ETHANOL:
Chemistry and Physiology of the World's Second-Most Popular Drug

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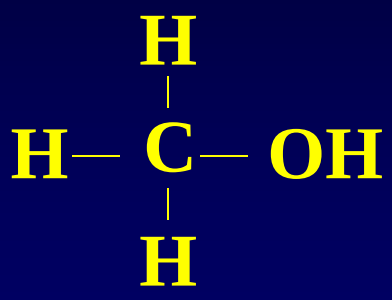
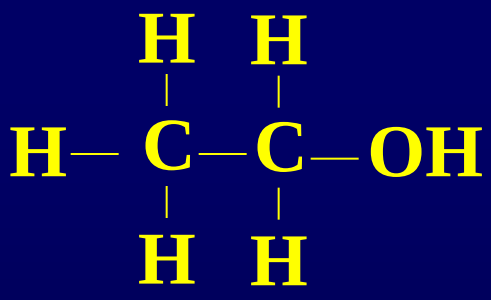
AND PUBLIC HEALTH

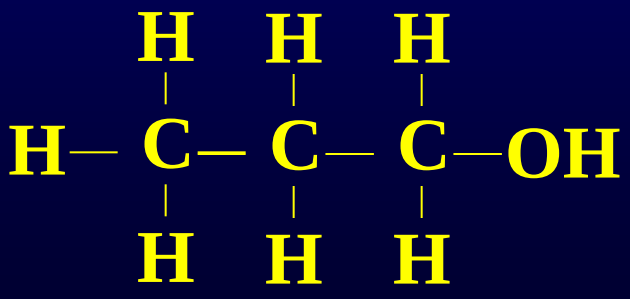
Alcohol Structure



Methanol



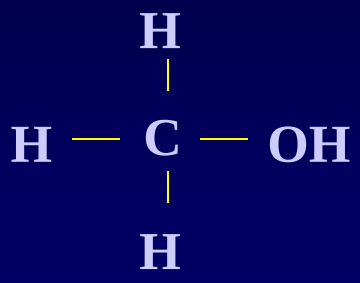
Ethanol



Propanol

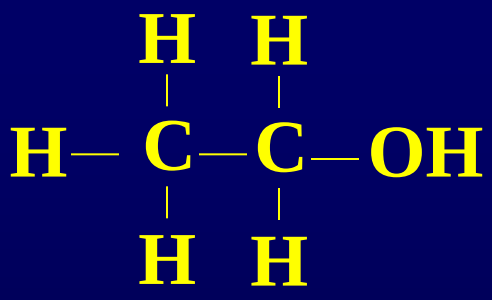
There are many different types of "alcohol;" what they have in common is an "OH" group bound to carbon.

Alcohol Structure



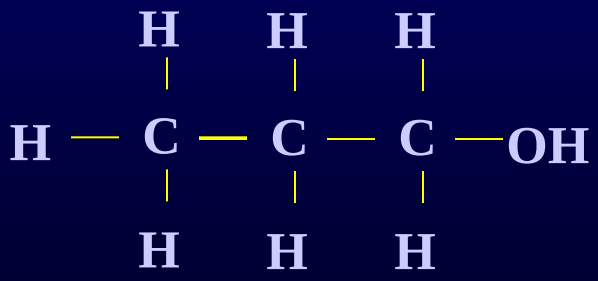
Methanol

Ingestion→blindness



Ethanol

THE alcohol



Propanol

Many alcohols are toxic to the body; the ethanol found in alcoholic beverages have reversible effects at low doses.

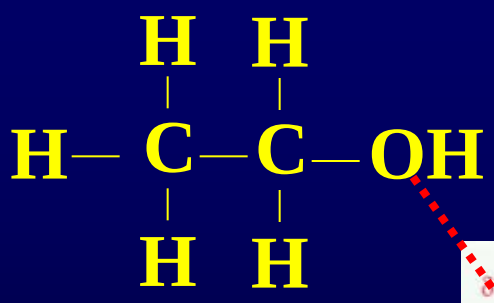
From this point in the presentation, ethanol will be referred to simply as “alcohol”

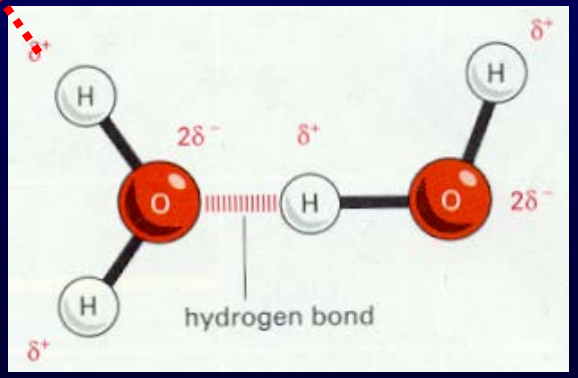
Ethanol Structure

- Clear, colorless liquid, miscible with H20 and Organics

Carbon-Hydrogen chains dissolve in lipids (hydrophobic)

This end interacts and dissolves in water (hydrophilic)

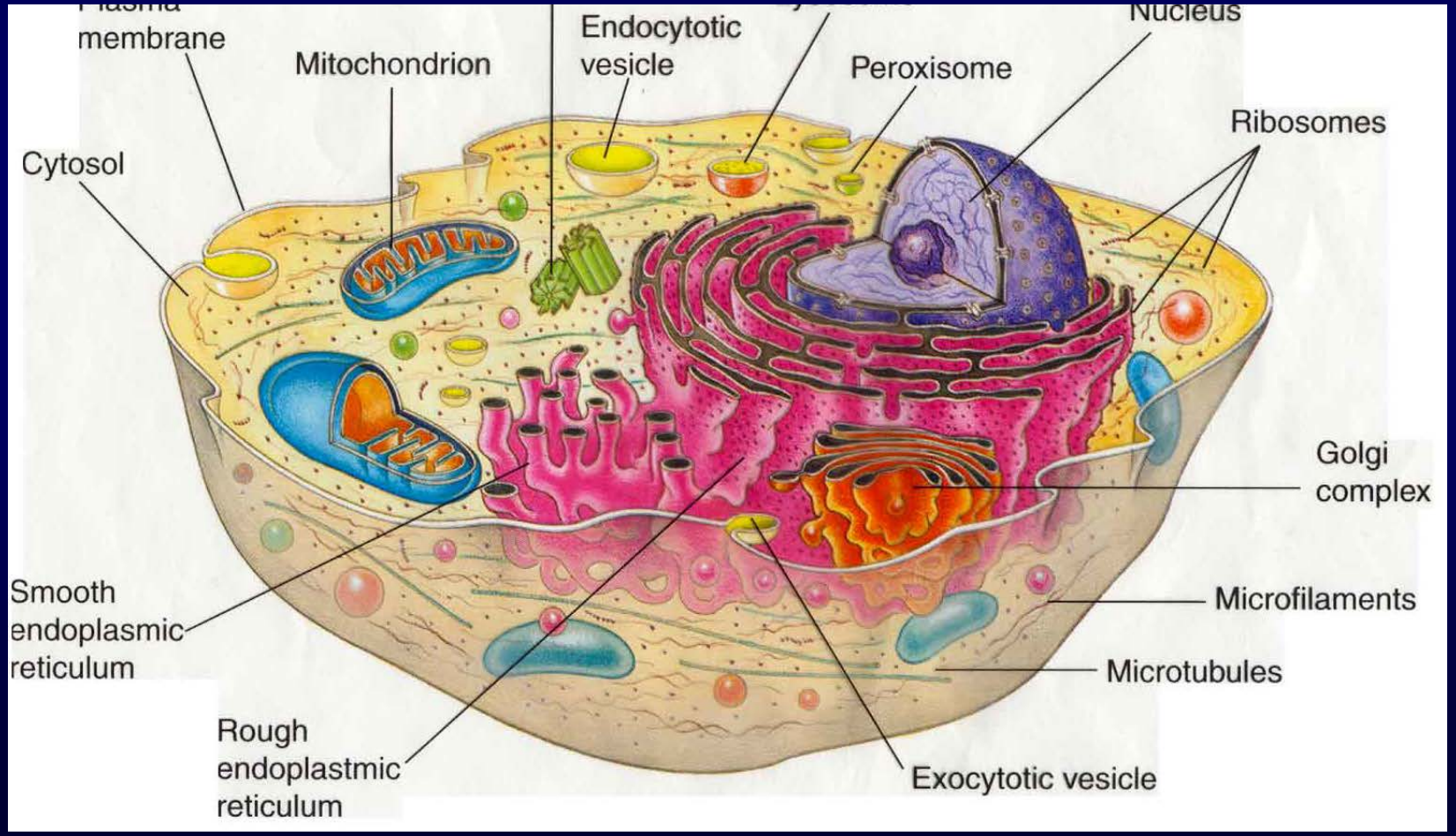




Ethanol is "amphipathic;" it can interact both with aqueous and organic chemical environments (like oils/lipids)

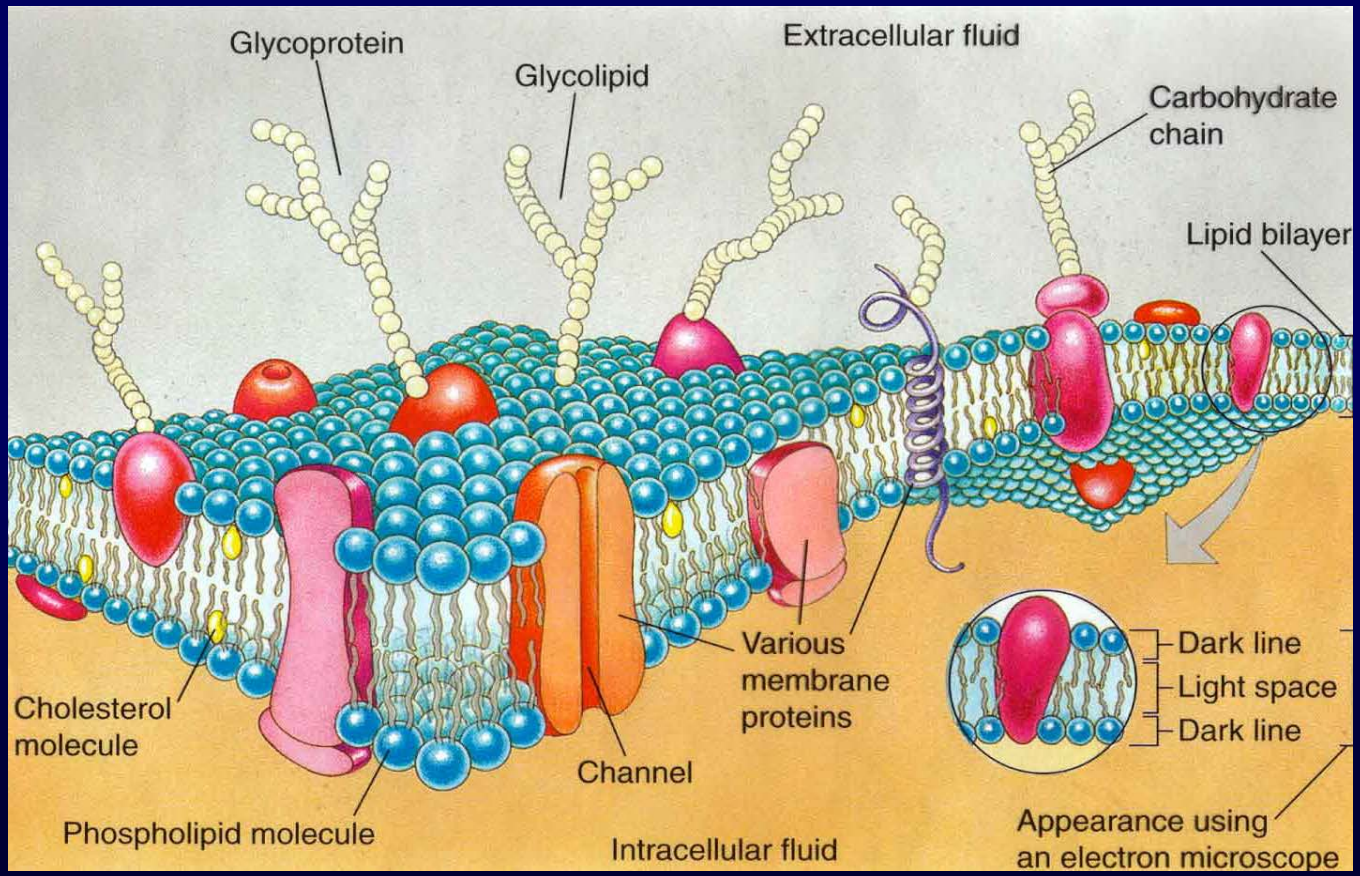
Basic Structure of Body Cells

Our bodies are made of 75 trillion specialized cells with phospholipid membranes, and aqueous environments inside and out.



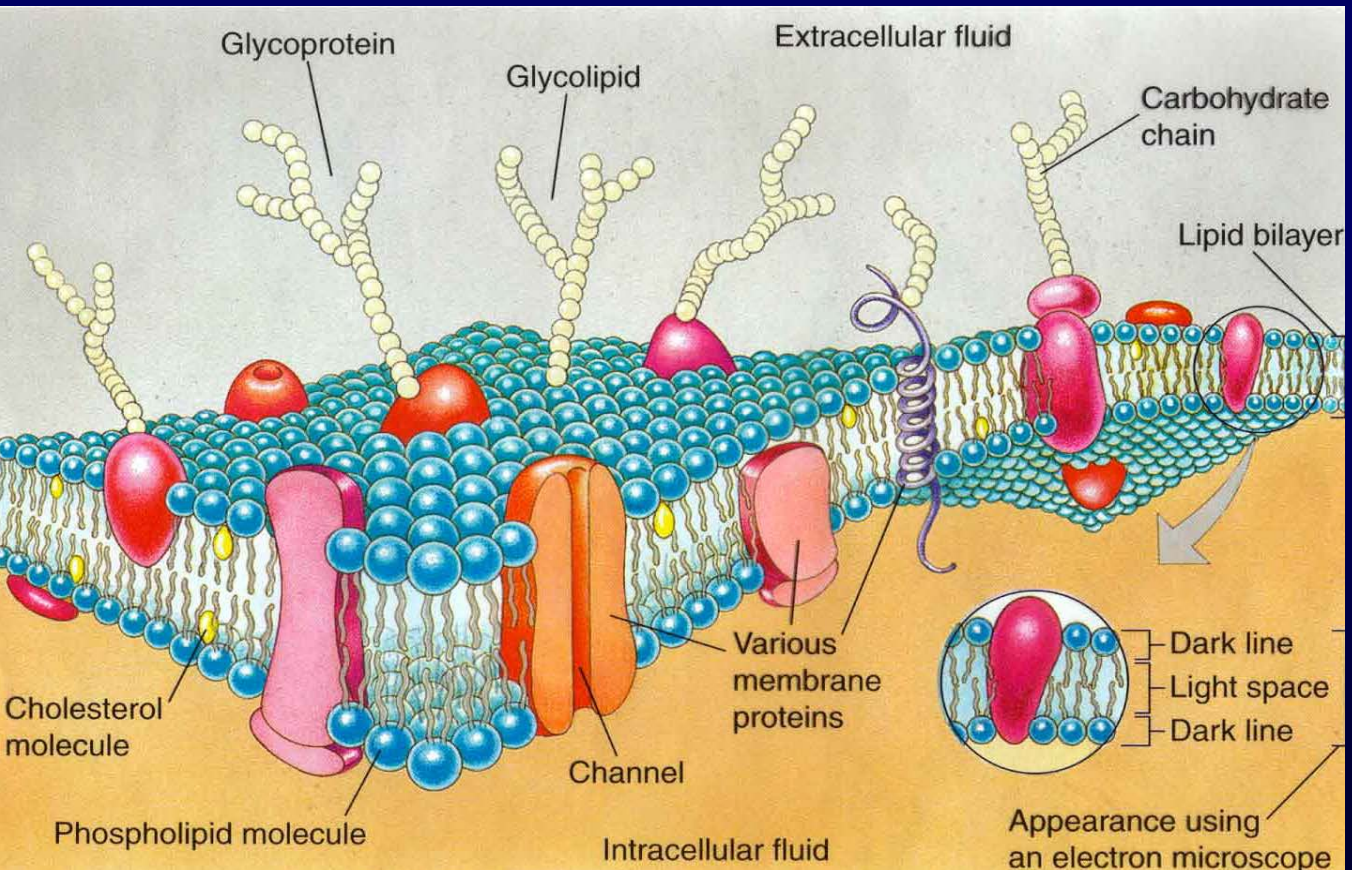
Basic Structure of Body Cells

Cell membranes are essentially oily bubbles formed from a bilayer of phospholipid molecules



Basic Structure of Body Cells

Proteins are the machinery that determine the function of different cell types; they're found floating free and within membranes



Ion channels
(Na+, K+, Ca+2)

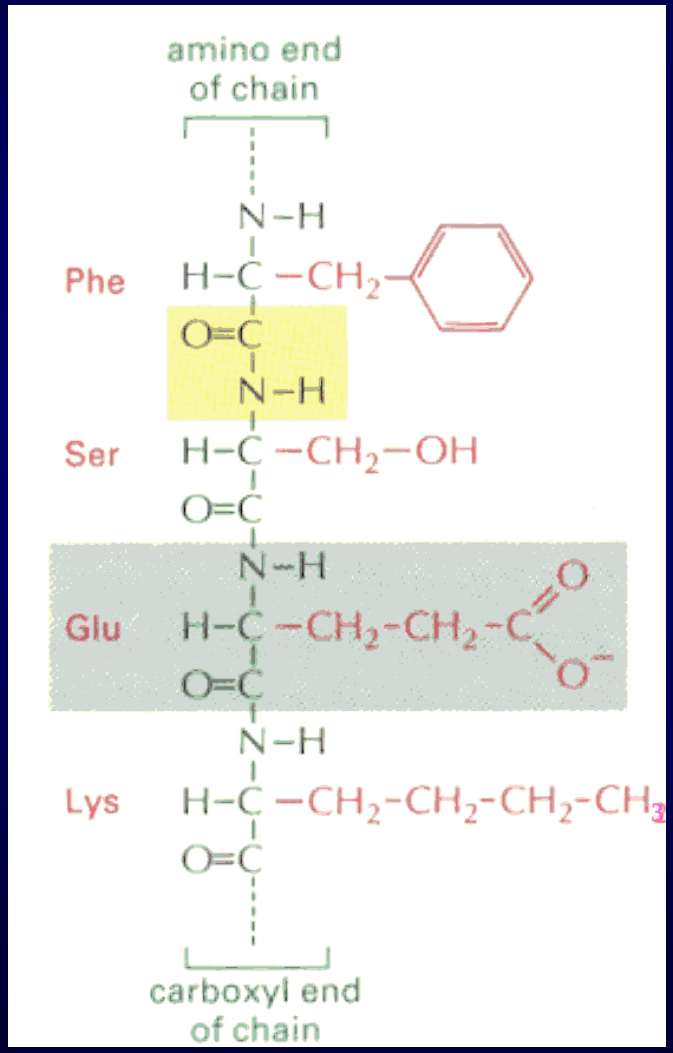
Enzymes

Receptors

Signals

Basic Structure of Body Cells

Proteins are made of amino acid chains:

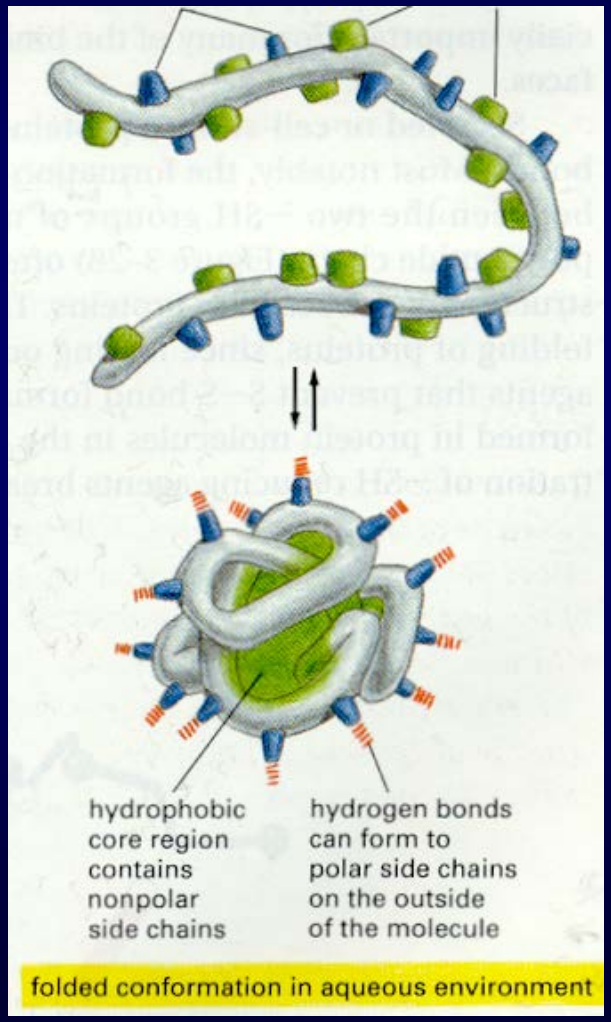


20 different amino acids have unique "R" groups:

- **Some are hydrophilic (interact with water)**
- **Some are hydrophobic (interact with lipids)**

Basic Structure of Body Cells

Proteins are made of amino acid chains:



The "R"-group sequence determines the complex folding and final shape of a protein.

If you put an elongated protein into an aqueous solution like the bloodstream, it will fold into a shape that minimizes exposure of hydrophobic R-groups to the solution. It's like mixing oil and water in a jar; they separate into distinct layers with minimal interaction.

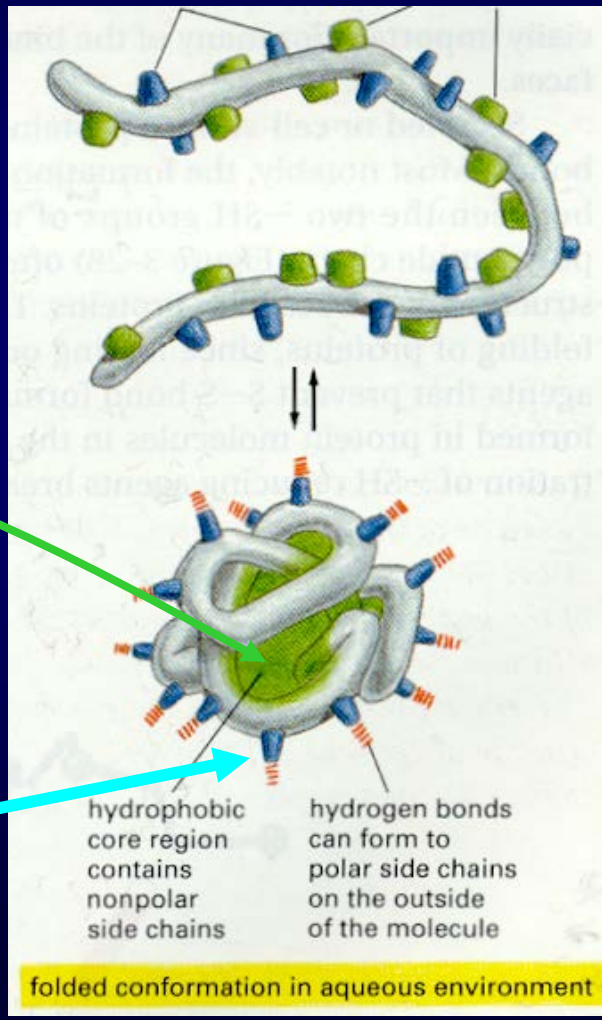
Ethanol Interacts with Cell Proteins

Ethanol's unique chemistry makes it a universal key that can interact with protein machinery of cells throughout the body.

By interacting with both hydrophobic and hydrophilic regions of proteins, alcohol can alter their function

(hydrophobic)

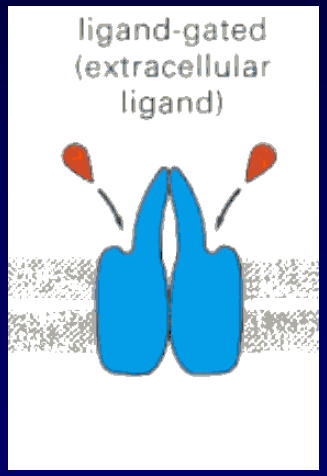
(hydrophilic)



Why Does Whiskey “Burn”?

Why is it that spirits containing a high alcohol content are perceived as “burning” in the mouth and throat even when they are at room-temperature?

Why Does Whiskey "Burn"?



This is a protein found in the membranes of nerve cells in the mouth and throat.

← "TRPv1 (Vanillin1) receptor" (mouth, throat)

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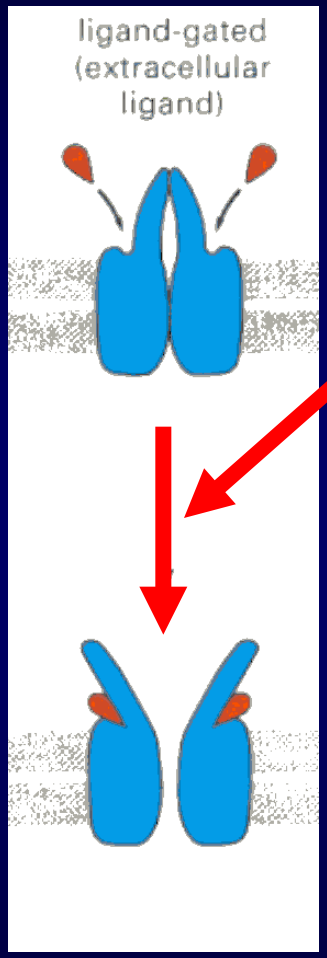
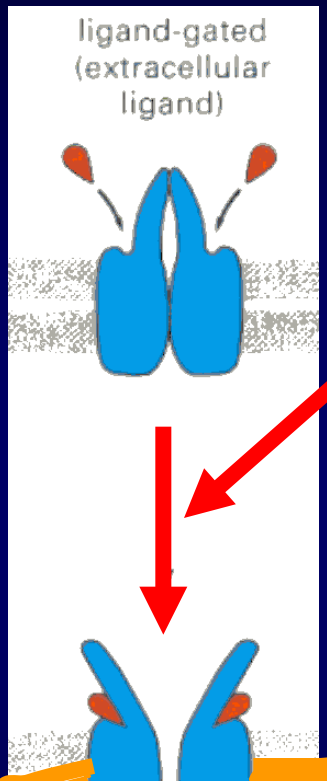


Heat, capsaicin…

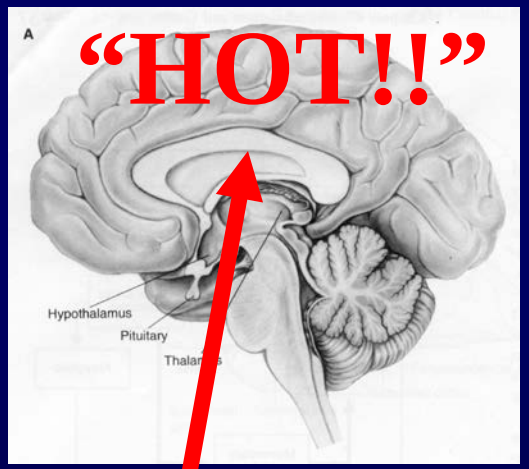
It is an ion channel that is normally opened by the presence of high heat, and also by the binding of a chemical found in hot peppers called capsaicin

Why Does Whiskey "Burn"?



Heat, capsaicin….and Ethanol!

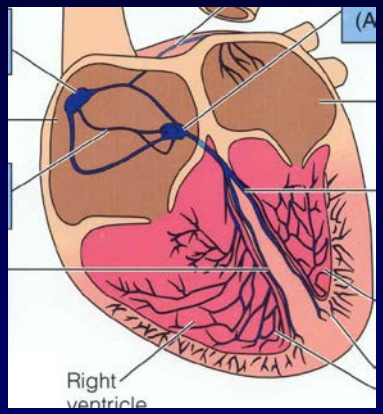
Ethanol also binds and opens this protein. When the protein opens, charged ions enter the cell and an electrical signal is sent to the brain that we perceive as "hot," even though the ethanol may be cool!



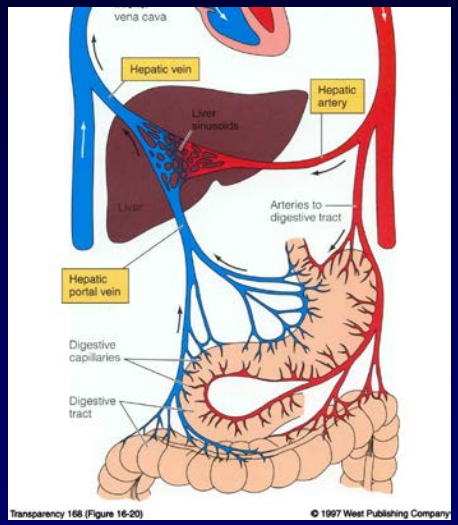
"HOT!!"

Nerve signal to brain

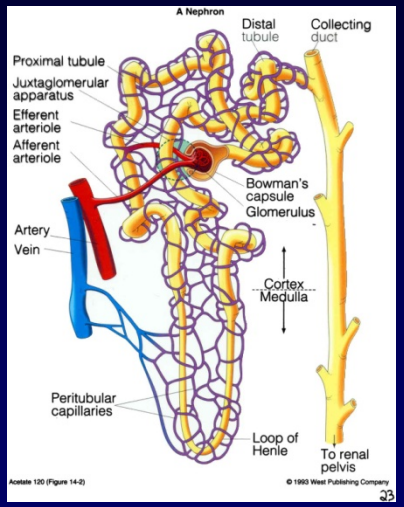
Ethanol Affects All Body Systems



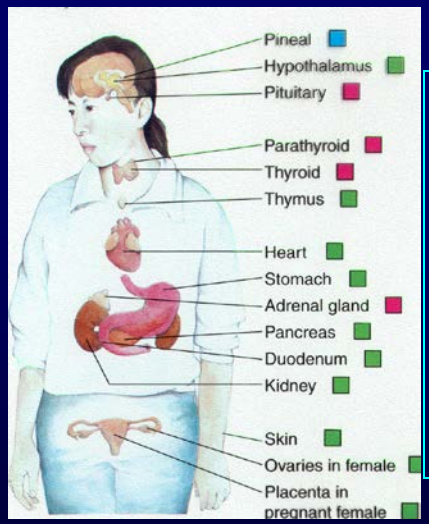
Cardiovascular



Gastrointestinal

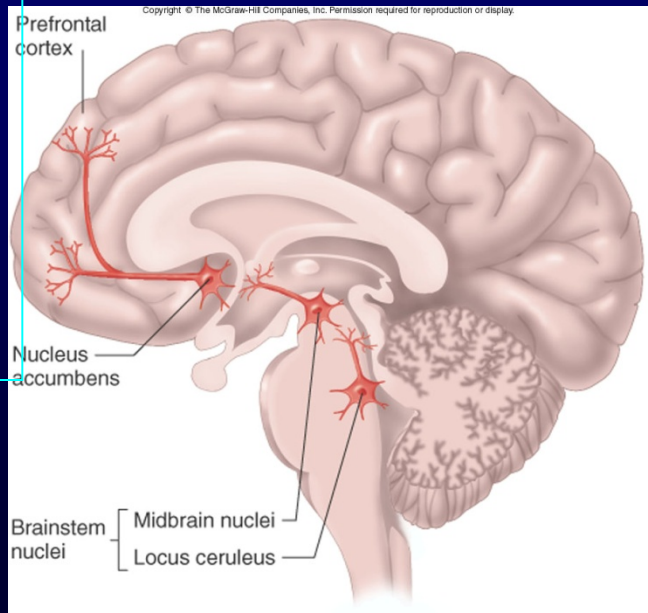


Urinary



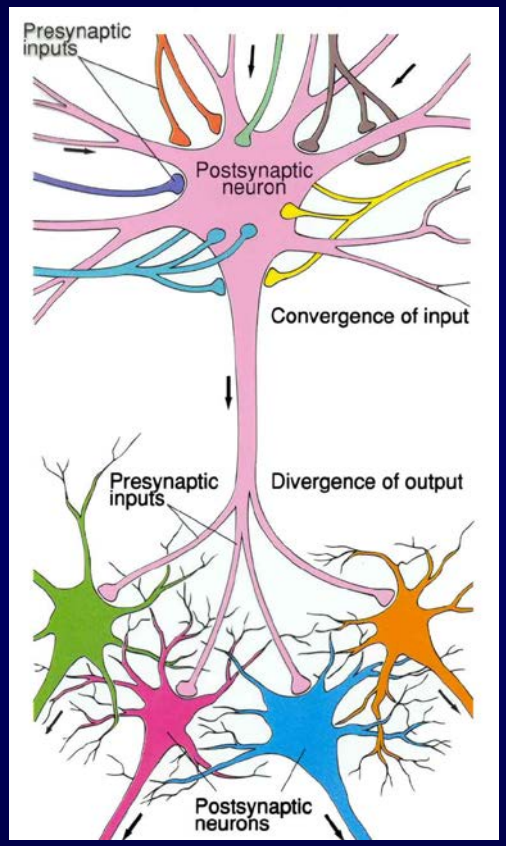
Endocrine/ Reproductive

Ethanol interacts with proteins in cells of all organ systems, explaining the wide variety of effects of acute and chronic alcohol ingestion. We will focus on effects on the brain.



Effects on the Nervous System

Ethanol affects synapses

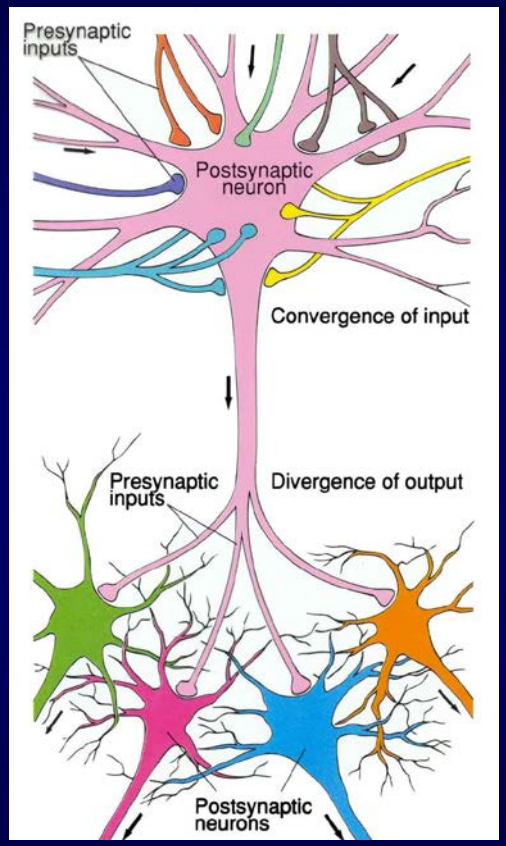


Neuron signals and networks

(x 100 billion!)

The human brain has more than 100 billion cells called "neurons," each of which can be connected to thousands of other neurons at junctions called synapses. At those junctions, neurons send either excitatory or inhibitory messages to other neurons. Every second of every day of your life, each individual neuron receives thousands of inputs; if most are positive the neuron will fire a signal toward other neurons. If most of the inputs are negative, the neuron's activity will be quieted. The activity of those synaptic connections encode your personality, your memories, your talents, your fears, and your ability to act on those things. Everything that makes you who you are!

A close look at a synapse reveals the presence of many different proteins involved in releasing and detecting the "neurotransmitter" chemical that carries the signal across the synapse. The function of many of those proteins is altered by ethanol!



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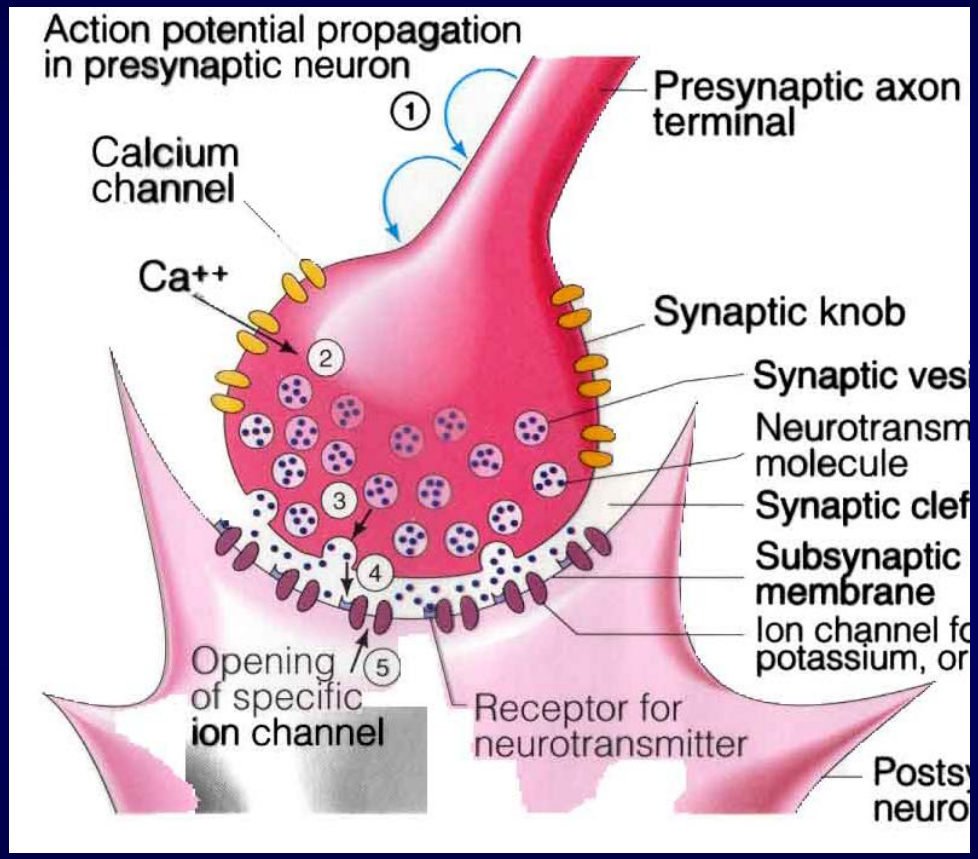
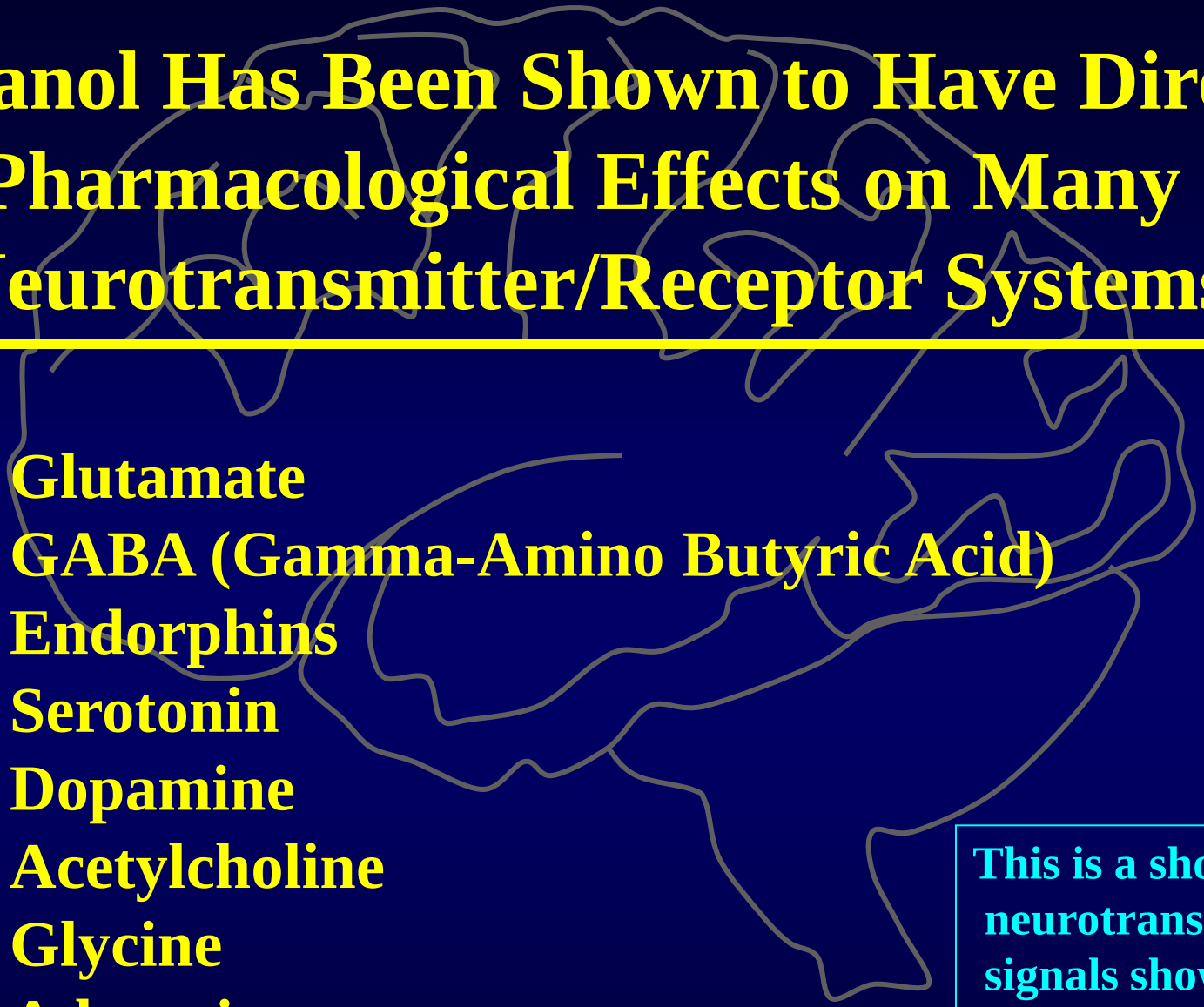


Synapses, Neurotransmitters and Receptors

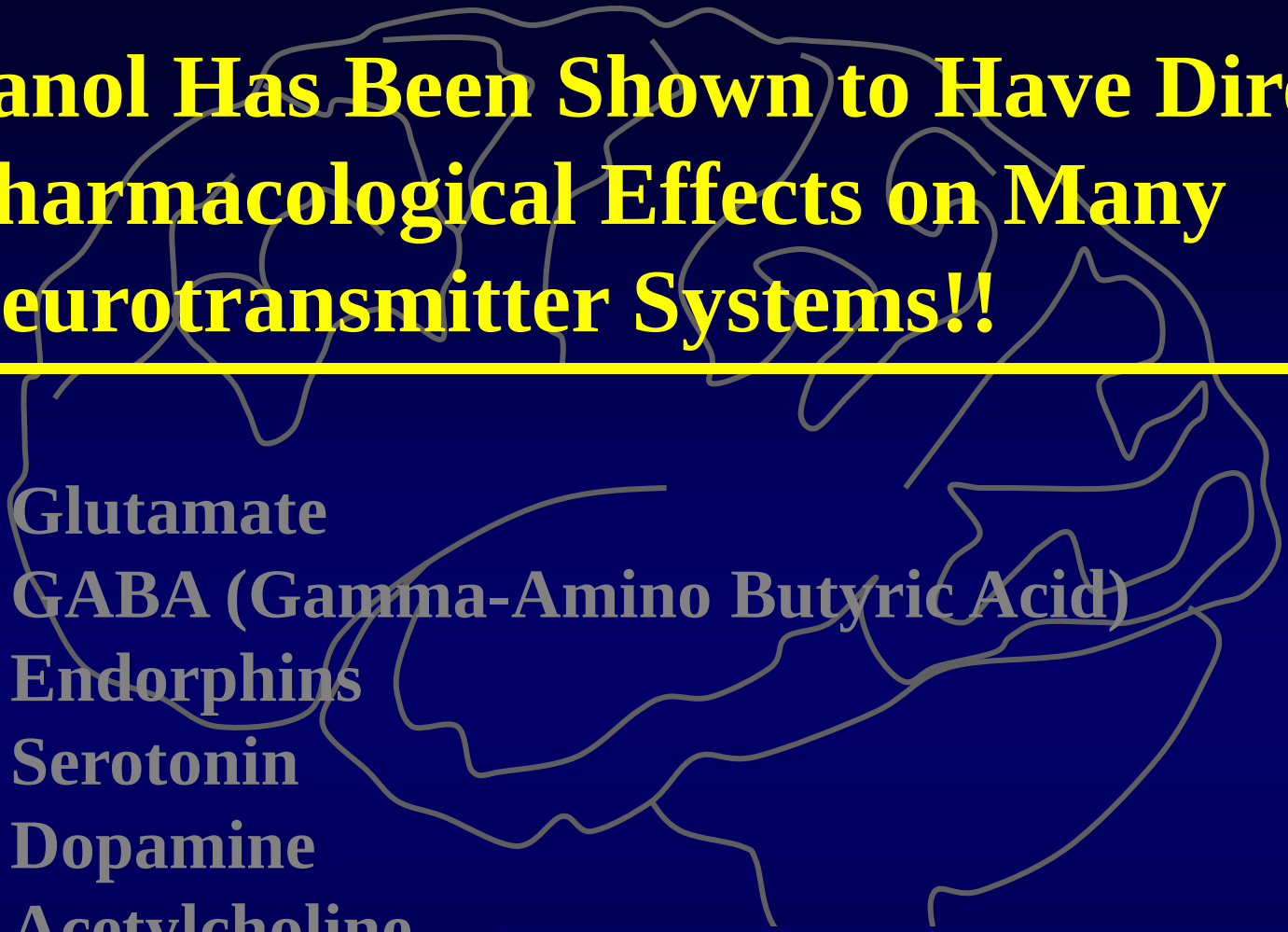
Ethanol Has Been Shown to Have Direct Pharmacological Effects on Many Neurotransmitter/Receptor Systems



- Glutamate
- GABA (Gamma-Amino Butyric Acid)
- Endorphins
- Serotonin
- Dopamine
- Acetylcholine
- Glycine
- Adenosine

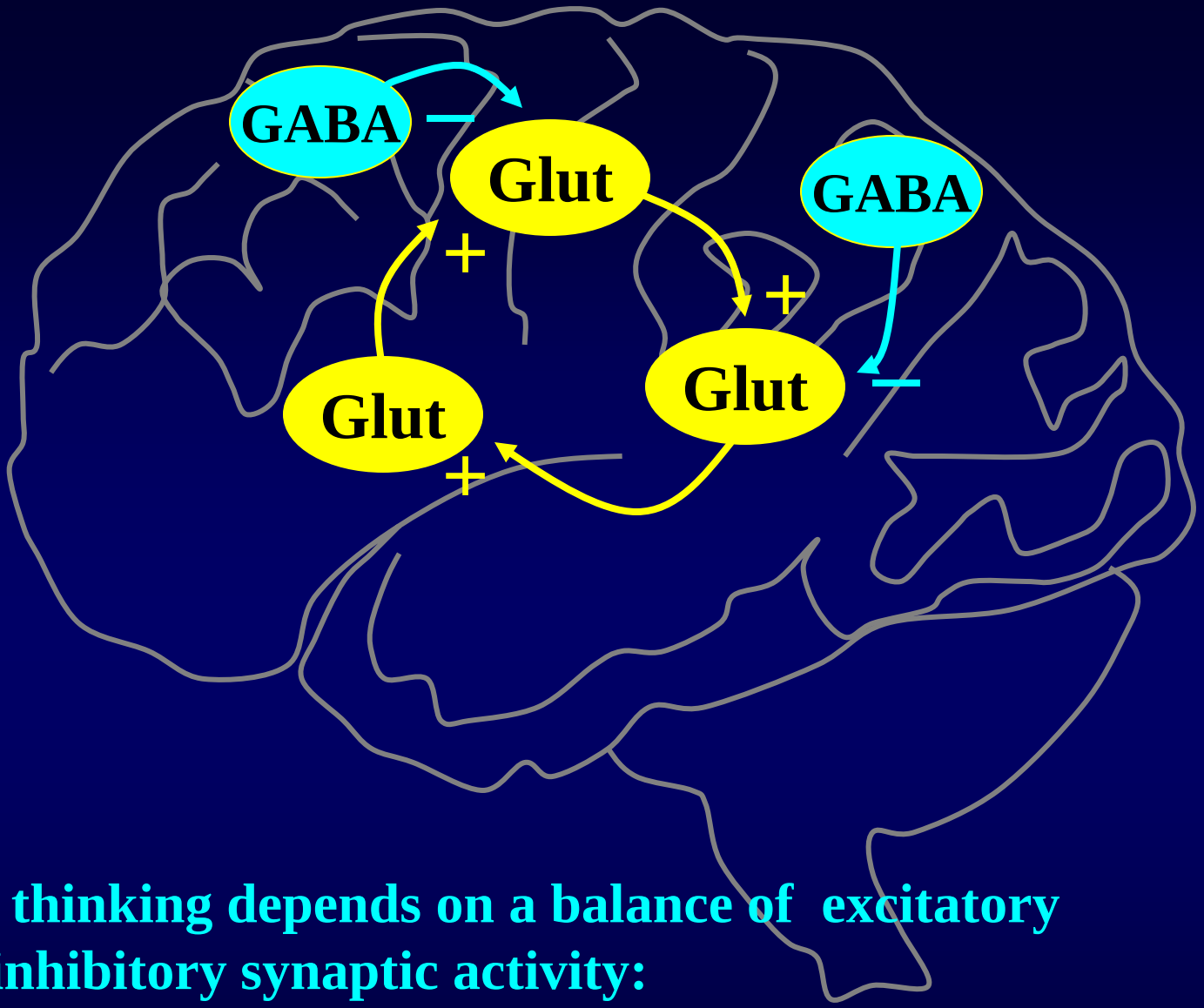
This is a short list of neurotransmitter signals shown to be altered in the presence of ethanol.

Ethanol Has Been Shown to Have Direct Pharmacological Effects on Many Neurotransmitter Systems!!



Glutamate
GABA (Gamma-Amino Butyric Acid)
Endorphins
Serotonin
Dopamine
Acetylcholine
Glycine
Adenosine

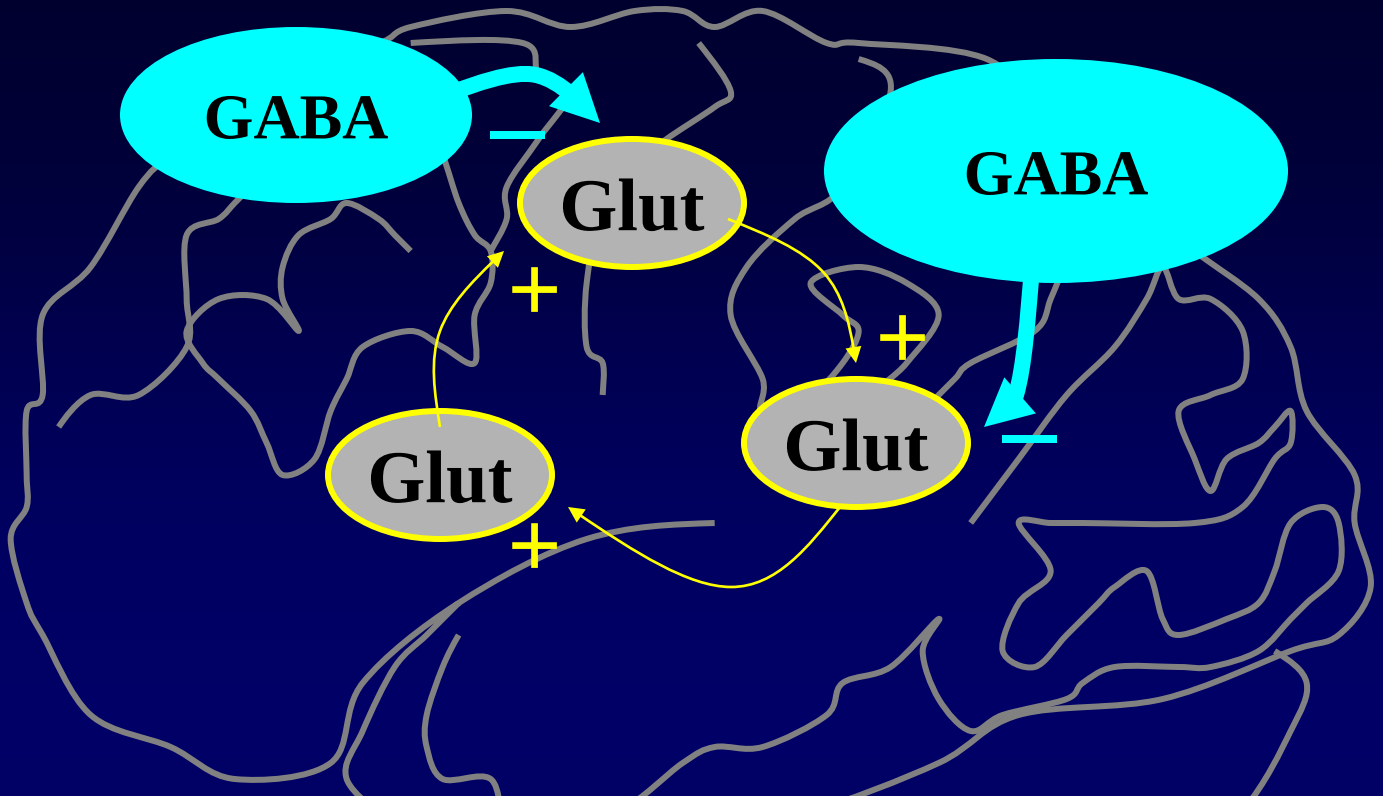
Differential sensitivities of these systems to dose, time course, and context can make alcohol a bizarre and unpredictable drug!



Normal thinking depends on a balance of excitatory and inhibitory synaptic activity:

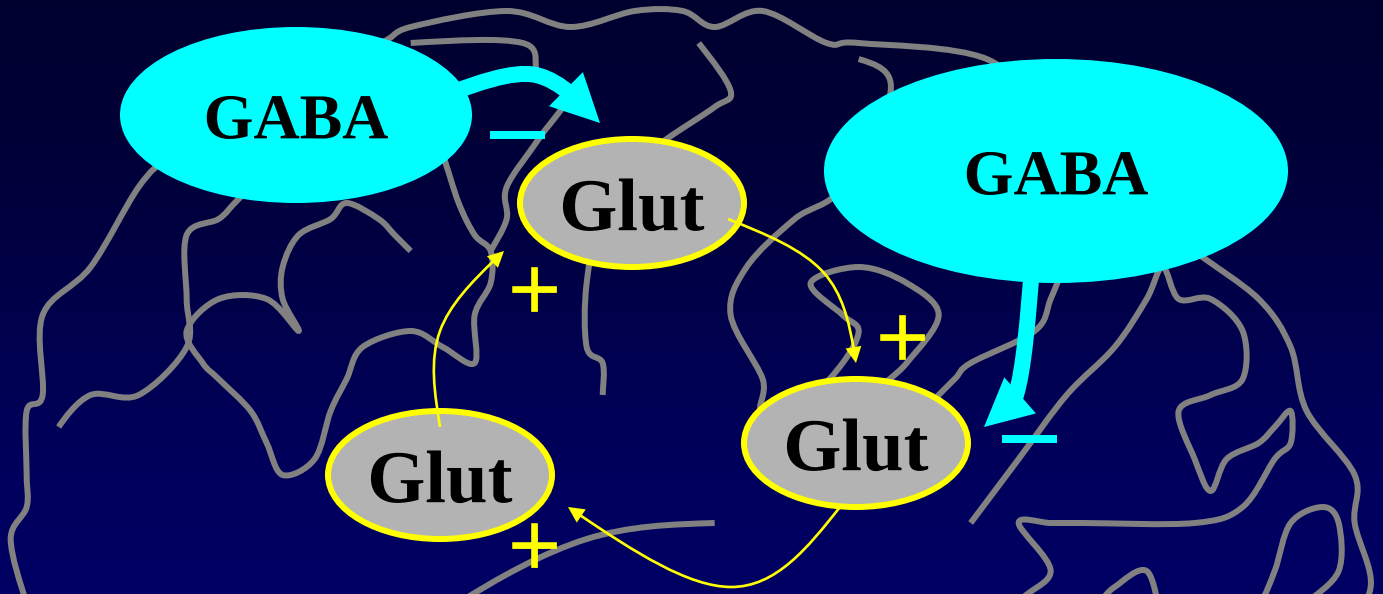
→50% of the brain's synapses use Glutamate (excitatory)

→40% use GABA (gamma-amino-butyric acid) (inhibitory)



Well-documented pharmacological effects of ethanol include stimulation of GABA signaling and inhibition of glutamate signaling.

This means your processing power slows down in a dose-dependent manner as the dose of ethanol increases. After one or two drinks there is little impairment, but binge-drinking (5 or more) leads to seriously impaired processing and judgement….



Another Consequence:
Context-dependent change in mood/emotion….

When the global processing power of the brain slows down, people begin to react emotionally to the most immediate inner thought or outer event. Mood changes radically depending on what is focused on. Alcohol doesn't cause any one particular mood; it just exaggerates whatever mood you are in.

“Alcohol Myopia” Can Explain Variable Neural Effects

The basic idea:

Ethanol globally suppresses cognition, reducing the mental focus of an individual to immediate internal thoughts or external stimuli.

"Alcohol Myopia" Can Explain Variable Neural Effects

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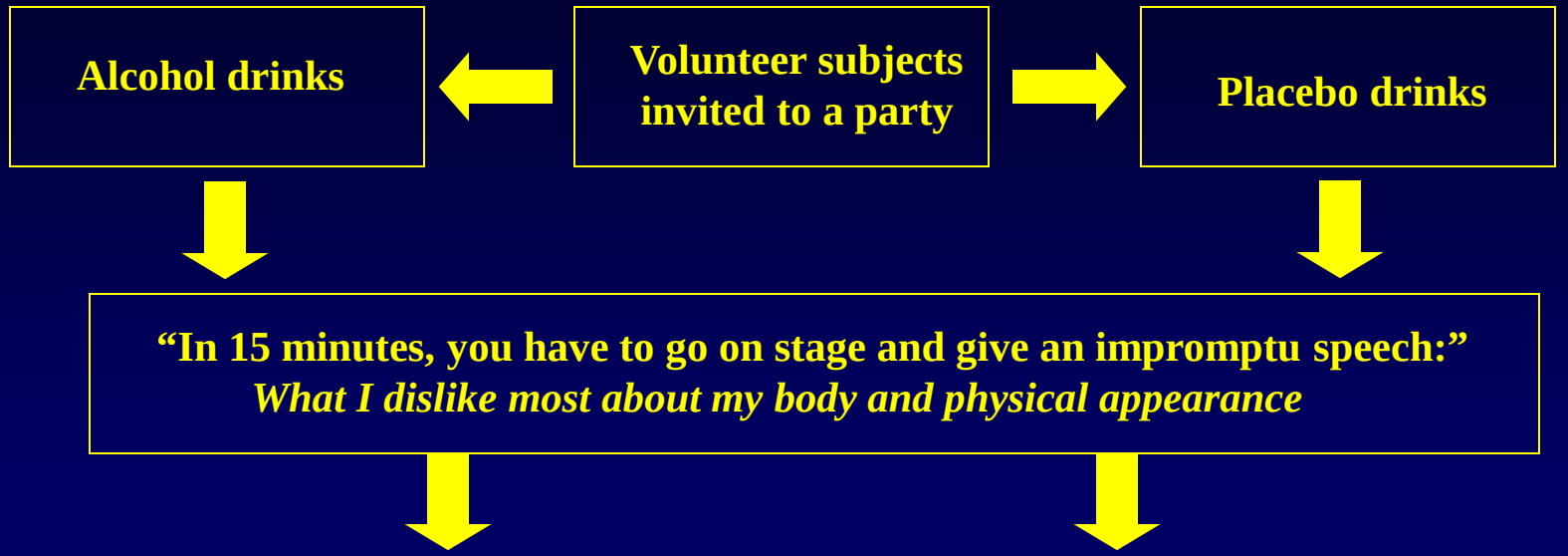
Ethanol globally suppresses cognition, reducing the mental focus of an individual to immediate internal thoughts or external stimuli.

Example: Study demonstrating that ethanol is NOT a good anti-anxiety drug….

Alcohol, Anxiety, and Public Speaking

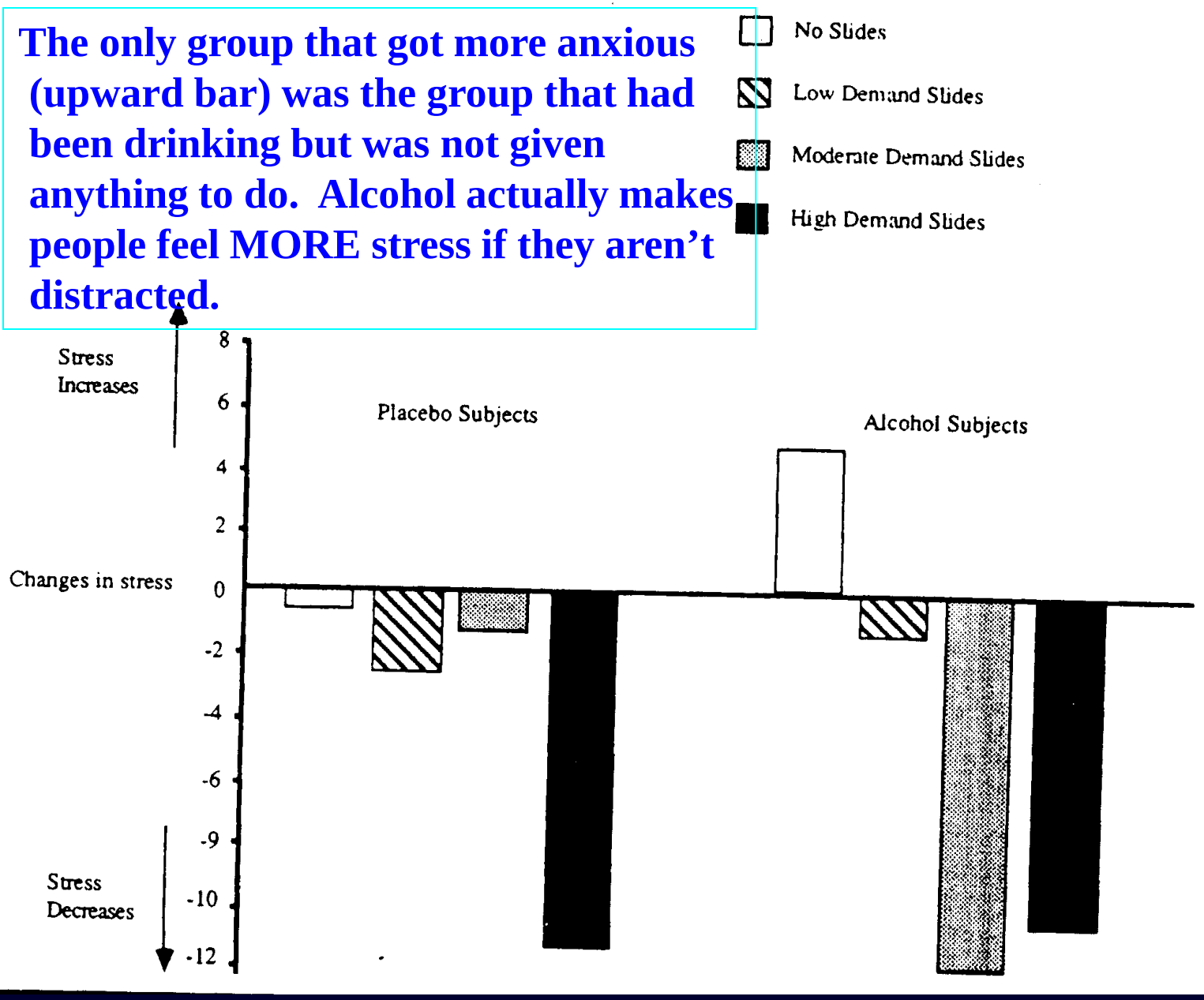


ANXIETY		ANXIETY
	Sit and think	
	Easy slide sorting task	
	Moderate difficulty slide sorting task	
	Complicated slide sorting task	

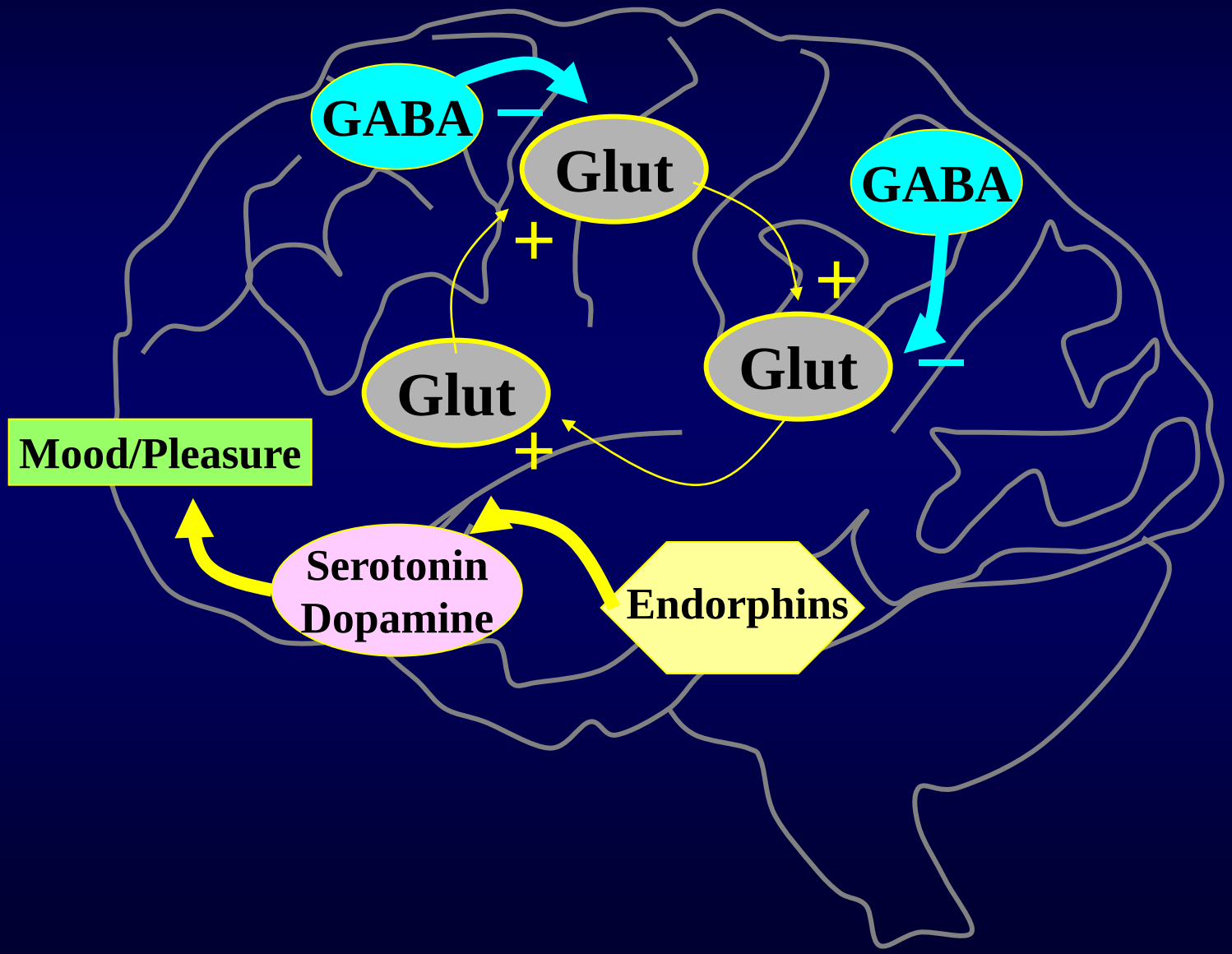
In this study researchers compared anxiety of people asked to give a speech, half were drunk and half were sober. Some were kept busy sorting slides while they waited.

Alcohol, Anxiety, and Public Speaking

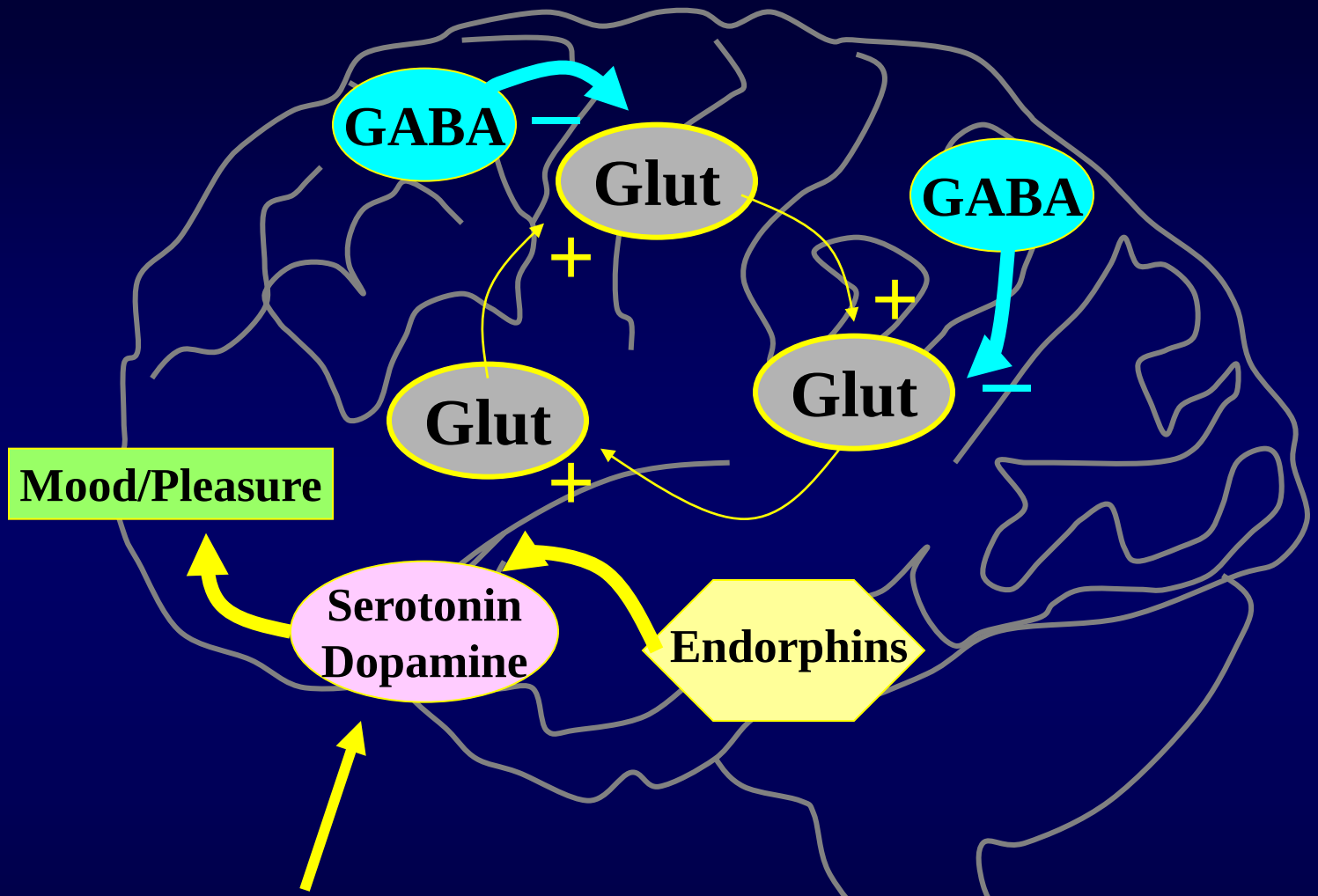
The only group that got more anxious (upward bar) was the group that had been drinking but was not given anything to do. Alcohol actually makes people feel MORE stress if they aren't distracted.



OTHER NEUROTRANSMITTER EFFECTS



Acute Tolerance and the Rising Phase Effect

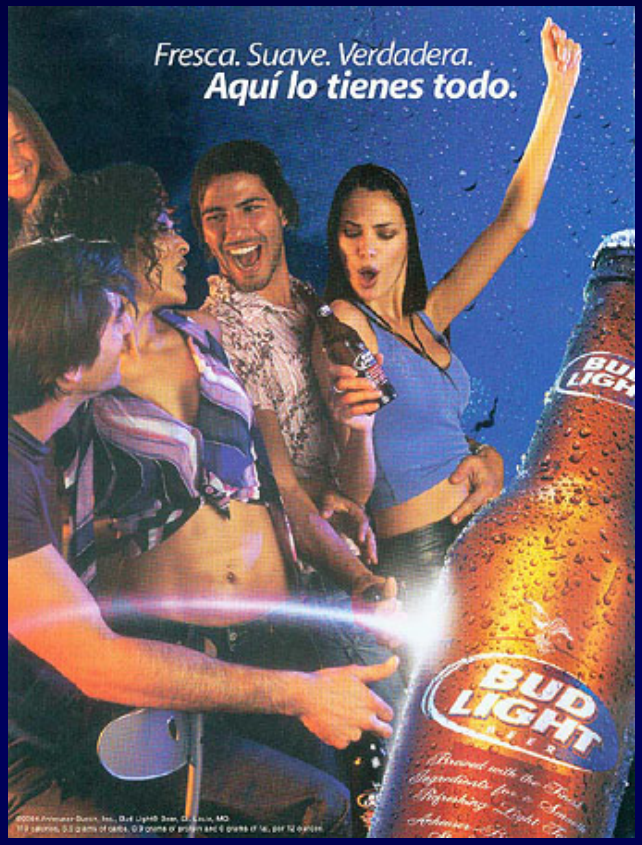


Ethanol pharmacologically stimulates brain reward centers, but "tolerance" develops rapidly…..

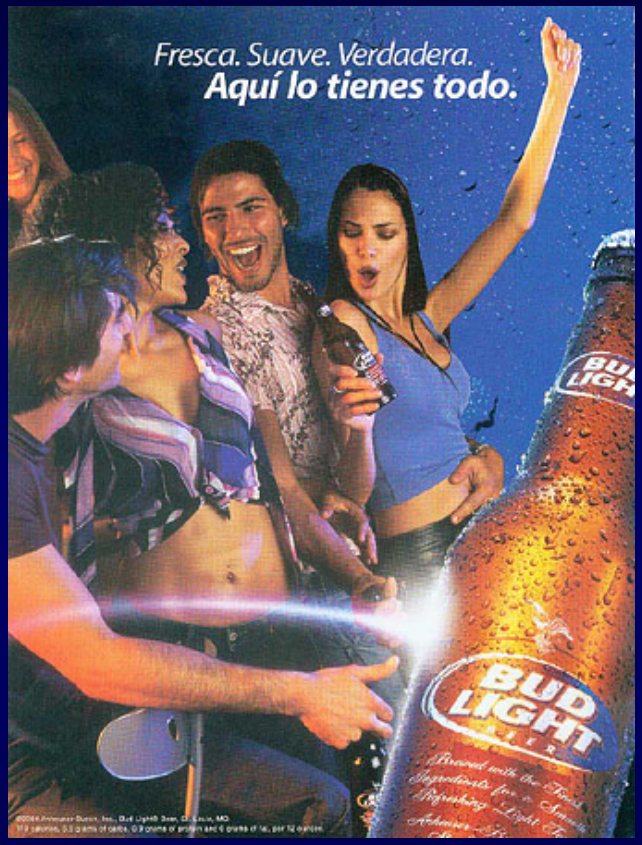
Acute Tolerance and the Rising Phase Effect

….which can explain why:

Short-term: Drinking leads to more drinking and often to extreme excess drinking



The intention



The intention

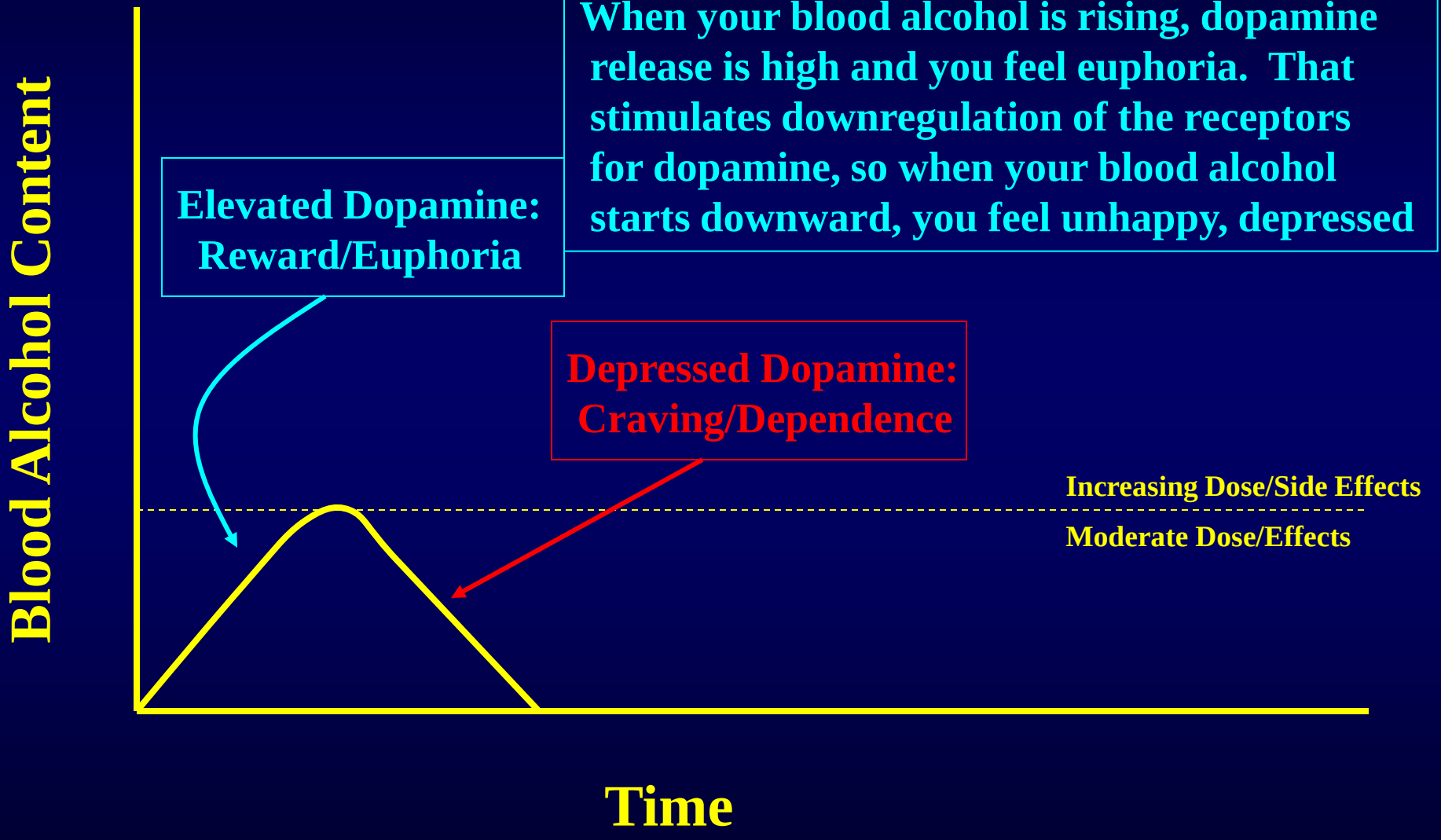
The reality

….and this can also explain why, with chronic heavy use, people can become alcohol dependent.

Rising Phase Effect

Moderate Dose and Rate

When your blood alcohol is rising, dopamine release is high and you feel euphoria. That stimulates downregulation of the receptors for dopamine, so when your blood alcohol starts downward, you feel unhappy, depressed

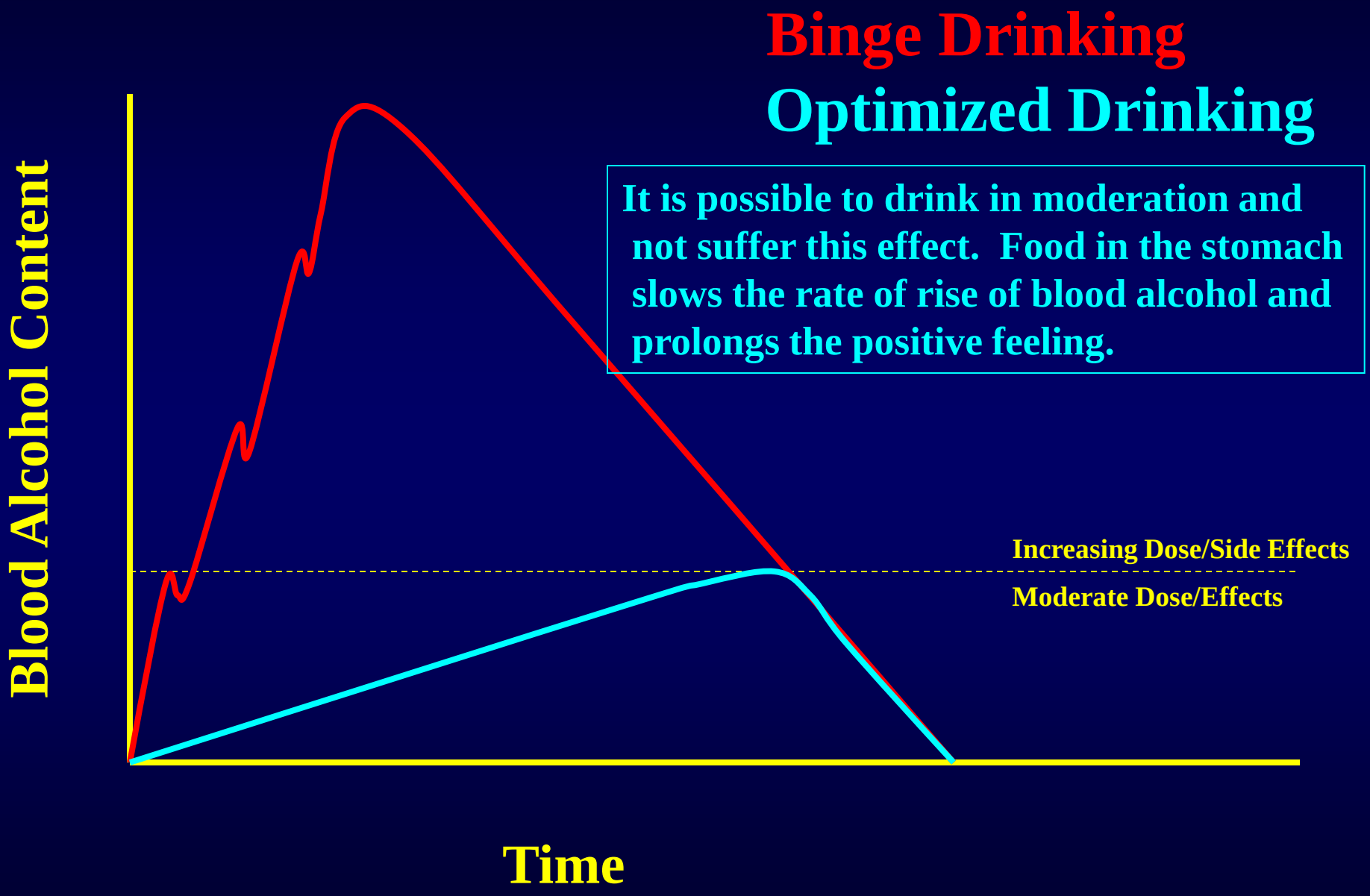


Rising Phase Effect

Binge Drinking

It shouldn't be surprising that people binge on alcohol: During a prolonged bout of drinking, any time the blood alcohol starts downward, the person must drink more to get the euphoria to come back again. People are especially susceptible to this before they reach their 20's.

Rising Phase Effect



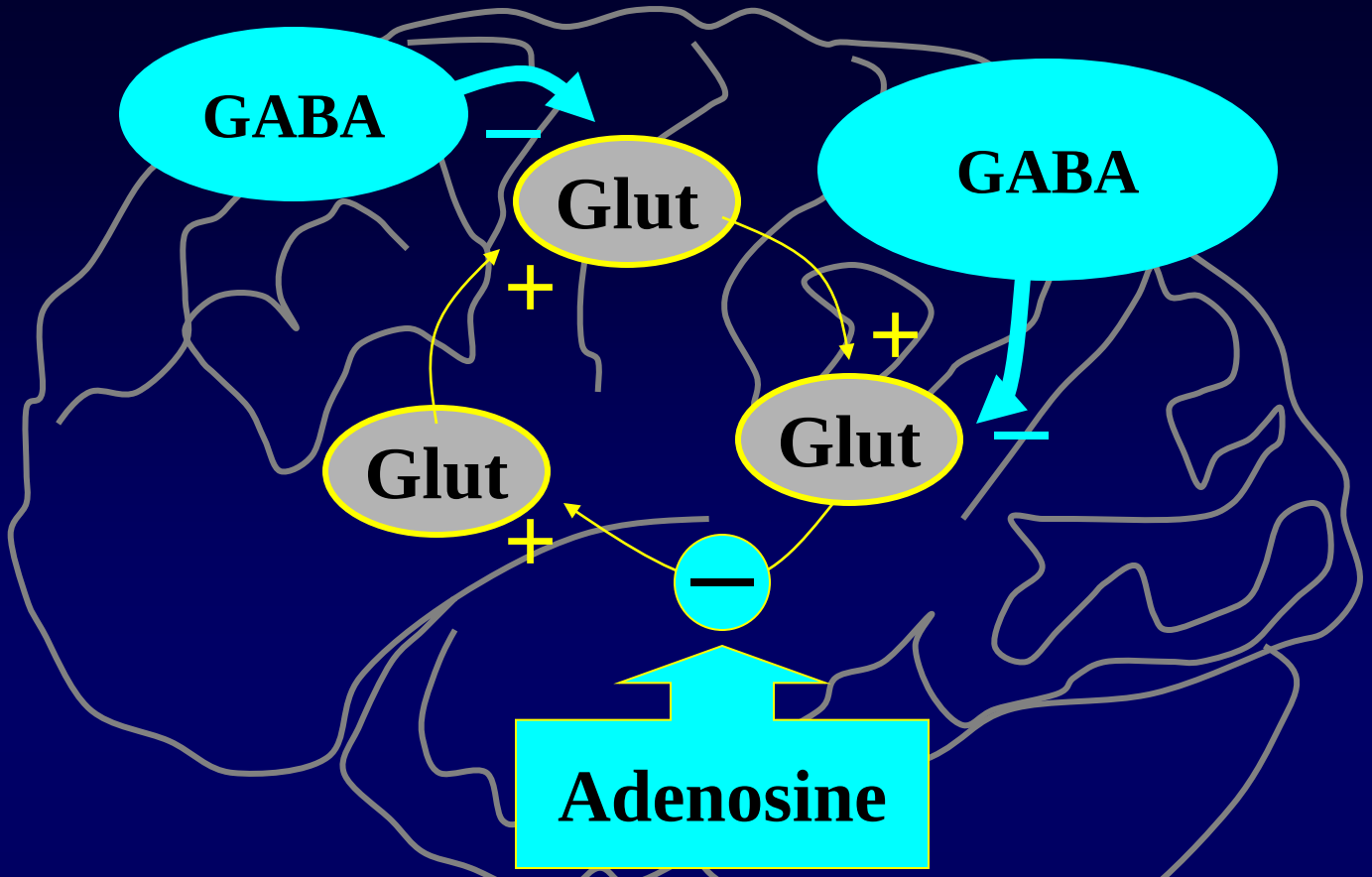
Ethanol, Sleep and Memory

Short-Term Memory ("Working memory") (RAM)

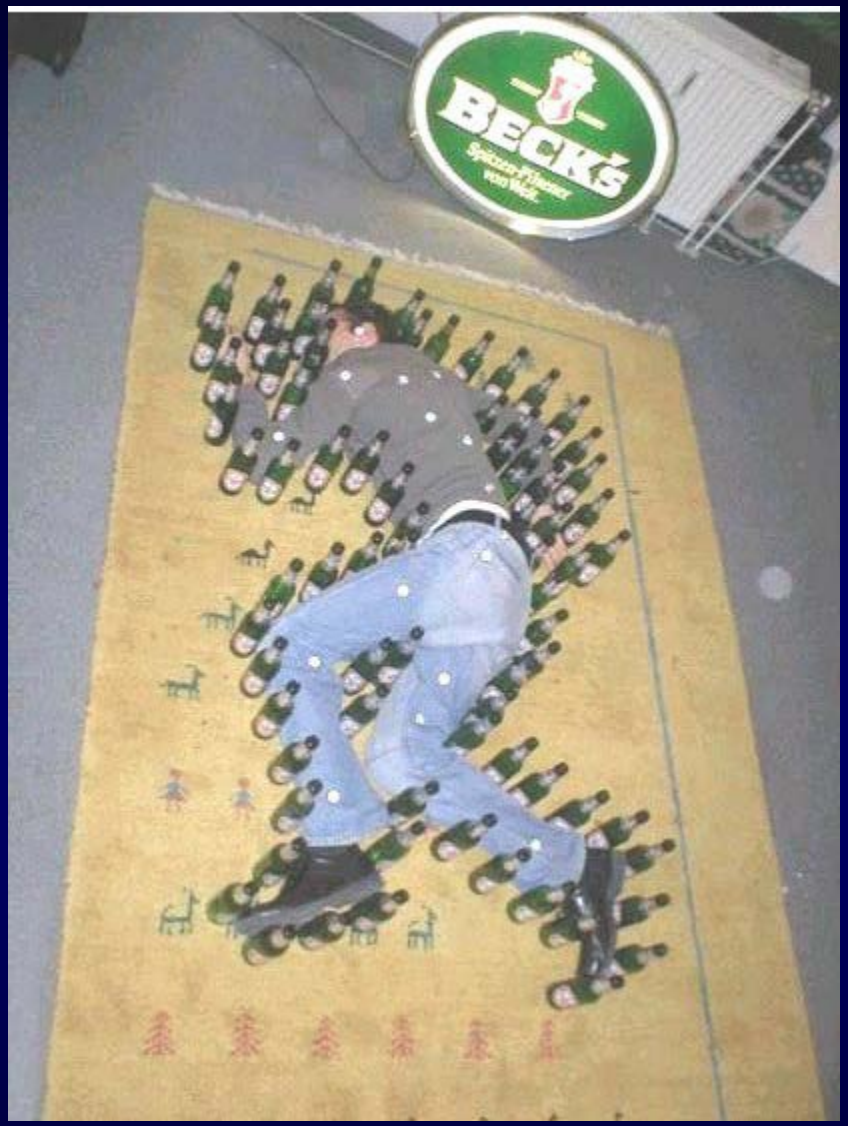
Long-Term Memory ("Learning") (Hard-drive)

Memories of thoughts, events and facts you encounter are permanently recorded in the structure of your brain; one process thought to underlie this is long-term potentiation (LTP)

Research suggests that this process occurs best when a person is sleeping, in a phase of sleep called Rapid Eye-Movement sleep



Alcohol affects neurotransmitters in a way that DOES make you go to “sleep” but…..

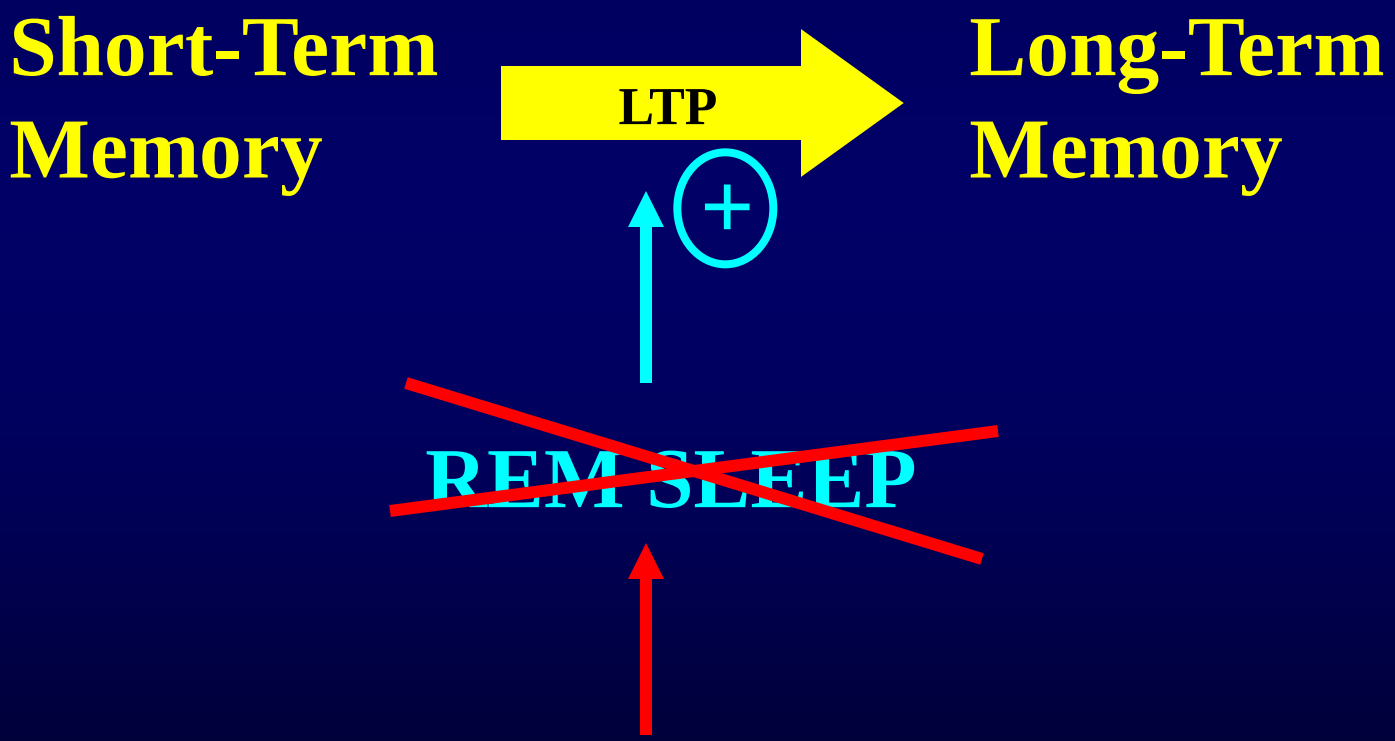


…but it is actually more like surgical anesthesia

…and you can’t be roused or protect yourself…

Although some find this a source of humor, many people die every year from aspirating vomit after "passing out" on their backs. Also, alcohol is a leading factor in many incidents of sexual assault.

Alcohol impairs memory formation for two reasons:

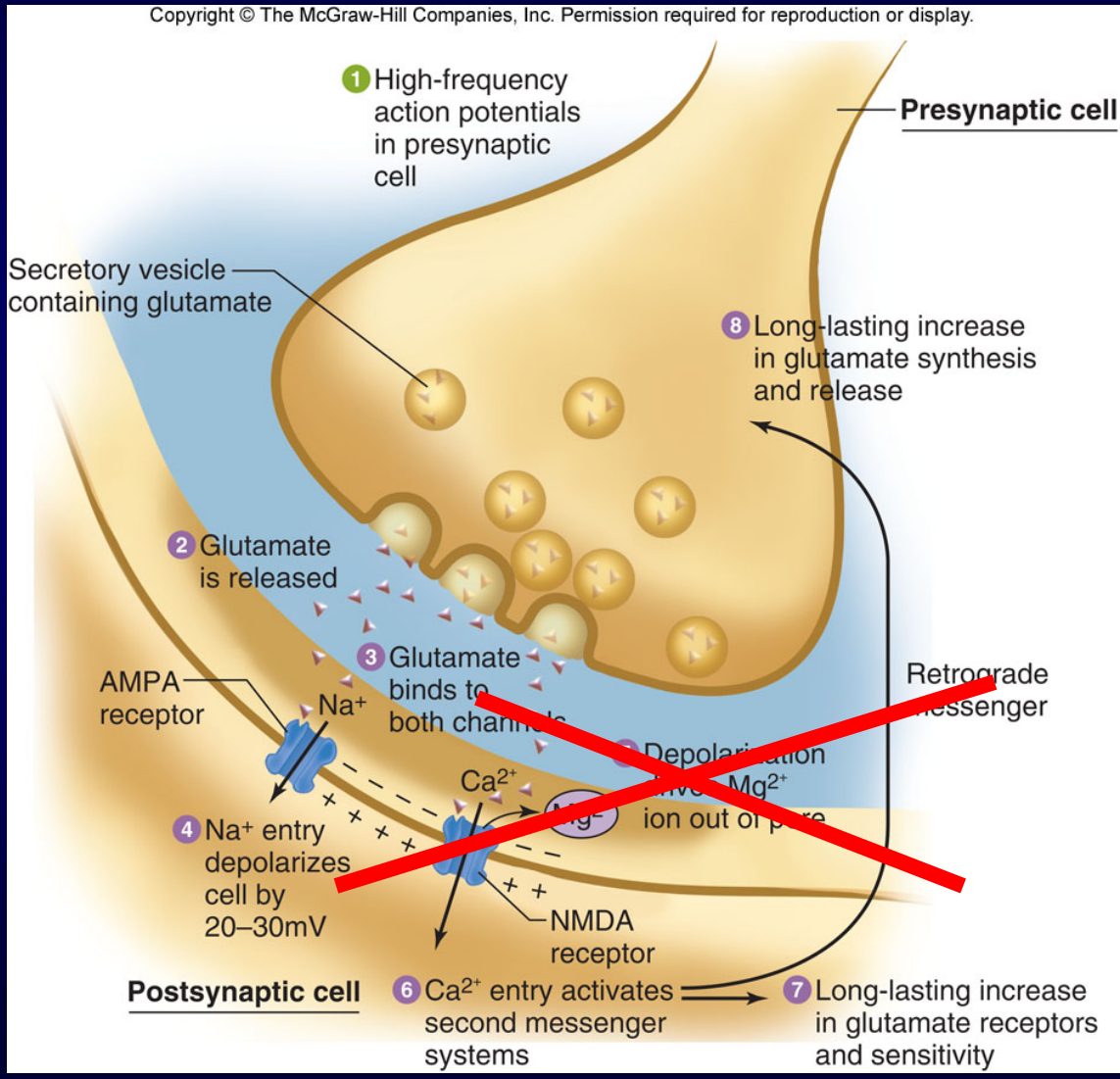


1. ETHANOL BLOCKS REM SLEEP

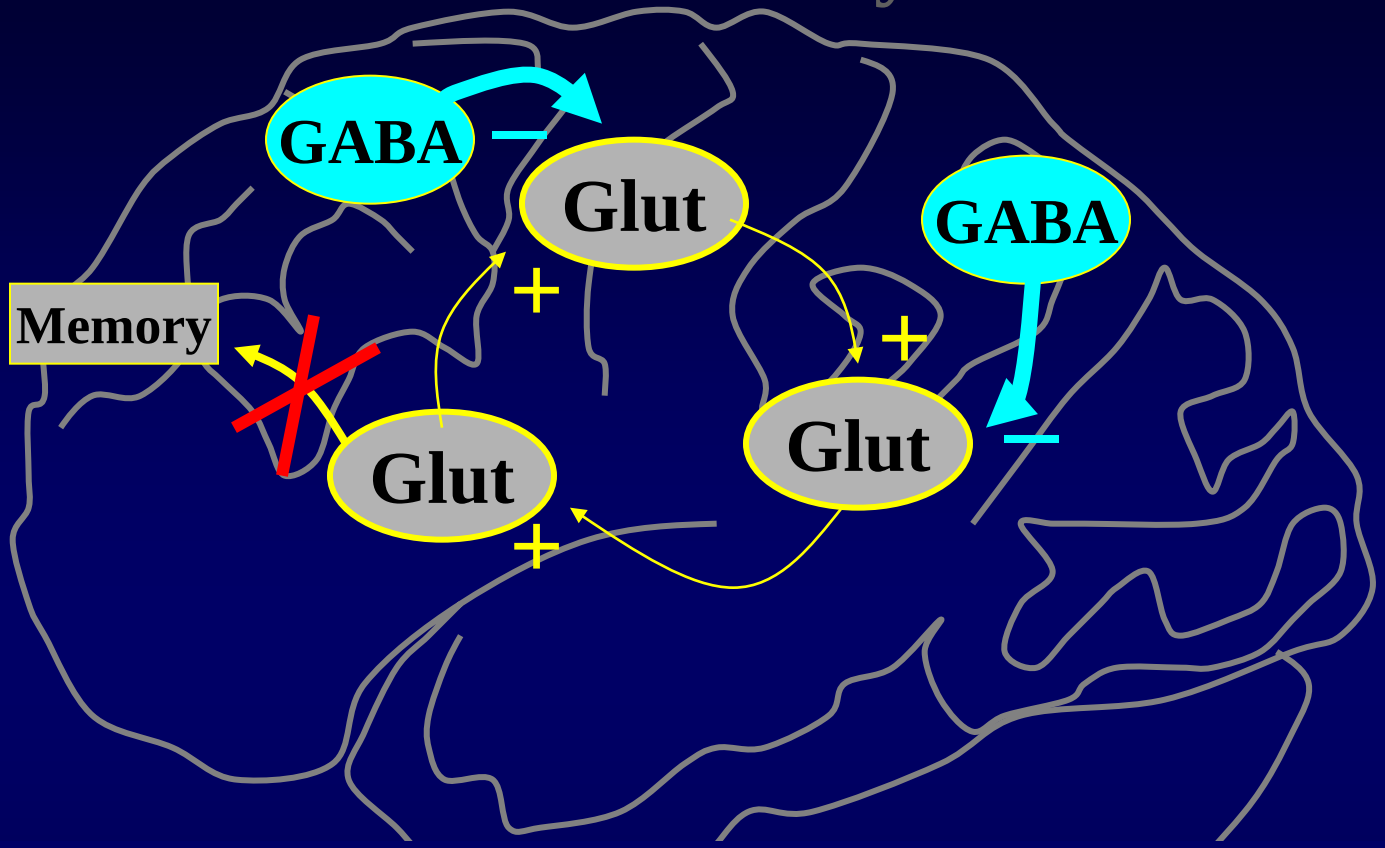
2. ETHANOL INHIBITS LTP

Long-term potentiation at glutamate synapses is a cellular correlate of memory formation

Even at moderate doses alcohol begins to inhibit LTP….



Inhibition of memory formation



Impaired long-term memory formation:

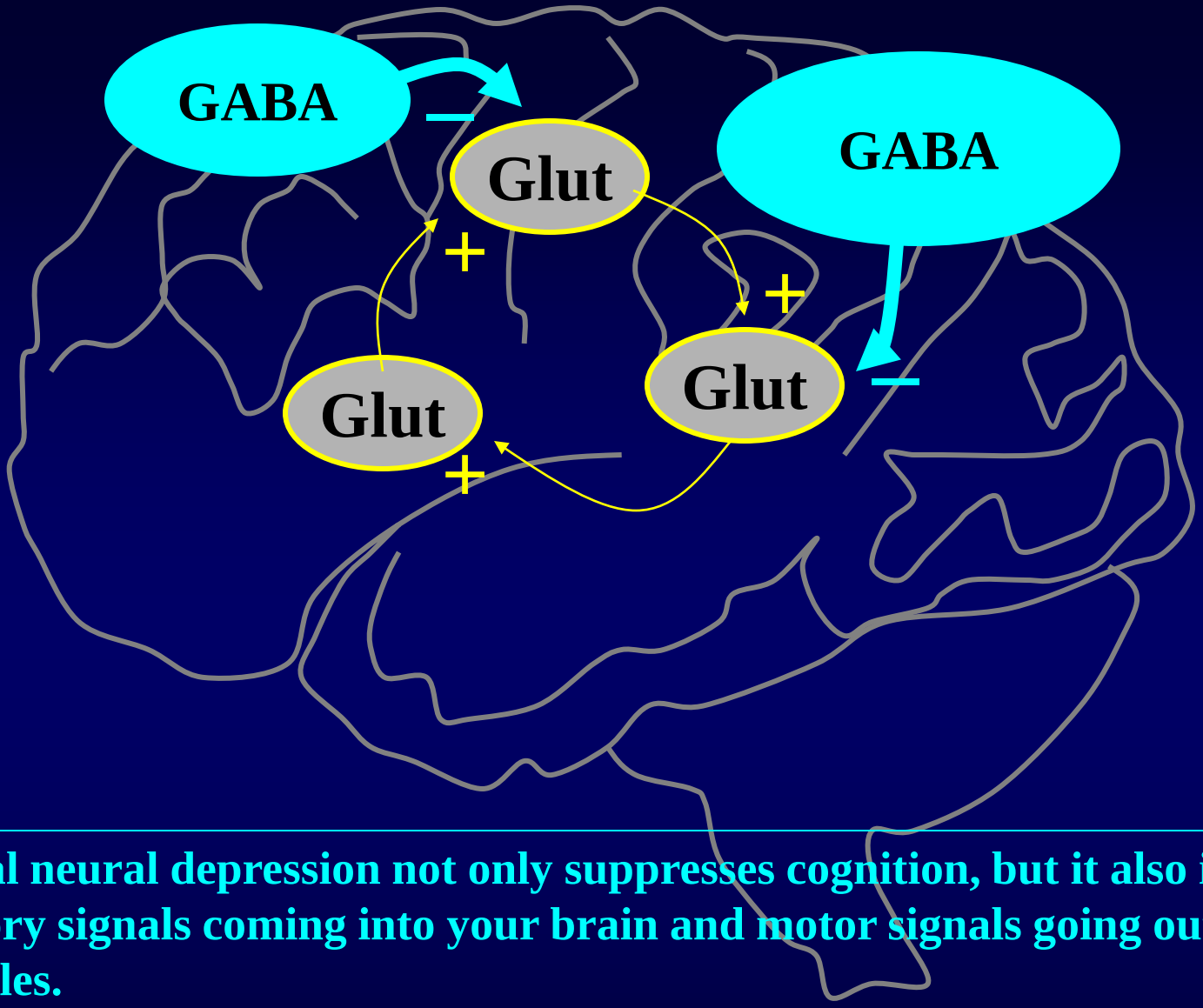
After a single drink, LTP is reduced 30%

At BAC of 0.2%, LTP is reduced 80%

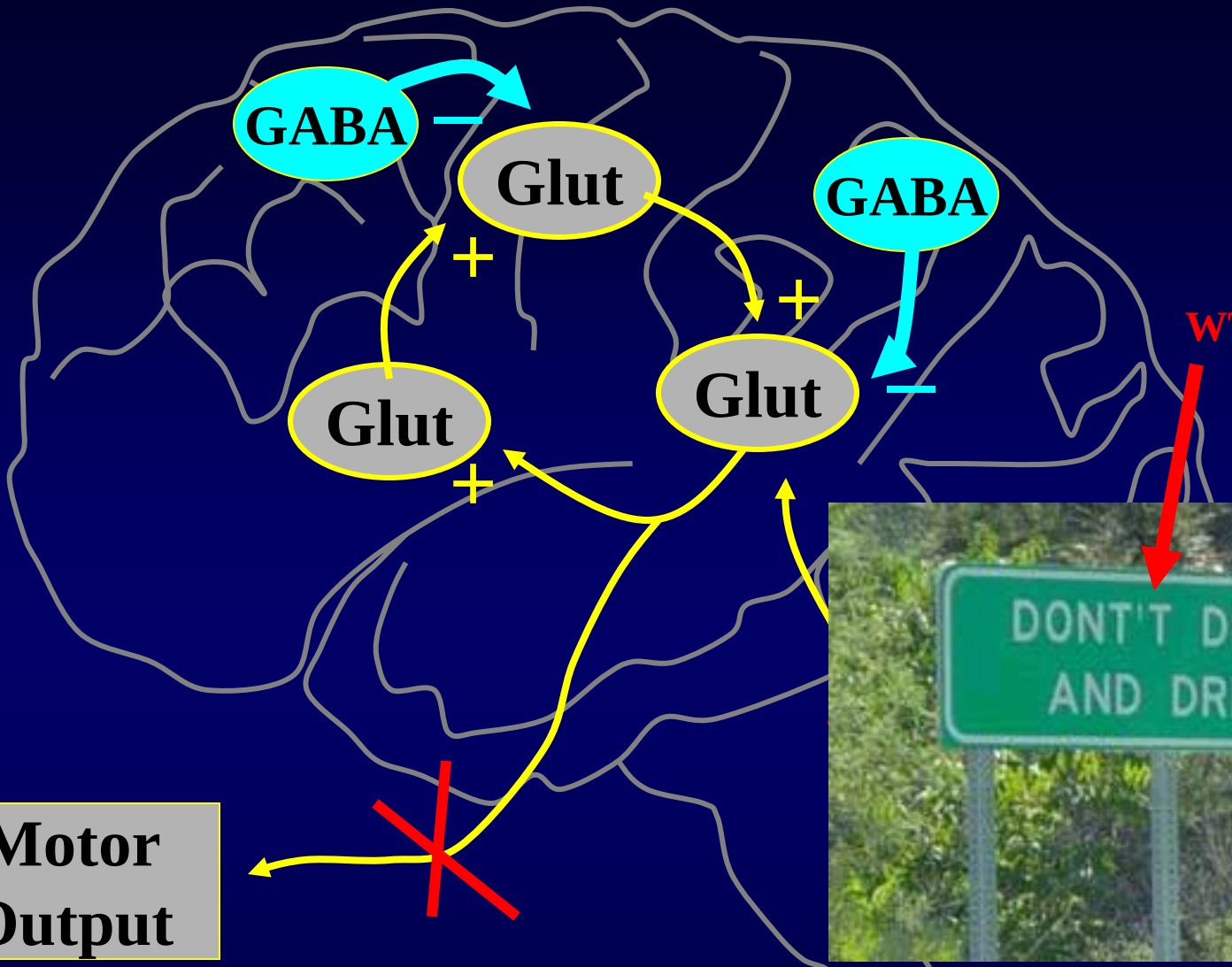
Total amnesia/blackout can occur at higher levels…

Why college students often fail:

Why Do Drunks Talk Loud, Fall Down, and Get the Bed Spins?



Global neural depression not only suppresses cognition, but it also impairs sensory signals coming into your brain and motor signals going out to your muscles.



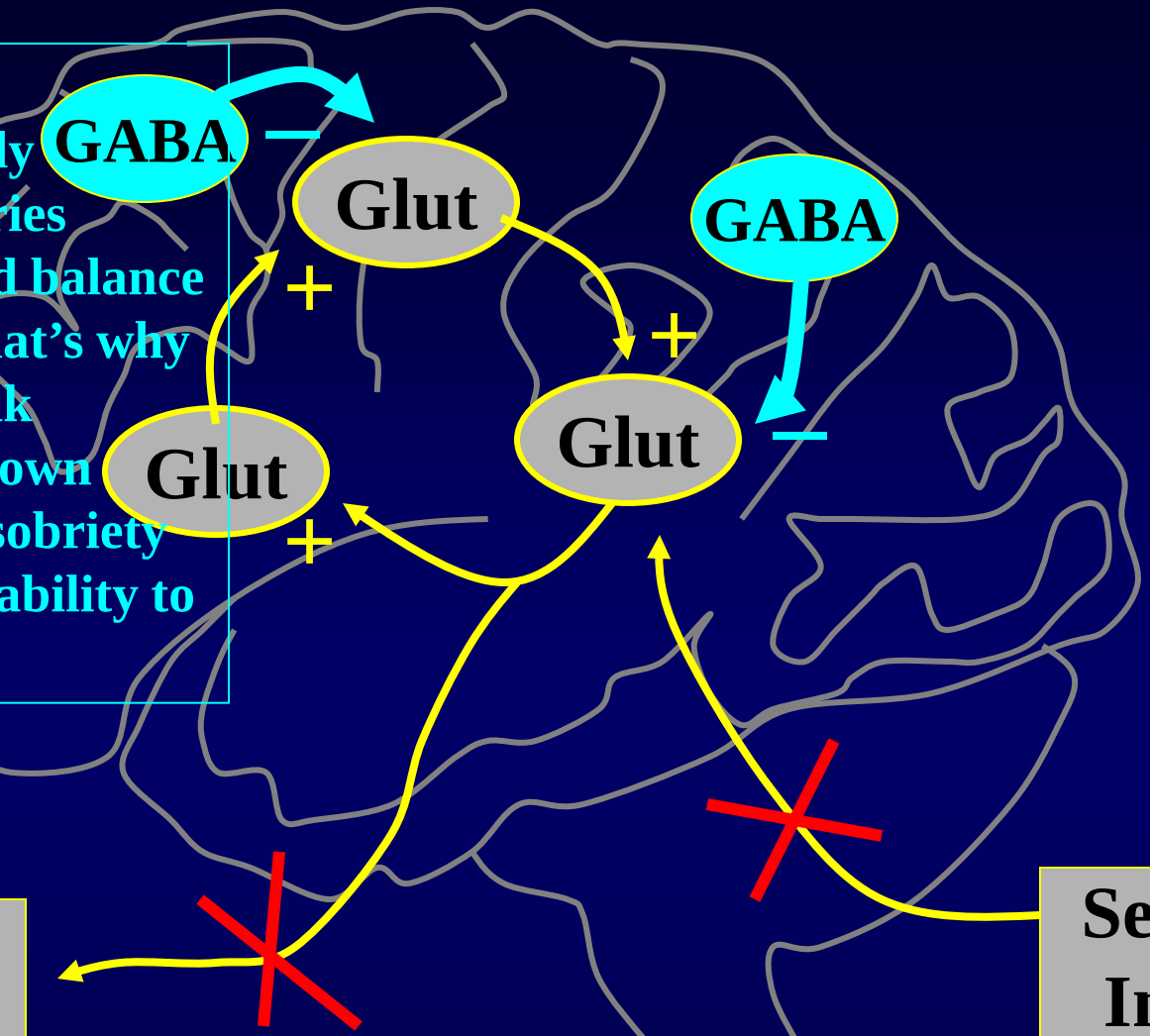
WTF!?

SIDE EFFECT: Depression of motor output and sensory input

1. Loss of coordination

There is a drunk-driving accident every 2 minutes in America; every 30 minutes there is a fatality. Inhibition of nerve signals to your muscles is one reason, alcohol –induced "falling asleep" at the wheel.

The 8th cranial nerve is especially sensitive. It carries both hearing and balance information. That's why drunk people talk loudly and fall down a lot! The field sobriety test assesses the ability to balance.



SIDE EFFECT: Depression of motor output and sensory input

1. Loss of coordination (*see drunk driving stats*)
2. 8th Cranial Nerve especially sensitive

(*"Dude, turn it up!"*) (*Field sobriety test*) (*Bed spins*)

Calling alcohol a “Drug” doesn’t mean it is evil….

Calling alcohol a “Drug” doesn’t mean it is evil….

Prescription	Illegal	OTC
Oxycontin	Cocaine	Tylenol
Prozac	Ecstasy	Nyquil
Valium	THC	Ipecac
Penicillin	Heroin	Aspirin

What do all “drugs” (and alcohol) have in common?

1. **Sought-after effects**
2. **Unintended side-effects**
3. **The dose determines the effect/side-effect ratio**

Calling alcohol a “Drug” doesn’t mean it is evil….

In moderate doses (<1-2 drinks/day), alcohol appears to cause no harm*, and much evidence suggests that it may have positive effects.

***EXCEPT in those who are pregnant, under 21, or susceptible to alcoholism.**

In excess, however……..

…..it is.

The End

Questions? kstrang@wisc.edu