nucleus accumbens.
- There is structural volume loss in this region with repeated heroin administration.



Neuron



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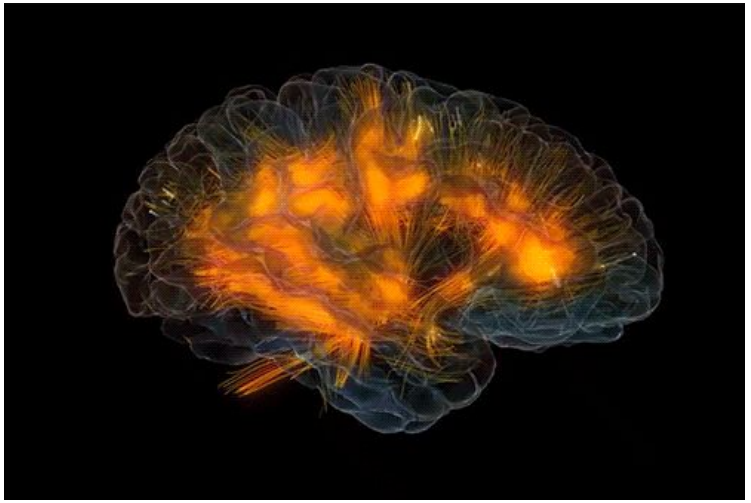
Neurons: Receptors

- On neurons there are receptors for chemicals (neurotransmitters, opioids, etc..)
- Drugs bind to these receptors and allow ions in and out of the neuron. This movement of ion changes the electrical charge of a neuron.

Opioid receptors are found throughout the brain

- Opioid receptors are found in many areas of the brain..
  - Brainstem
    - Medulla
    - Pons
    - Midbrain
  - Amygdala
  - Hippocampus
  - Hypothalamus
  - Thalamus
  - Cerebellum
  - Nucleus accumbens
  - Ventral tegmental area
  - Frontal, parietal, temporal, and occipital lobes
  - Regions of the prefrontal cortex



Opioids work by making changes to neurons

- **Resting Potential:** slight electrical imbalance caused by different ions inside and outside the neuron.
- Some ions want to enter into the neuron and some want to leave. The **Cell Membrane** helps maintain this balance.
- At rest the inside of the neuron is negative at about -70mv.

Outside the Axon Positive charge

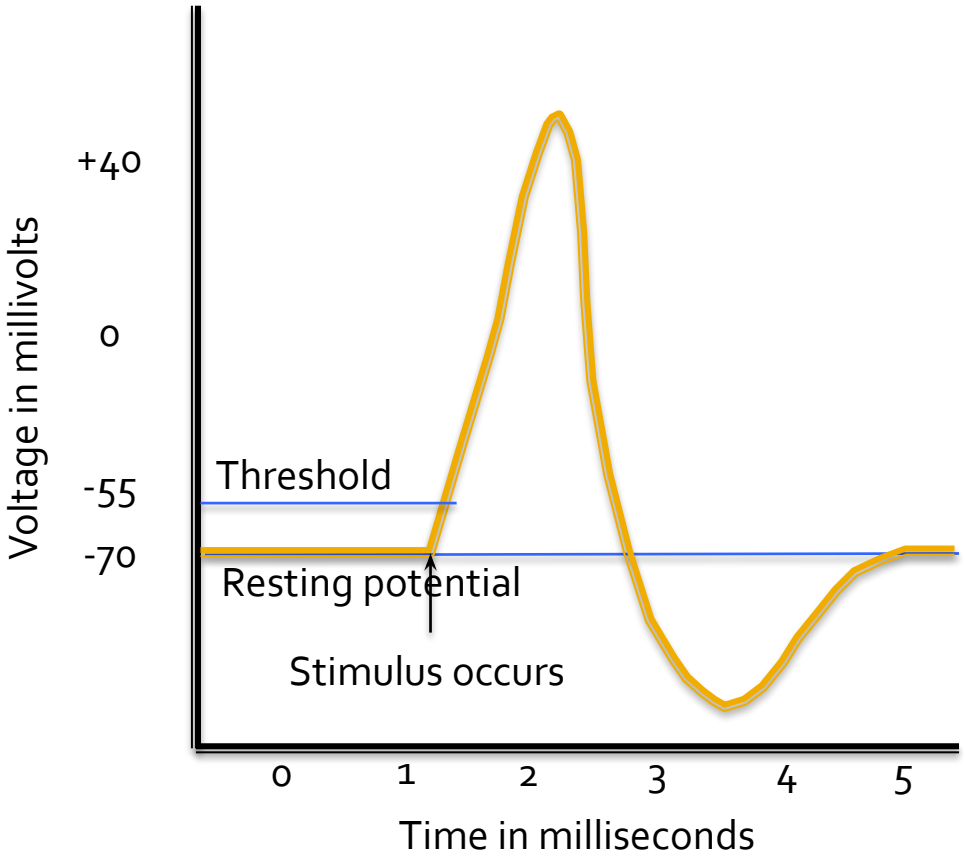
Inside the Axon Negative charge

Outside the Axon Positive charge

When opioids bind to receptors on neurons, they make the neuron more negative which prevents them from firing.

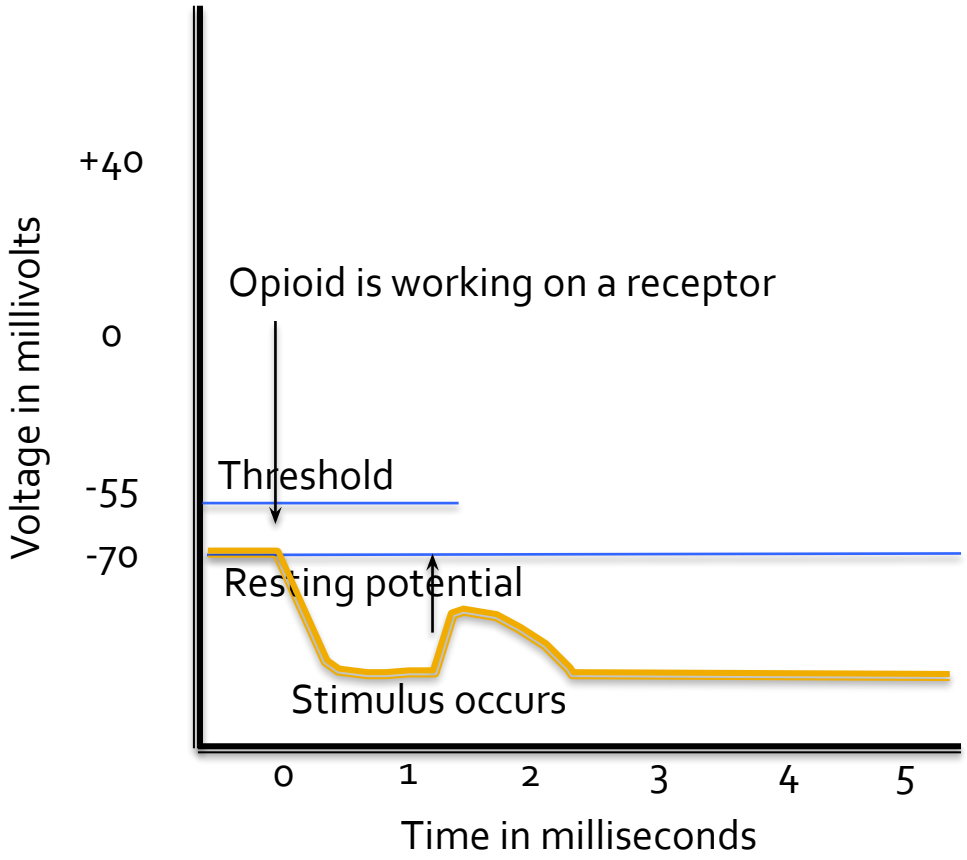
Opioids work by making changes to neurons

- A neuron activating or firing is called an action potential. The figure below shows the change in electrical activity when a neuron fires.



Opioids work by making changes to neurons

- Opioids force the membrane potential to below its normal resting state of -70 mv. When a stimulus occurs the neuron does not reach the threshold and therefore does not fire.



Let's apply this to the real world

- The part of the brain that allows us to hear is called the primary auditory cortex (also called Heschl's gyrus).
- The primary auditory cortex is located on the temporal lobe.
- When we hear a sound neurons in the primary auditory cortex fire.

- David just injected heroin. The drug reaches the brain in about 10 seconds and has lowered the membrane potential of neurons in the primary auditory cortex.
- "David, are you OK?" No response.
- Or screaming "David, are you OK?" Some sounds but unintelligible.

Endogenous neurotransmitters & their receptors

- There are four different types of opioid receptors in the body and the brain.
- There are five different endogenous (made by the body) neurotransmitters.

Endogenous Opioid Neurotransmitter	Receptor activates
Beta-endorphin commonly written as "β-endorphin"	mu (the symbol is μ) delta (the symbol is δ)
Met-enkephalin	mu delta
Leu-enkephalin	mu delta
Dynorphin	Kappa (the symbol is K)
Nociceptin	ORL-1

Opium

Opioids

- Opioids can be divided into three broad categories:
  - **Natural compounds** that can be extracted from opium.
  - Compounds that can be created by making specific changes in the chemical composition of these natural compounds.
  - Compounds synthesized in the laboratory.

Opioids

OPIUM

MORPHINE → HEROIN

CODEINE → HYDROCODONE (VICODIN)

THEBAINE → OXYCODONE (PERCOCET)

Synthetic Opioids

BUPRENORPHINE (SUBOXONE, SUBUTEX)

METHADONE

FENTANYL

Half-lives of different opioids

- **Half-life**: The amount of time it takes for the body to eliminate half of a given blood level of a drug.

Drug	Half-life
Morphine	2 hours
Heroin	Less than 8 minutes
Codeine	3 hours
Oxycodone	2.5 to 3 hours
Methadone	12 to 150 hours
Buprenorphine (Subutex)	38 hours (sublingual)

Elimination

- Opioids are primarily metabolized by the liver.

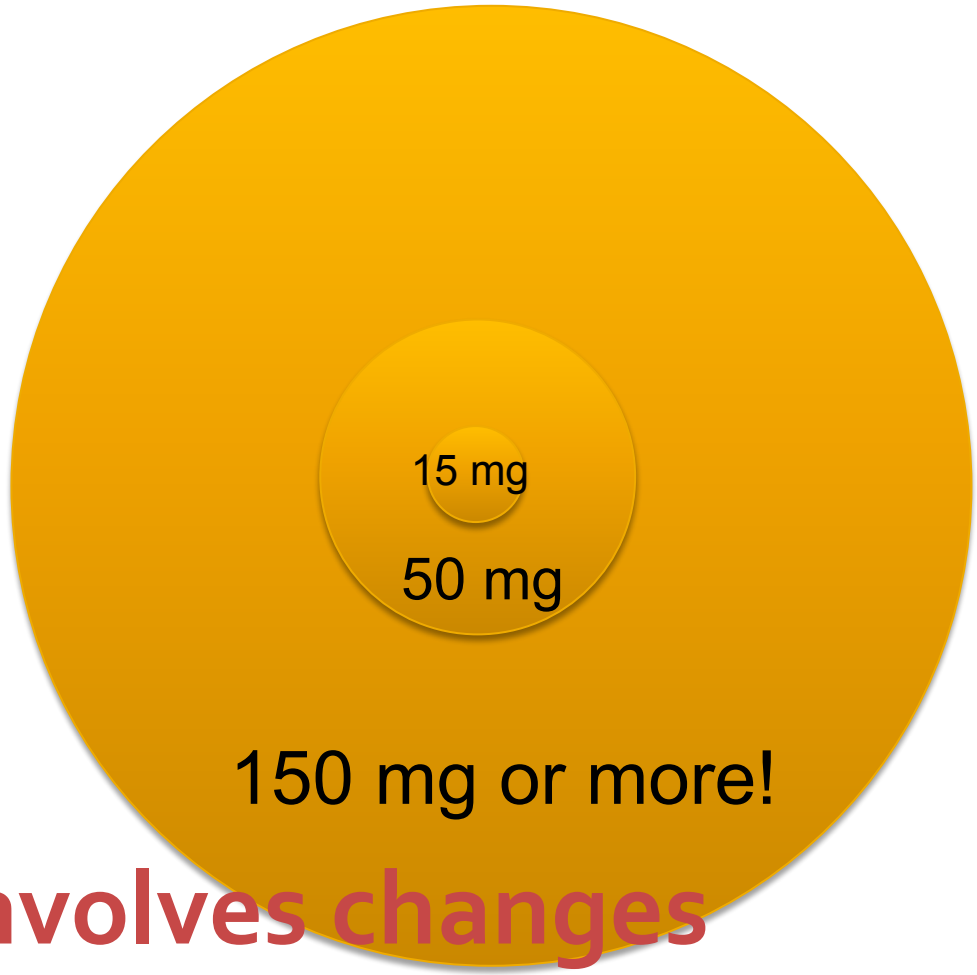
- There are two phases of opioid metabolism.
  - Phase #1 – The drug is changed by the enzymes CYP3A4 & CYP2D6
  - Phase #2 – The drug or metabolite combines with a hydrophilic (water-loving) substance.

Opioid metabolism

- Some opioids are broken down into inactive metabolites and some are broken into active metabolites. Some of these metabolites are more potent than the original drug.

Tolerance

- Effective dose of heroin (~15 mg)
- Lethal dose of heroin for a non-tolerant individual (~50 mg)
- After several months of use, consumption can increase 10 fold or more!



Tolerance involves changes to receptors on neurons

Receptor changes with repeated administration

- Because the drug reduces neuronal activity, with repeated administration, your brain tries to adapt by reducing sodium-potassium pump activity; thereby increasing excitability and counteracting the drug effect.

Receptor changes with repeated administration

- Acute tolerance: Almost immediately after drug administration the number of opioid receptors decreases.

Treatment for Heroin Abuse

- Methadone – a long-lasting opioid agonist
  - Its long duration of action prevents withdrawal symptoms for 24 hours or more. Therefore, it can be administered once a day.
  - High affinity for binding to mu receptors, therefore if someone takes heroin while on methadone, they won't get the usual high.

Treatment for Heroin Abuse

- Suboxone – contains both buprenorphine and naloxone (a opioid antagonist)
  - Through oral administration, buprenorphine can easily enter into the general circulation. Naloxone, on the other hand, is poorly absorbed into the general circulation through oral administration.
  - If Suboxone is snorted or injected, the naloxone reaches the general circulation and the brain and therefore counteracts the effects of buprenorphine.

Rescue Medication

- Naloxone– A competitive antagonist for opioids.