The Neuroscience of Addiction

Robert Walker, M.S.W., L.C.S.W.,
Assistant Professor
University of Kentucky
Department of Behavioral Science and
Center on Drug and Alcohol Research

Why do we need brain science on addiction for community projects?

- First, there is a vast and growing body of neuroscience about the brain as well as social and psychological research about behavior.
- Much of the research challenges our daily attitudes and beliefs about addiction.
- Second, with any coherent treatment program, it can be useful to try and draw people together into a more closely shared perception of the problem to be addressed.

Vulnerability to Addiction

- There is a growing body of evidence of structural vulnerability of brains to the effects of intoxicating substances.
- Several factors contribute to this vulnerability:

1. Genetic – both the core DNA and also gene promoters that "turn on" certain genes
2. Early developmental influences and environmental factors
3. Effects of stressful life events across the life cycle
4. Co-occurring mental disorders – principally depression and anxiety

Genetics

- Evidence has been found for a genetic influence on alcoholism, opiate dependence and, less robustly, other CNS depressants such as tranquilizers.
- Genes do not make the disorder; they merely present an increased vulnerability to having the disorder.
- Genetic vulnerability to depression and anxiety can also contribute to a vulnerability to drug dependence.
- Gene expression can also be altered by life experiences as with chronic severe depression.

Drug use and neuro-vulnerabilities

- Some brains may have impaired neurotransmitter availability and this can lead to vulnerability for substance abuse.
- Likewise, some brains may simply be more sensitive to the euphoriant effects of certain drugs.
- For example, opiates for most people are distasteful, causing vomiting and a foggy feeling. For those who have a particular mu-opioid receptor site gene (A118G), the opiate produces a feeling of wholeness and peace in the world.

Who is vulnerable?

- Persons most at risk for substance abuse and more so, dependence, generally have higher rates of impulsivity, more difficulty managing negative affects – their moods and feelings.
- There can also be early childhood environmental factors that affect how the brain adapts to environmental stress and those adaptations may pose a risk for addiction later in life.
- It might be said this way: the capacity may be limited for maintaining the optimal neurotransmission stability in some brains and this can affect a person's thinking, behaving, and range of emotions.
- The drug dependent person, even before ever using drugs, often has brain characteristics that may predispose a vulnerability to the effects of mind-altering drugs.
- In addition, after a long period of using drugs, the addicted person ends up with a substantially altered brain – chemically and even anatomically.

Brain & Behavior

- Neuroscience, over the past 50 years has shown that every thought, sensation, emotion, physical movement is accounted for in terms of brain structures and chemistry.
- This is not say that everything is *caused* by neurons, but nothing happens in human behavior except by the mechanisms of the brain.
- Behavior, including addiction is related to:
  1. Anatomical characteristics of brain regions;
  2. The functions of neurons, including their connectivity into pathways or "circuits"; and,
  3. The neurochemistry that exists between neurons that allows them to interact.

Brain and Behavior: The 2-Way Street

- Thinking, feeling and behaving *are* *produced* by brain anatomy and chemistry.
- Conversely, thinking, feeling and behaving *shape* the development of brain anatomy and chemistry.
- Just as brain structures can affect behavior (e.g., a stroke's effect on speech), likewise personal experience can affect brain structures.
- Neurodevelopmental studies have shown that many critical brain anatomy and chemistry functions get "set" by about age 22 months.
- The fundamental arousal levels and abilities to manage arousal states tend to be fixed by this early age.
- Also, the experiences of severe trauma, severe chronic depression, long term abuse of alcohol, and heavy use of marijuana have all been shown to result in loss of brain cells in the brain's memory-forming and retrieving center, the hippocampus.

It's all happening here

- With this new science, we can see how the brain shapes capacities to behave and also how environment and behavior shape future development of the brain.
- While early experiences are key, this process goes on throughout the life cycle.
- In fact, both positive and negative changes are detectable even in elder years.

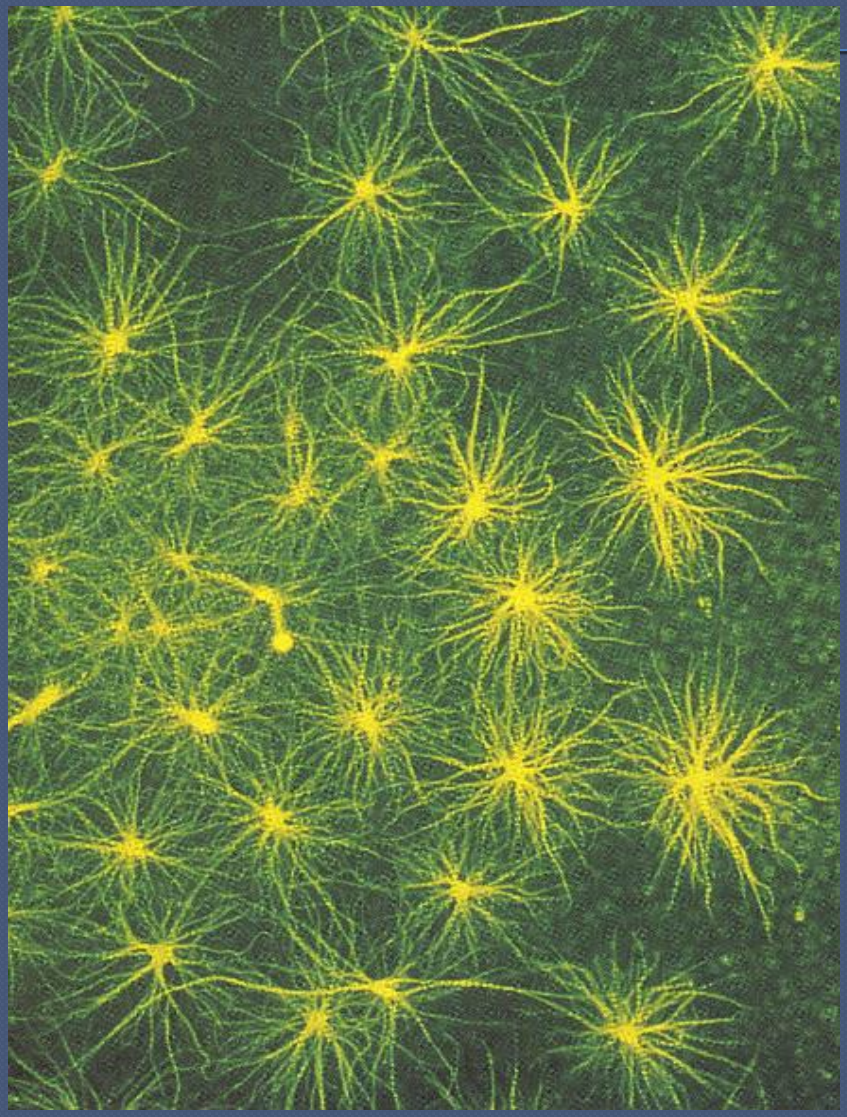
Let's start with anatomical structures: Cellular, then higher up

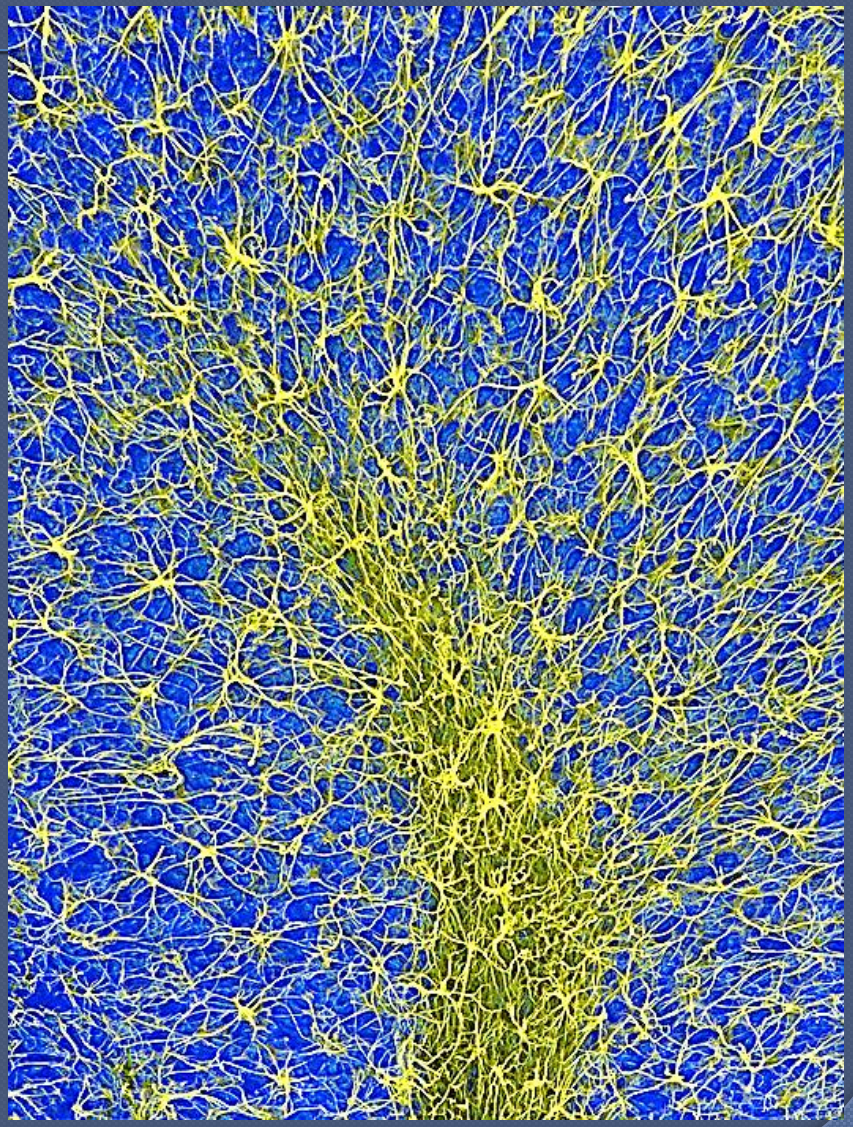
Neurons

- We need to think about the fundamental cells that make up the brain. Neurons will be our central concern.
- However, there are several other cells such as glial cells that help provide nutrients for neurons and that also serve early in brain development to assist in cell migration.
  - Glial cells are known as the "glue" of the nervous system.
  - The four main functions of glial cells are to surround neurons and maintain them in place, to supply nutrients and oxygen to neurons, to insulate one neuron from another, and to destroy pathogens and remove dead neurons.

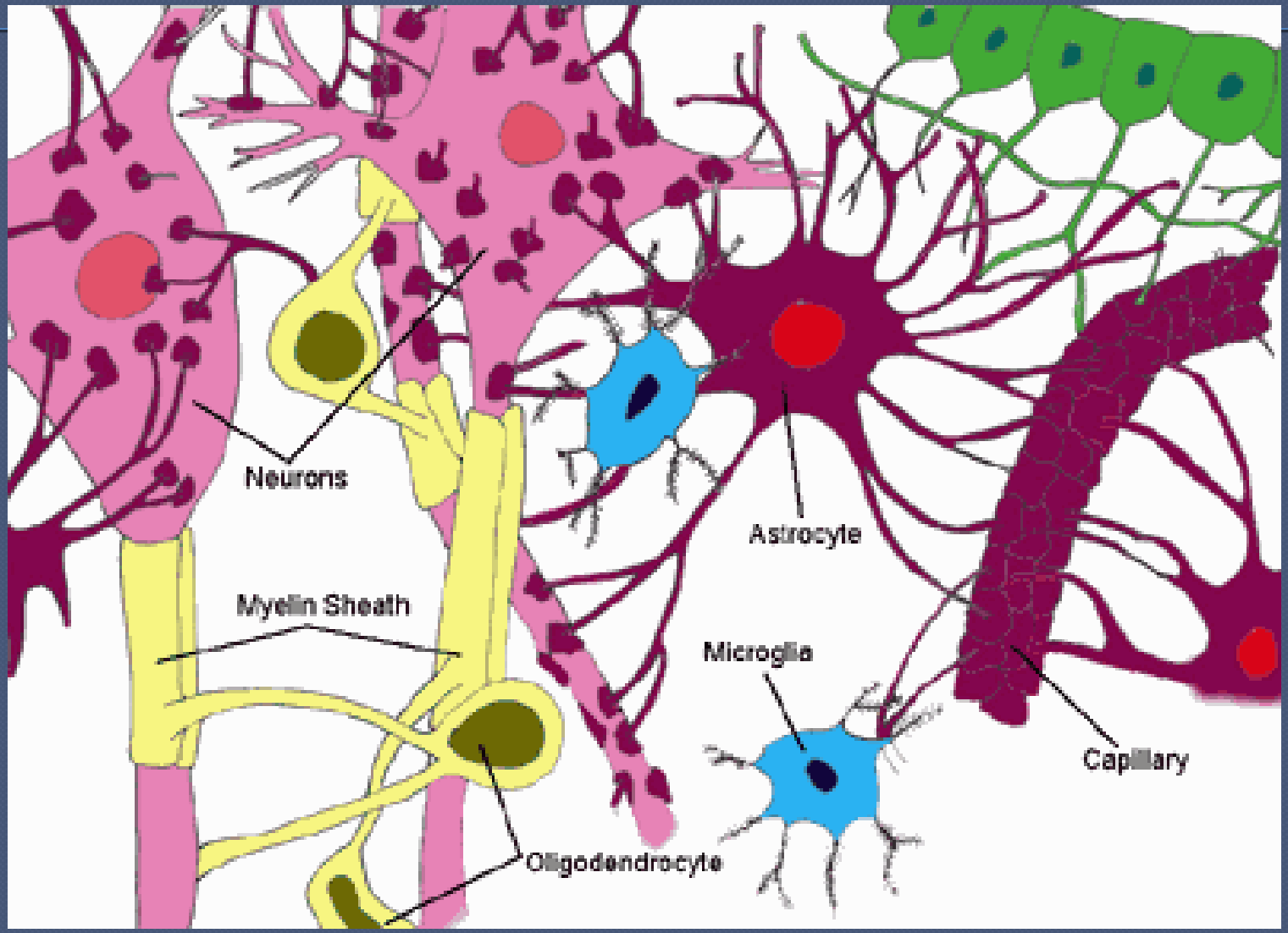
- There are about 100 billion neurons in the average adult brain – or about 1/2 to 1/3 the number of stars in the Milky Way galaxy.
- Since each neuron has many connections to others (6,000 to 10,000), there are about 100 trillion possible synaptic connections between nerve cells.

Astrocytes





Neurons and glial cells

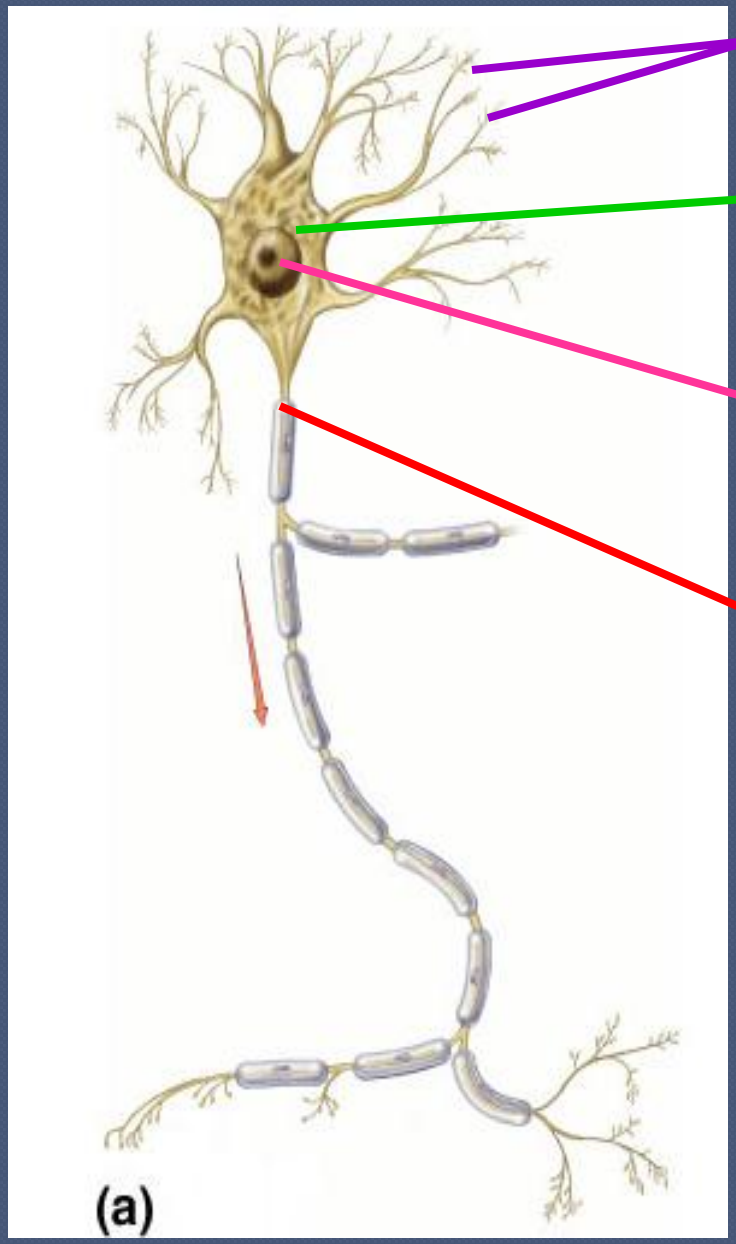


The Neuron

The cell body has a nucleus and numerous organelles

A single axon carrying impulses **away** from the cell body

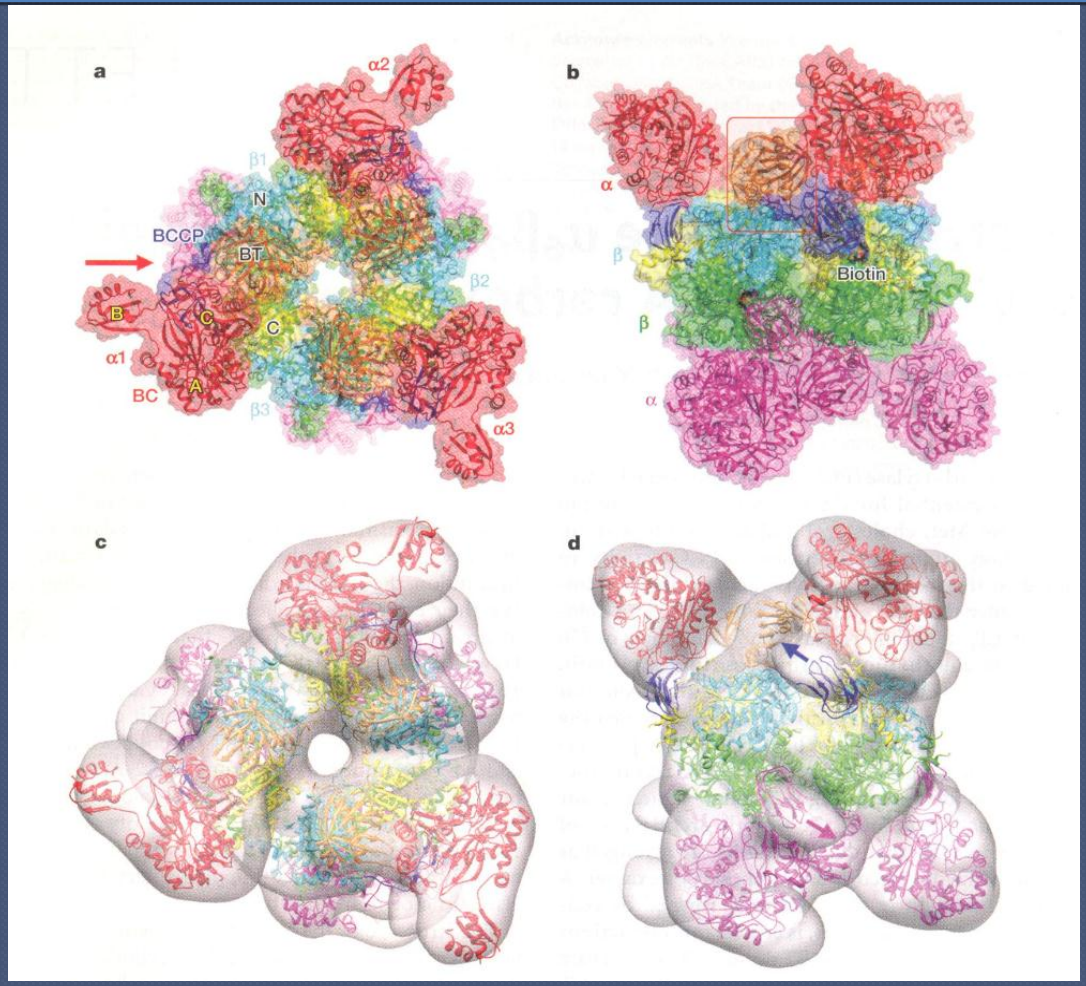
One or more dendrites bringing impulses **in** to the cell body



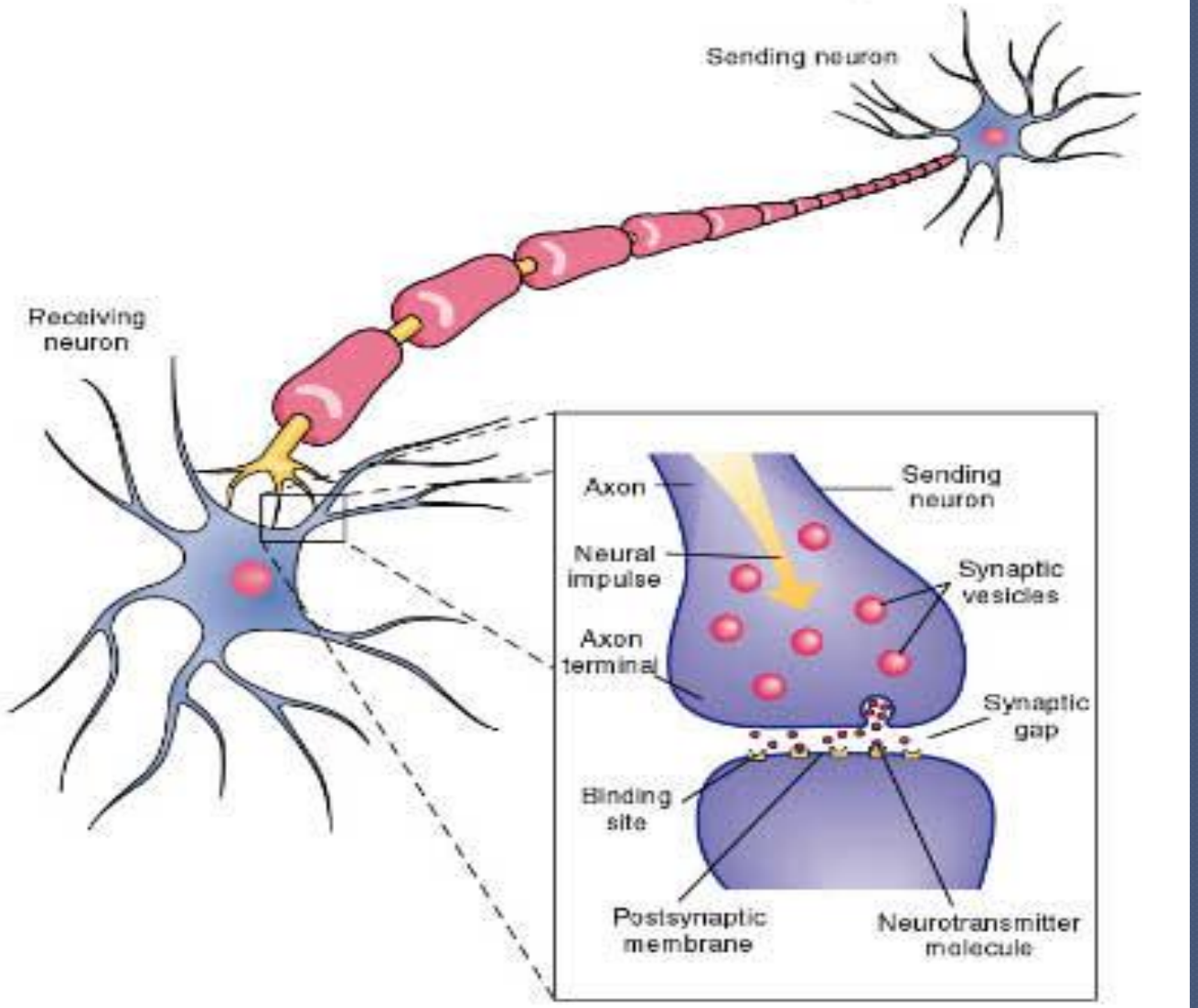
Neurotransmitters

- Neurons communicate across synaptic gaps by discharging and absorbing neurotransmitters.
- Neurotransmitters are complex organic messenger molecules.
- There is scientific data on about 50 neurotransmitters and there are probably some 300 neurotransmitters in the human brain.
- The production and absorption of neurotransmitters is basically set by genetic codes and both production and absorption can be altered by drug use, diseases, environmental exposures, and life experiences.

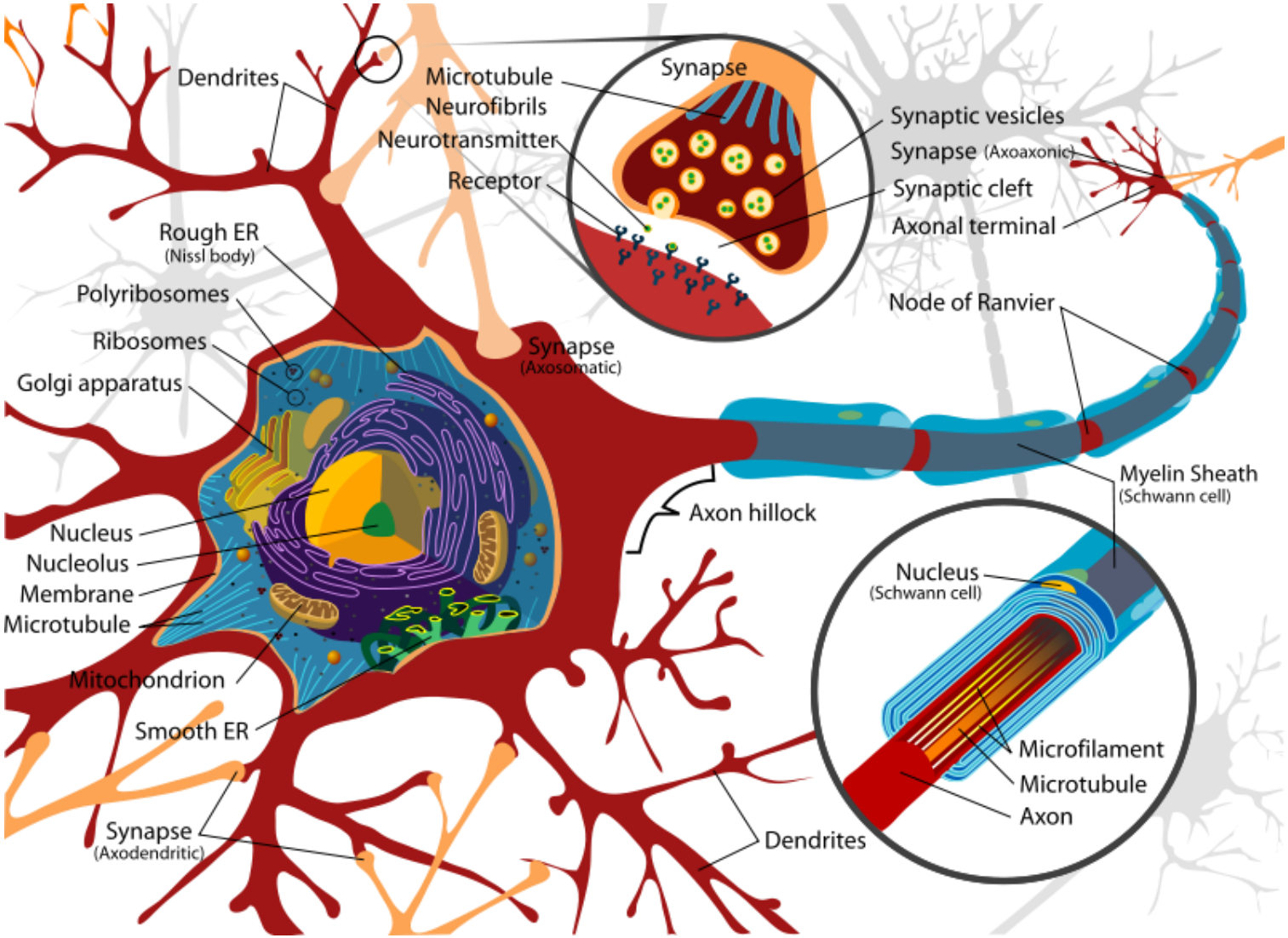
Molecular shapes

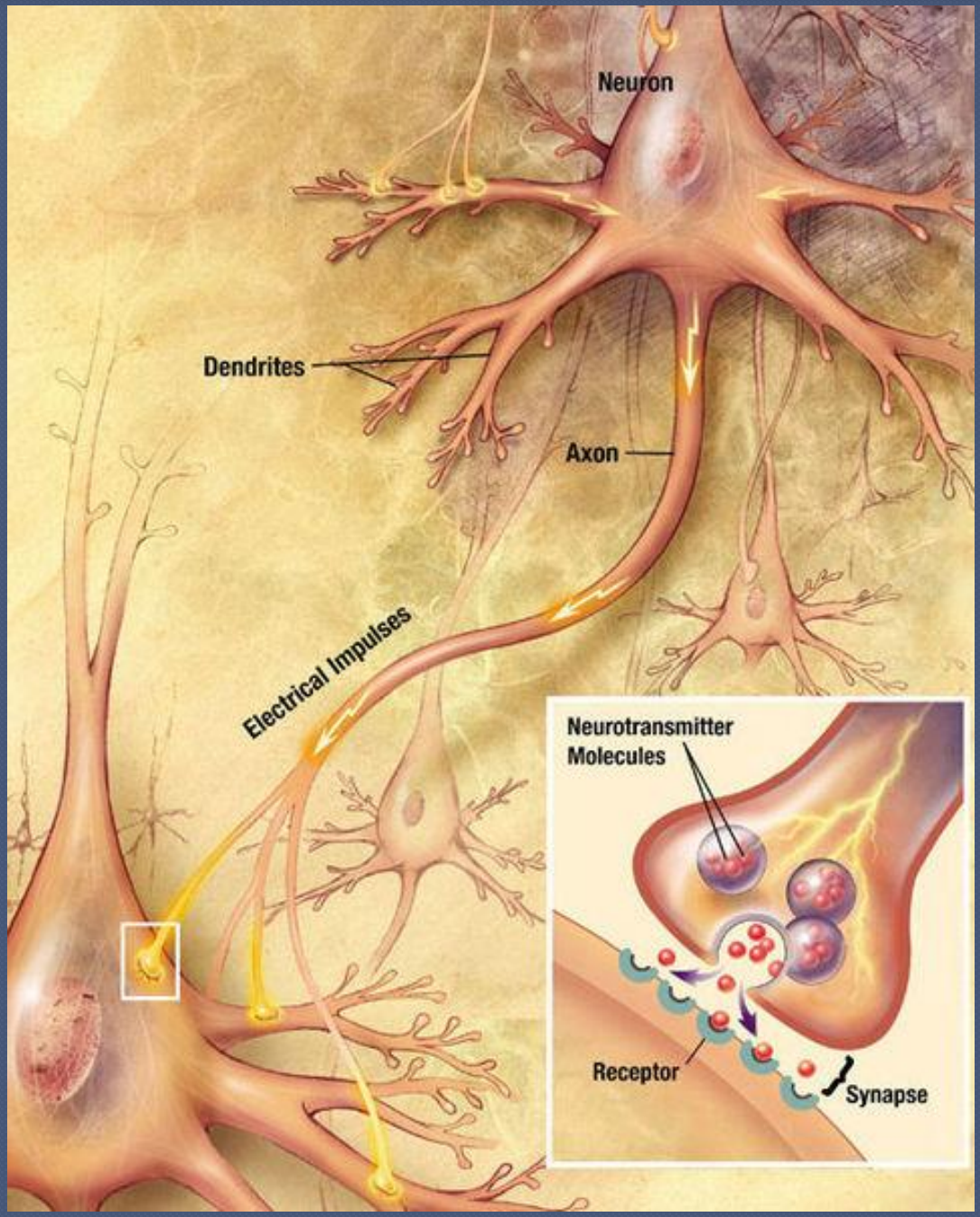


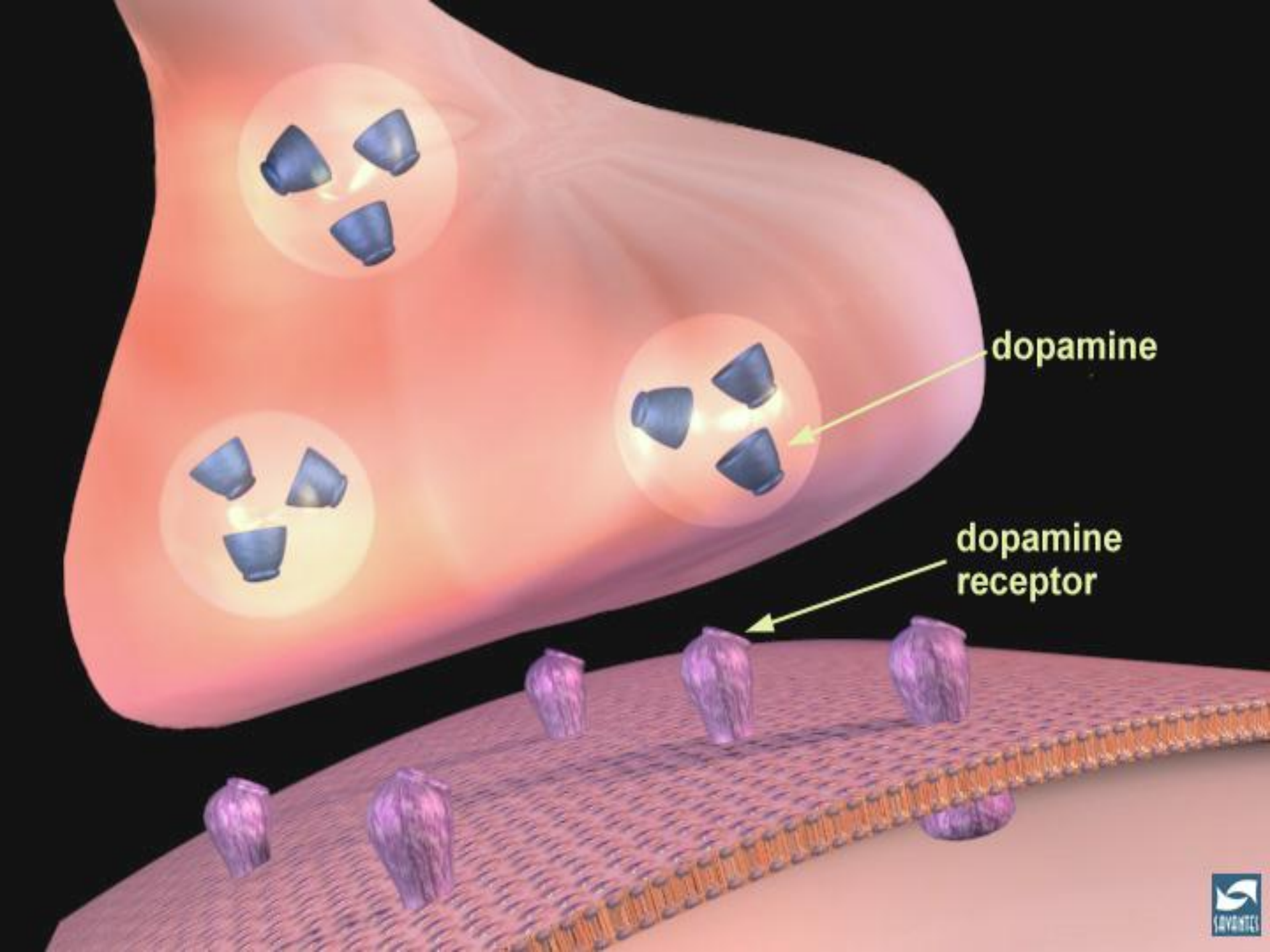
Neurotransmitters and the Synapse

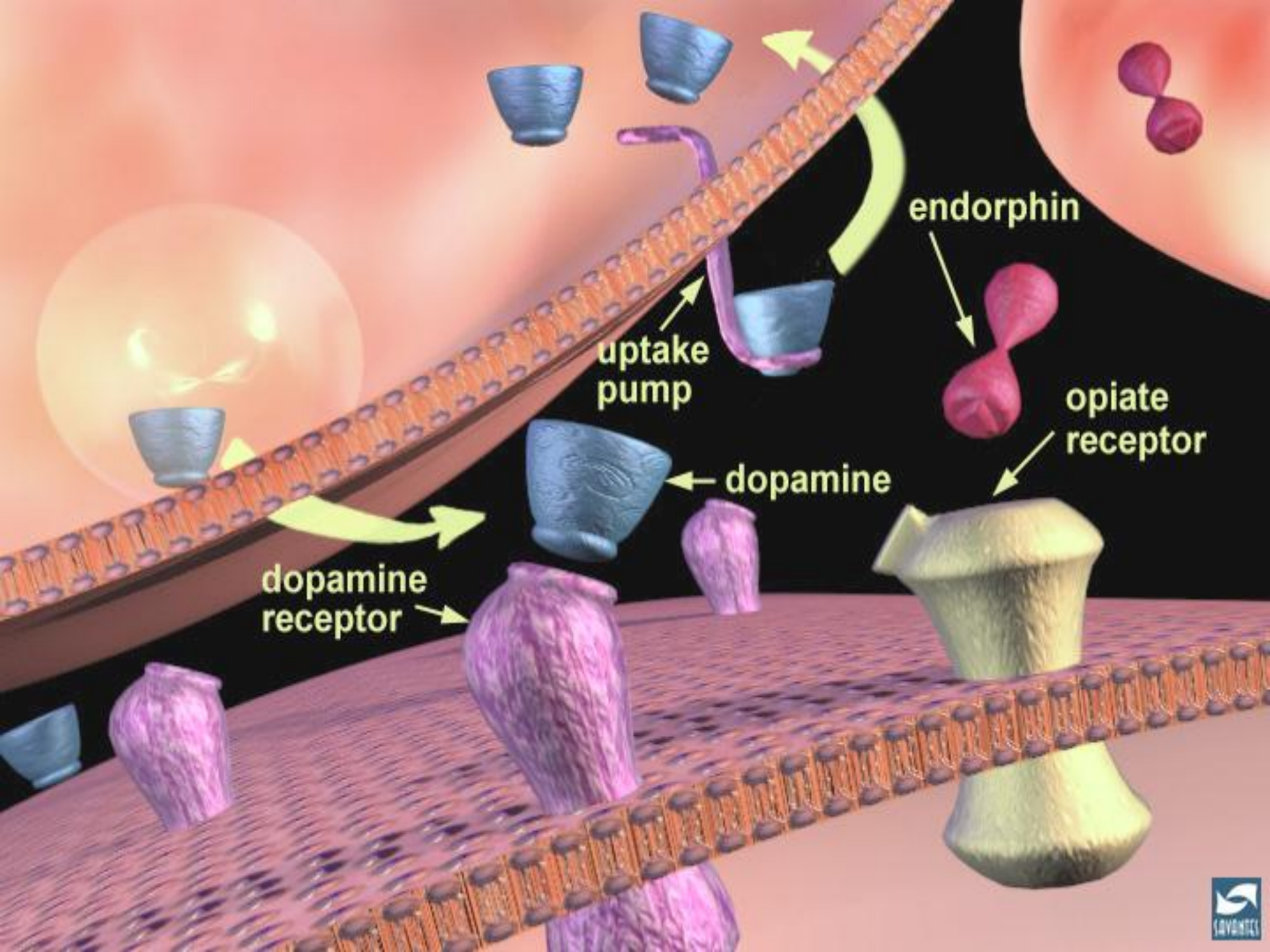


The neurotransmitter is released into the synaptic gap. There it may bind with receptors on the postsynaptic membrane.

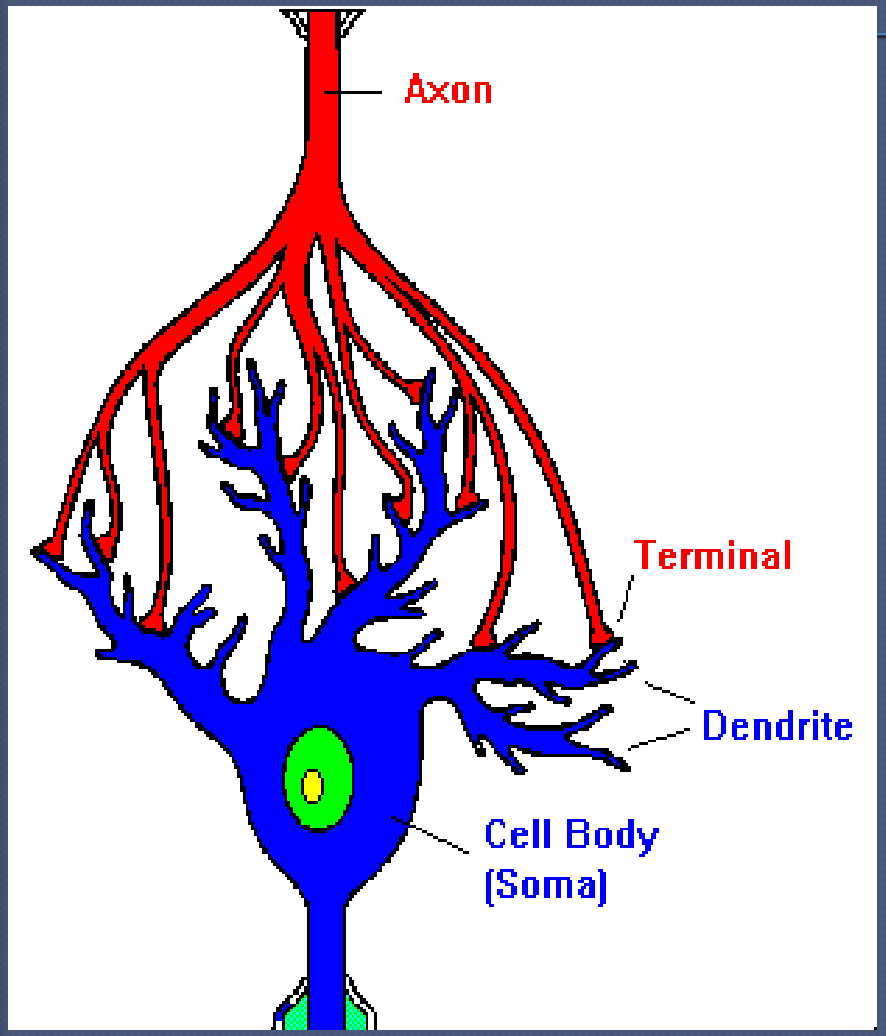

Dendrites
Microtubule
Neurofibrils
Neurotransmitter
Receptor
Synapse
Synaptic vesicles
Synapse (Axoaxonic)
Synaptic cleft
Axonal terminal
Rough ER
(Nissl body)
Polyribosomes
Ribosomes
Golgi apparatus
Synapse
(Axosomatic)
Node of Ranvier
Myelin Sheath
(Schwann cell)
Axon hillock
Nucleus
Nucleolus
Membrane
Microtubule
Mitochondrion
Smooth ER
Synapse
(Axodendritic)
Nucleus
(Schwann cell)
Microfilament
Microtubule
Axon
Dendrites

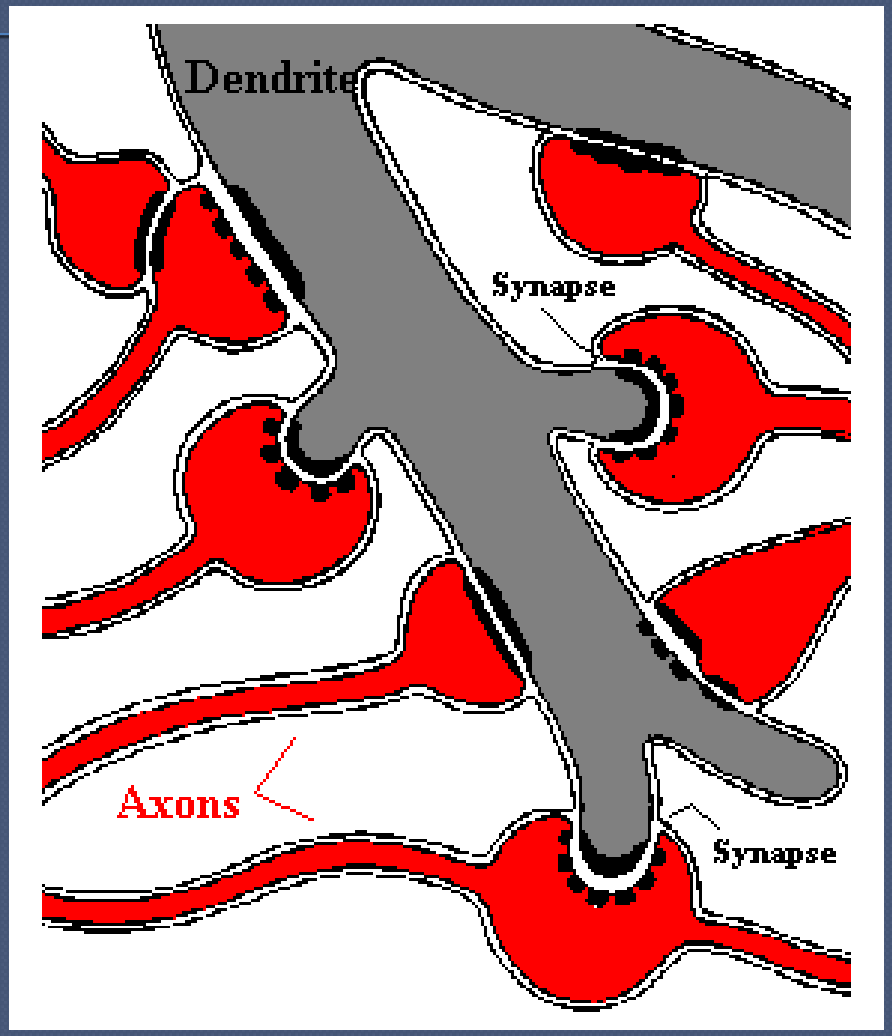

Neuron
Dendrites
Axon
Electrical Impulses
Neurotransmitter Molecules
Receptor
Synapse


dopamine
dopamine
receptor


endorphin
uptake pump
opiate receptor
dopamine
dopamine receptor

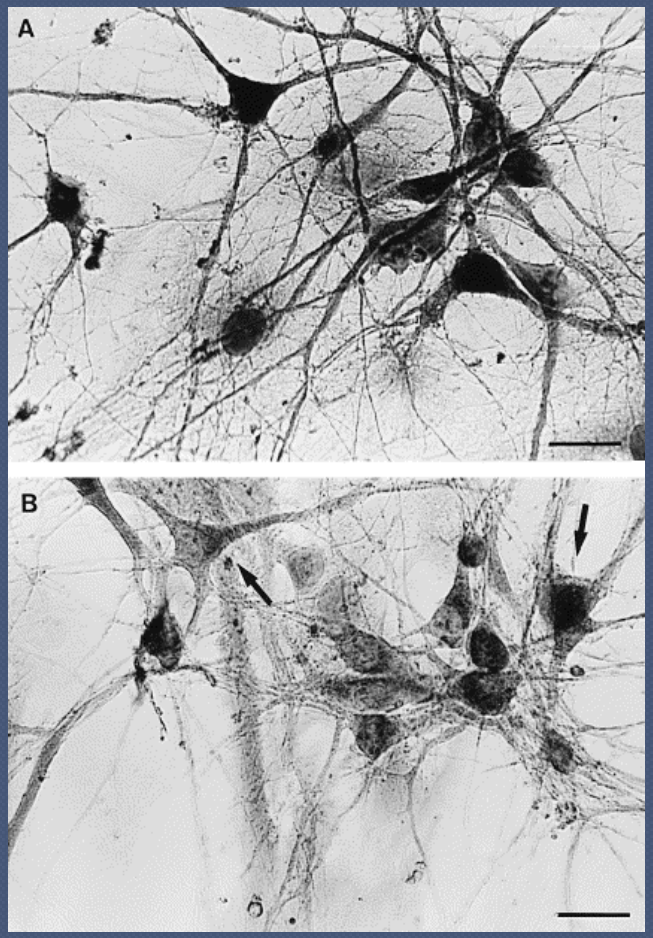
Neurons, receptors

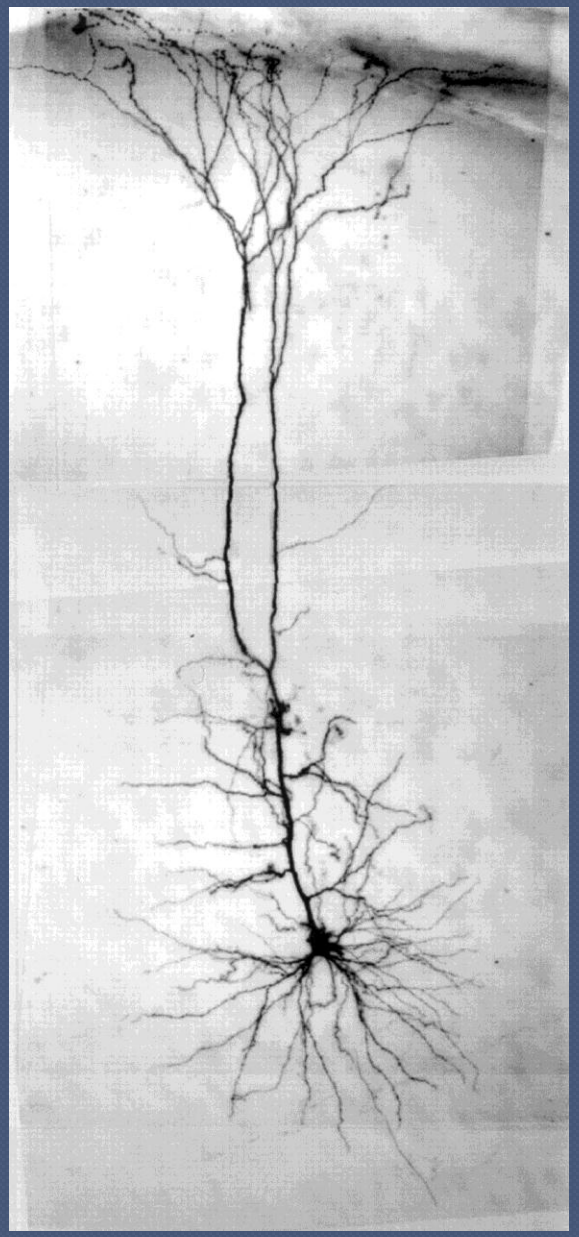




http://faculty.washington.edu/chudler/synapse.html

What they actually look like





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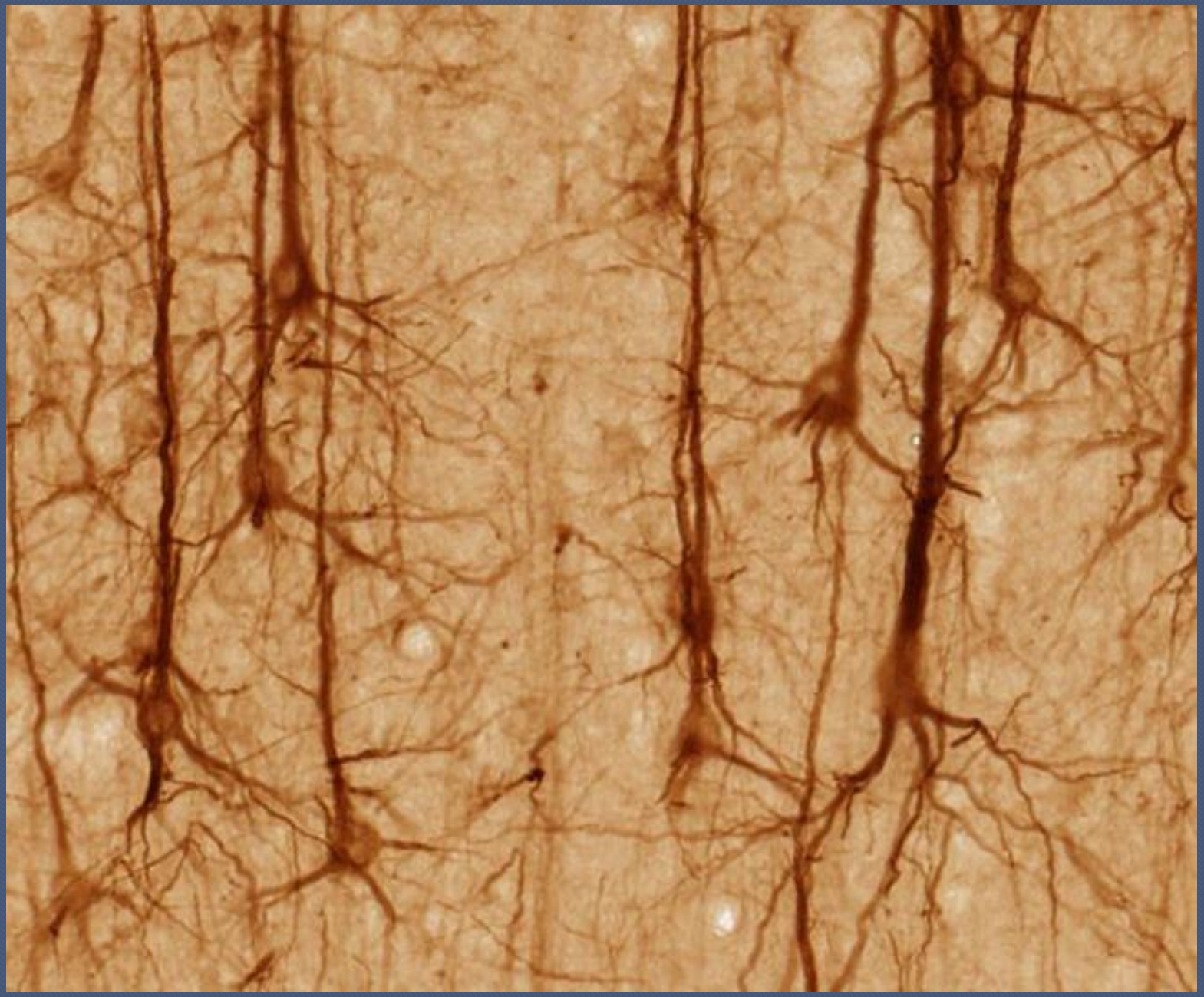
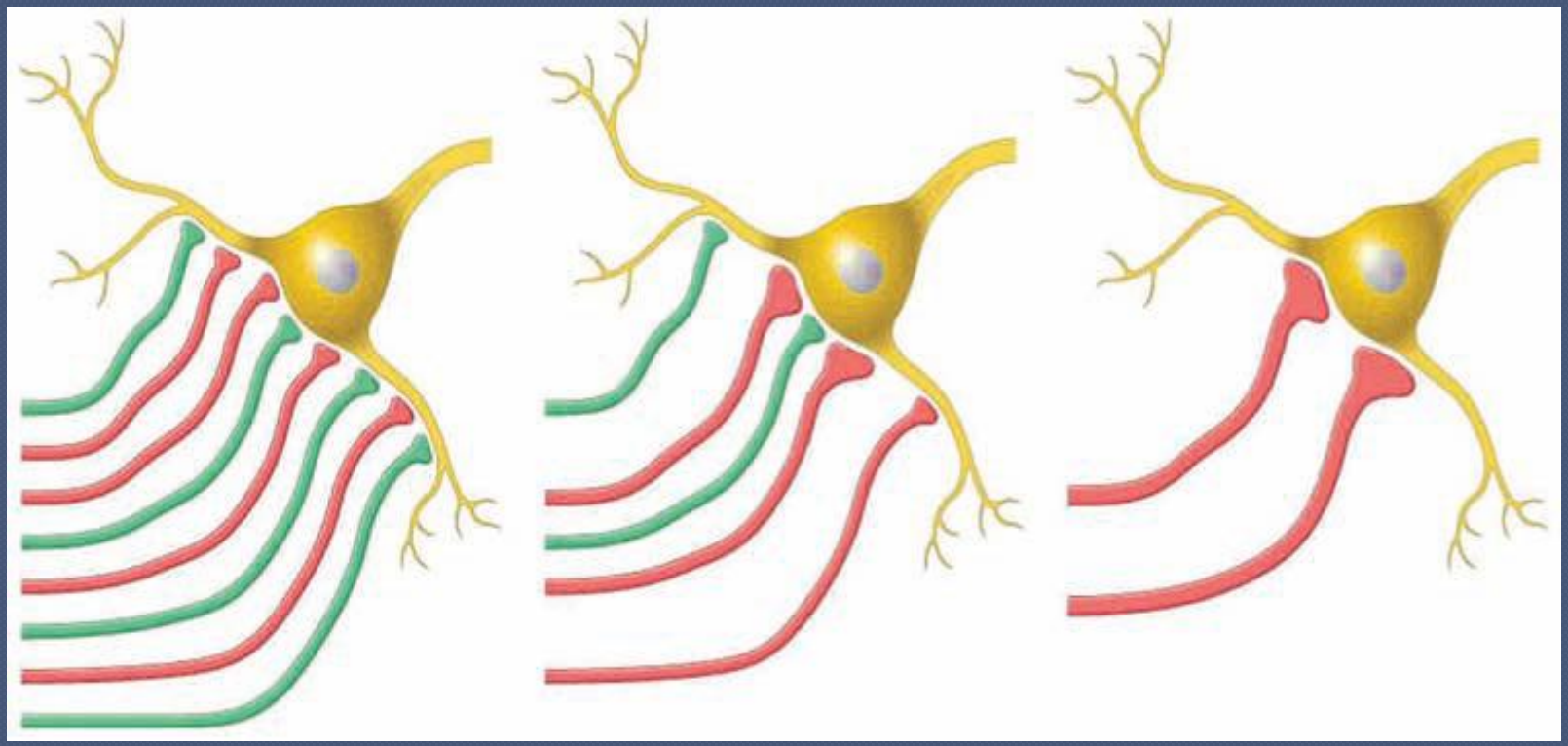


The natural development of neurons

- By age 2 one has the greatest number of neurons than at any other point in life.
- The efficient functioning of the brain requires pruning of excessive connections and too many neurons.
- Thus beginning around age 2, the neurons begin this pruning process in response to external stimulation of certain pathways.

Neural pruning showing two pathways gradually being pruned to one, with the one being strengthened



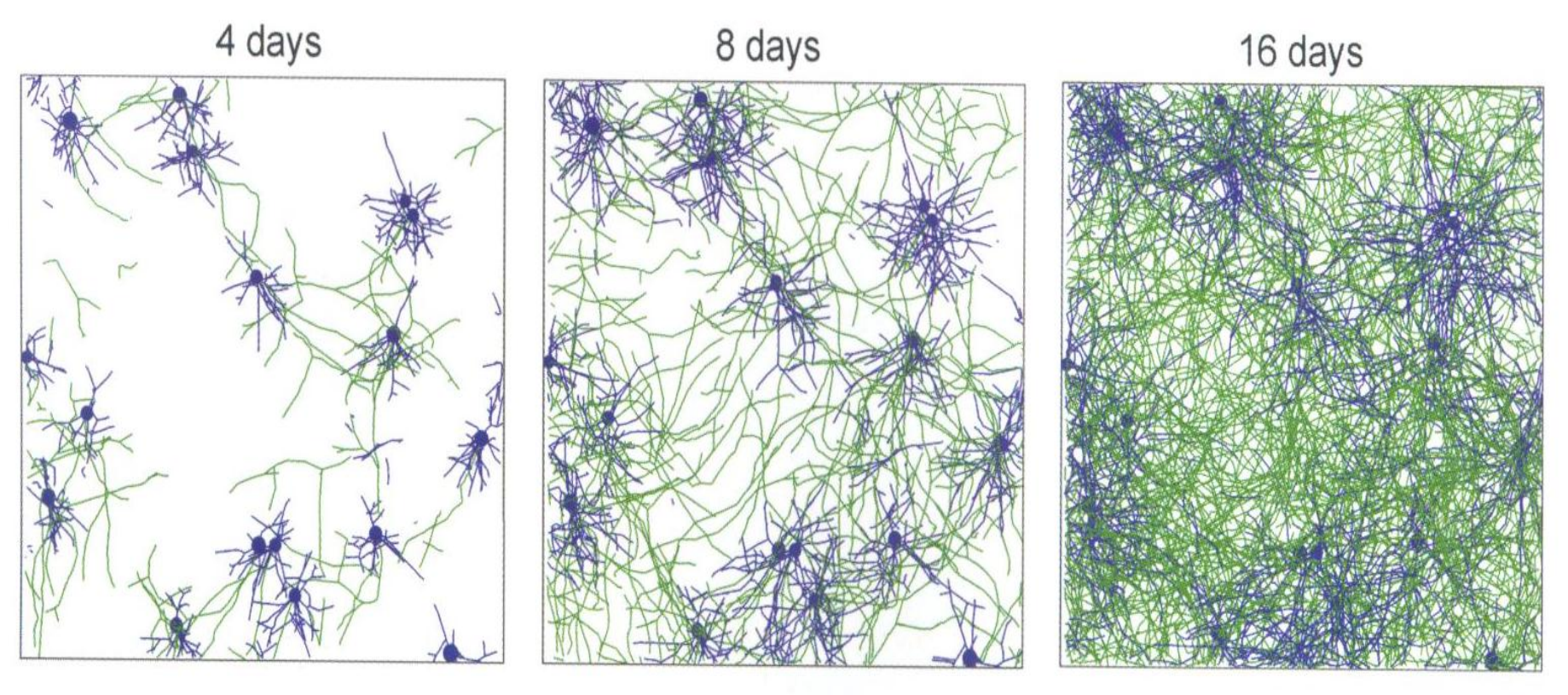
The natural development: nature/nurture

- Healthy infant stimulation guides this process toward nurture of positive neurobehavior and neurodevelopment.
- Mirroring enhances development of affective and cognitive pathways.
- Each stimulative act strengthens a neural pathway.
- Violent and/or under-stimulated (neglectful) environments affect this development very differently.
- Environments characterized by aggression, stimulate fight/flight pathways and the arousal system over-develops in one form or another.

But there is also growth

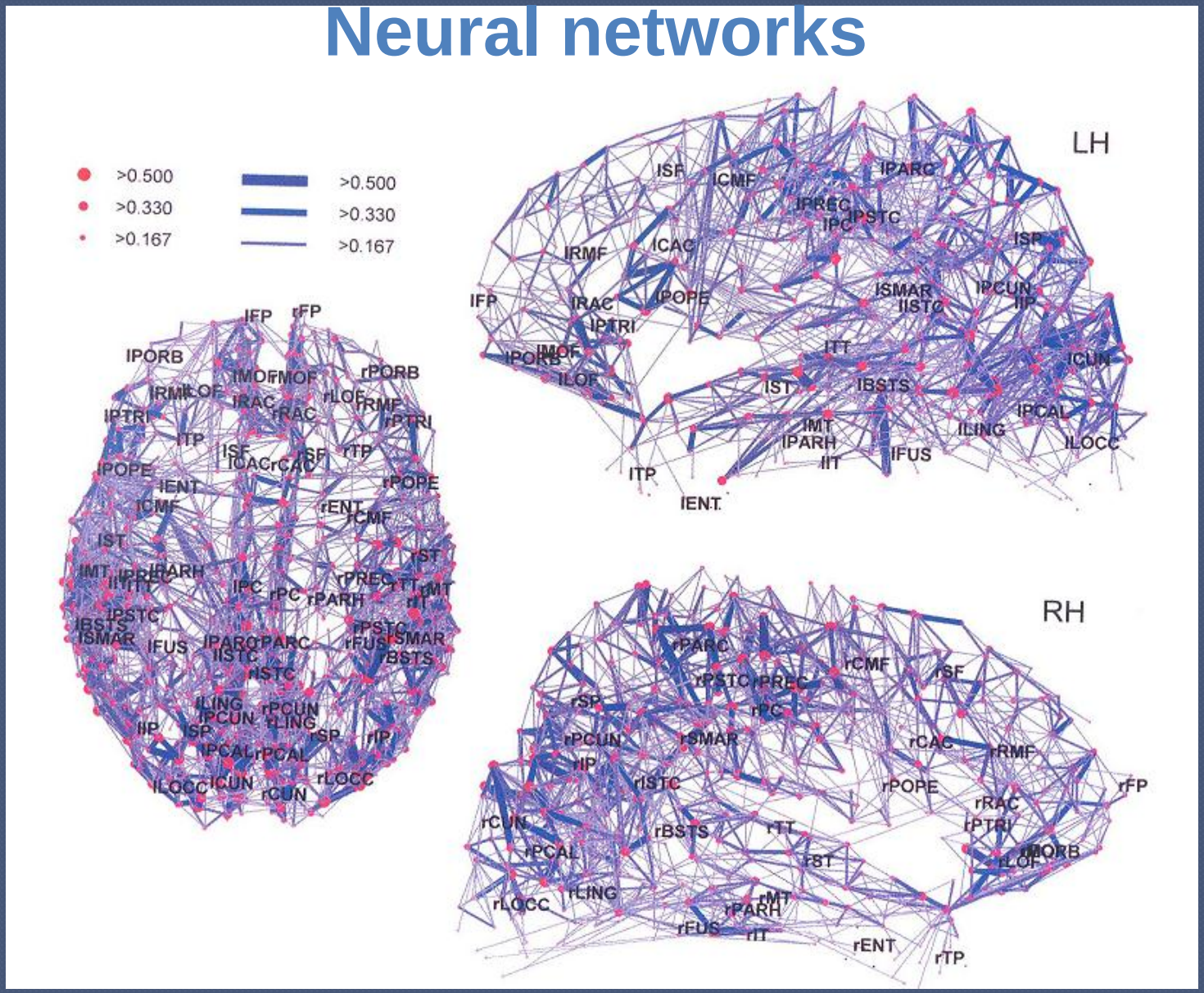
- While pruning is going on in many key pathways, there is also growth of additional connections between frequently used neural pathways.
- Repetitions enhance existing connections and also leads to forming more connections.
- Learning of any kind is instantiated by increased neural strength and increased connectivity.
- Memory (both declarative and performative) are instantiated by neuronal growth. There is a physical basis for every mental attribute.

Neural dendritic growth



Sporns, O. (2011). Networks of the Brain. Cambridge, MA: MIT Press.

Neural networks



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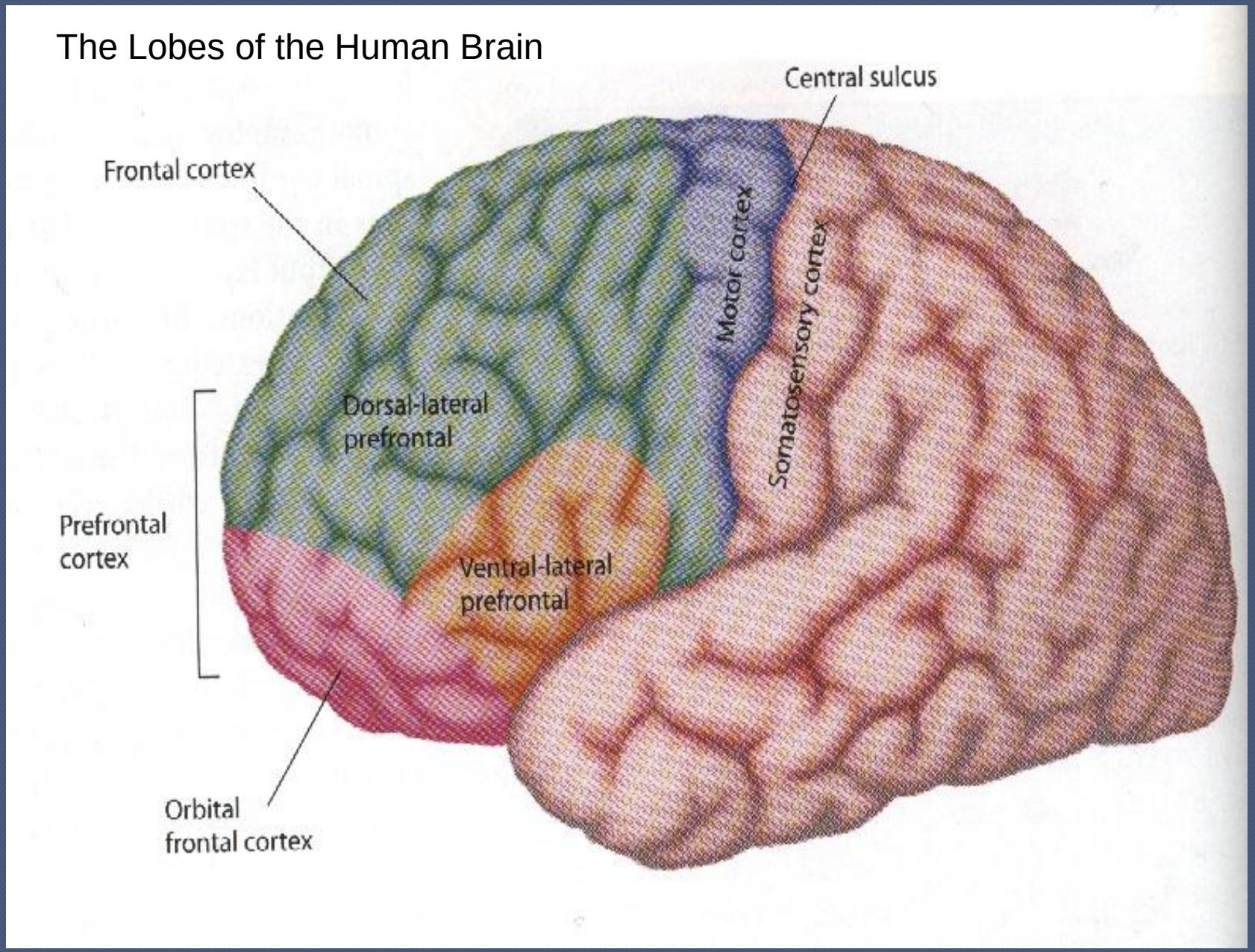
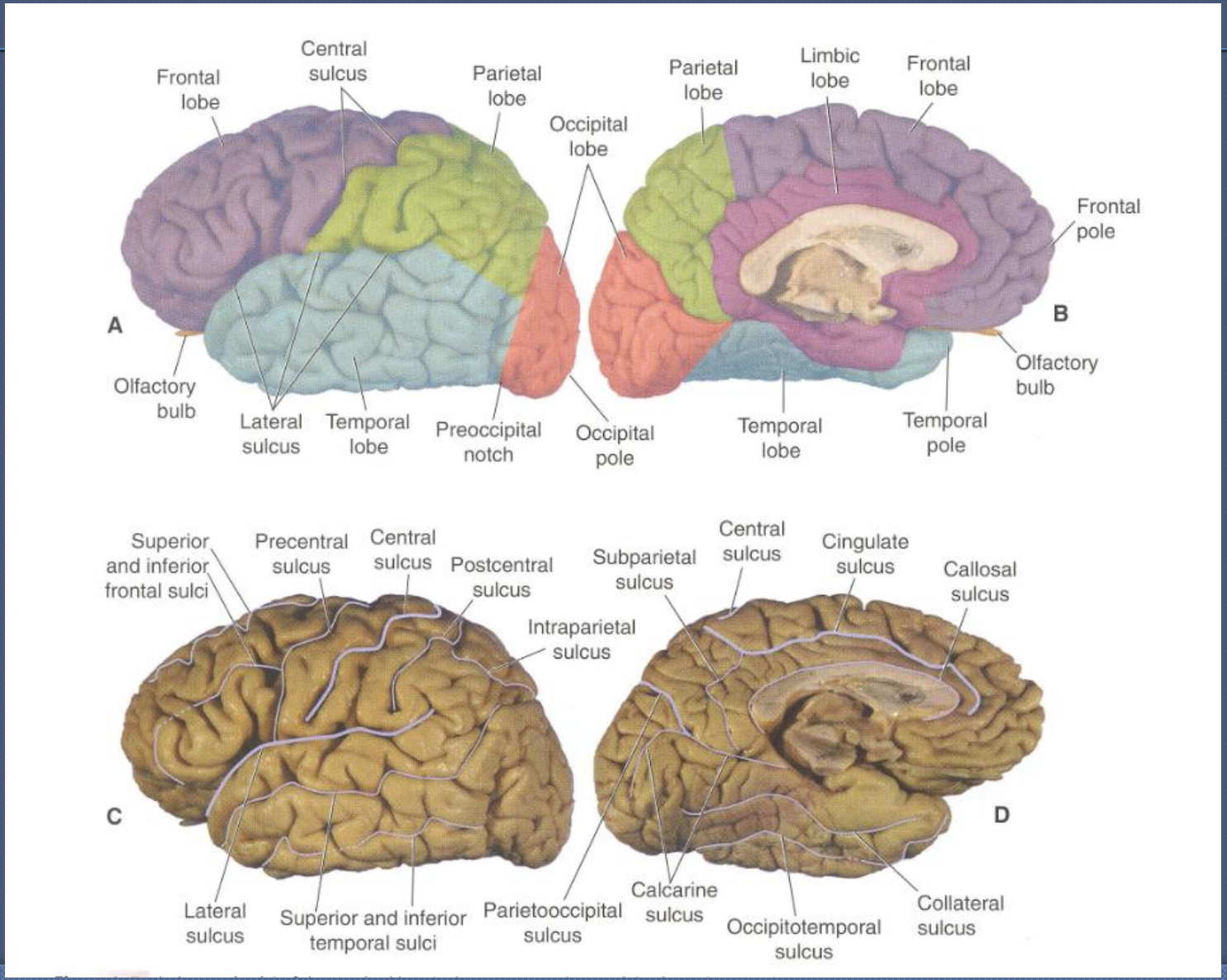
Moving from neurons to larger systems and anatomical structures

The Lobes of the Human Brain



Major brain regions



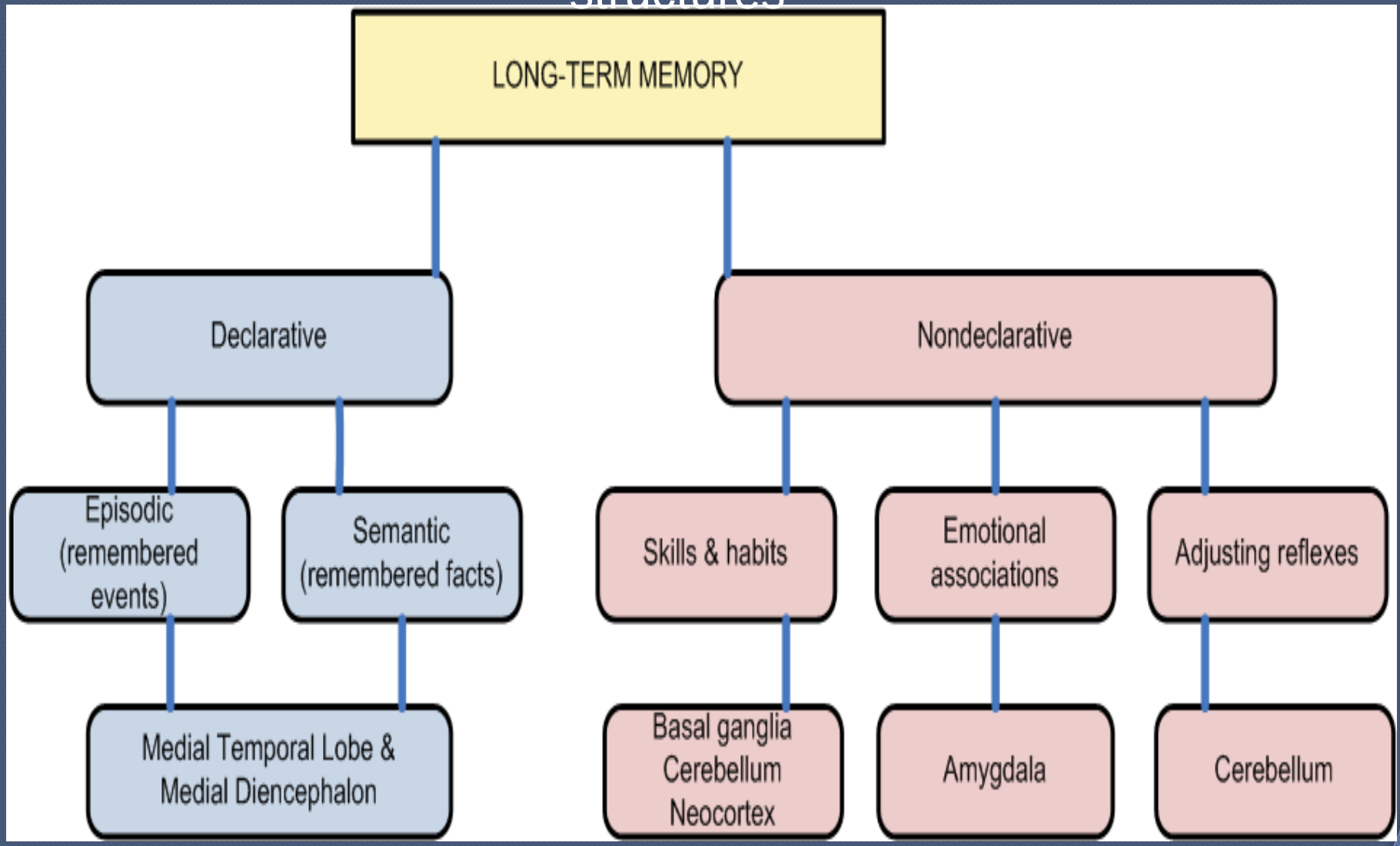
Larger systems affecting addictions

Memory and its structures

- All memoral functions have neurochemical and neuroanatomical correlates.
- Memory is widely distributed throughout the brain BUT all memory is mapped into neural pathways at specific regions of the brain.

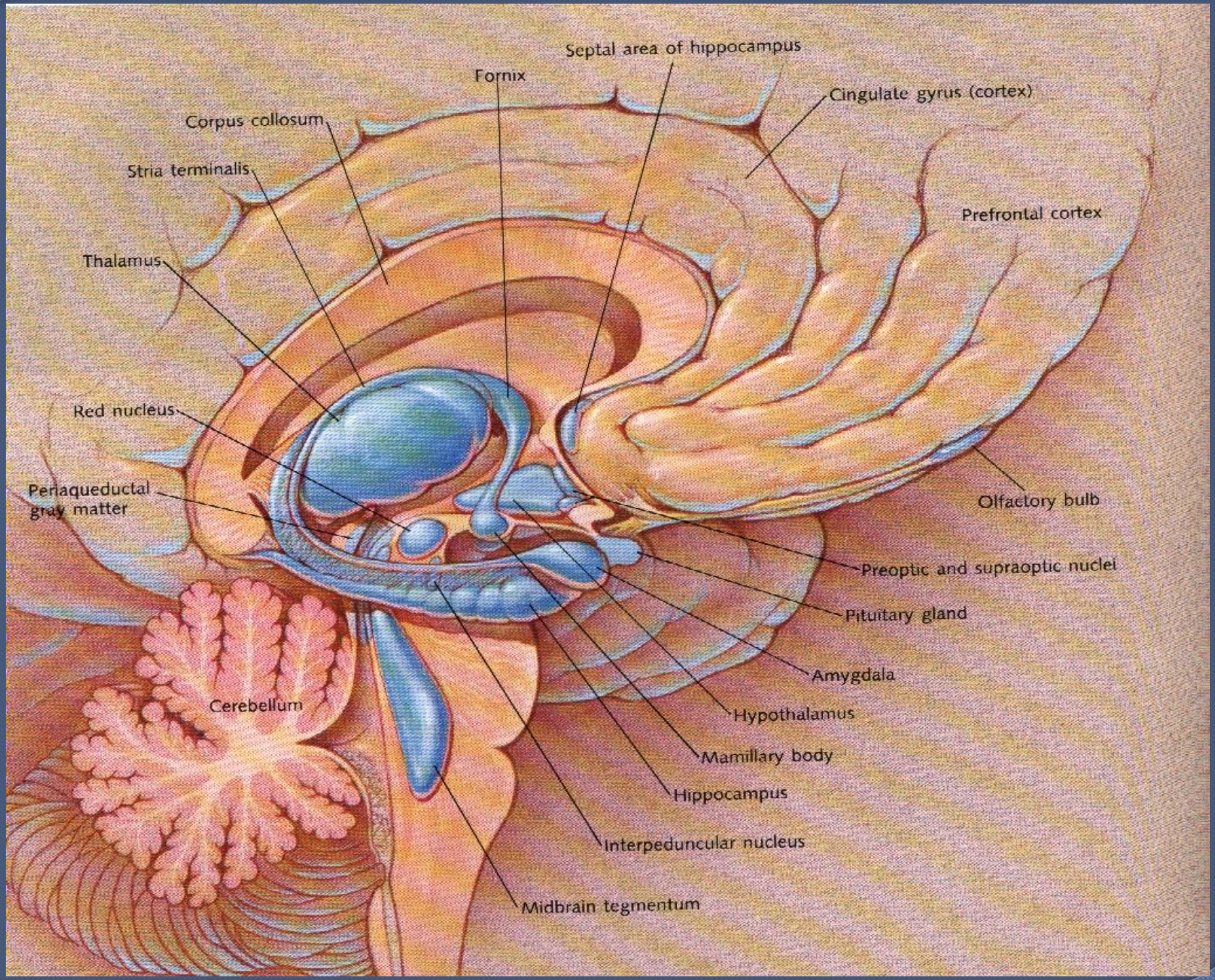
- We begin with working memory.
- Next comes short-term memory.
- Last is long-term potentiation.
- Memory is largely keyed into brain structures around sensory and emotional flavoring. That is, experiences or facts that carry zero valence are very unlikely to be remembered.

Memory and related neuroanatomical structures



Where are addictive memories?

- Widely distributed across memoral systems.
- Declarative and nondeclarative systems.
  - Procedural memory as well as episodic.


Septal area of hippocampus
Fornix
Cingulate gyrus (cortex)
Corpus collosum
Stria terminalis
Prefrontal cortex
Thalamus
Red nucleus
Periaqueductal gray matter
Olfactory bulb
Preoptic and supraoptic nuclei
Pituitary gland
Amygdala
Cerebellum
Hypothalamus
Mamillary body
Hippocampus
Interpeduncular nucleus
Midbrain tegmentum

Hippocampus

- The hippocampus is responsible for mediating short-term and working memory and encoding long-term potentiation (LTP).
  - Working memory and short-term memory are primarily mediated in the hippocampus but with attentional capacity mediated by the prefrontal and orbital frontal lobes.
  - This functions through continuous release of AMPA and glutamate throughout the memoral cycle.
  - Has some of the most densely packed neurons of any brain region.
  - N-methyl D-aspartate (NMDA) – facilitates depolarization of cells thus allowing influx of calcium which is associated with LTP. This chemical process stimulates LTP throughout the cortex.

Hippocampus

- The hippocampus also plays a role in retrieval of memories.
- It is sensitive to negative effects of cortisol and research has found decreased cell volume in the hippocampi of individuals with:
  - PTSD
  - Depression
  - Alcoholism
  - Chronic, heavy sustained use of marijuana
- The same finding for the amygdala, which is heavily involved with emotional memory.

LTP

- Is a lengthy process – can take 60 days or so.
- Is mediated by activation between the hippocampus and various regions in the cortex.
- Results in synaptic changes and changes in dendrites and axonal connections – all of which are triggered by neurochemistry.
- LTP is signaled by emotional tagging.

The arousal system

The arousal system

- The arousal system is one of the most primitive parts of the brain apart from basic physiological stasis regions.
- Once there are sensory stimuli (visual, etc), afferents to the amygdala are activated.
- The amygdala adds an emotion tag (positive, negative) to the perceived stimulus.
- If the tag is for ‘threat’, afferents to the locus coeruleus are activated.
- The locus coeruleus triggers release of norepinephrine (adrenaline) to all regions of the CMNS and PNS.

The arousal system

- The release of norepinephrine (NE) also stimulates neurohormonal activity to moderate the effects of NE.
- Cortisol in the neural environment for too long causes shut down of neuronal metabolism, causing cell death. (Normal half-life of cortisol is 60-90 minutes)
- NE triggers activation of the HPA Axis
  - Hypothalamic-pituitary-adrenal axis
  - A sequence of feedback interactions among neuronal and hormonal nuclei.
  - Begins with locus coeruleus activation and afferents to the hypothalamus

The arousal system

- The hypothalamus releases corticotrophin-releasing hormone (CRH) to the pituitary gland and to the adrenal gland.
- In response, the pituitary gland secretes adrenocorticotropic hormone (ACTH) which then triggers -
- The adrenal gland to secrete corticosteroids such as cortisol which suppresses the hypothalamus.
- Cortisol increases glucose in the blood stream and decreases it in other tissues. It also regulates vascular smooth muscle tension to increase blood pressure.
- Cortisol decreases REM sleep and reduces sleep length.
- Cortisol reduces T-cell development and thus has a negative impact on the immune system.

Image of HPA and arousal pathways

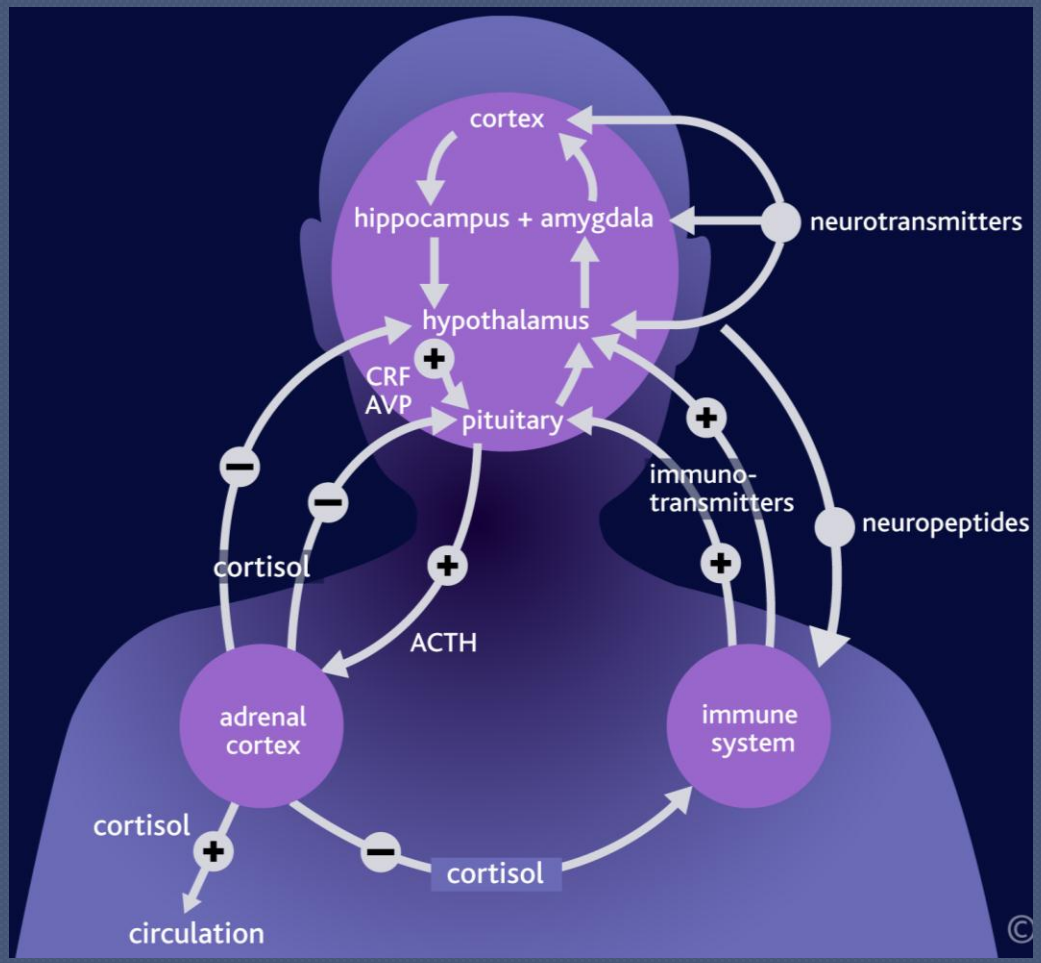
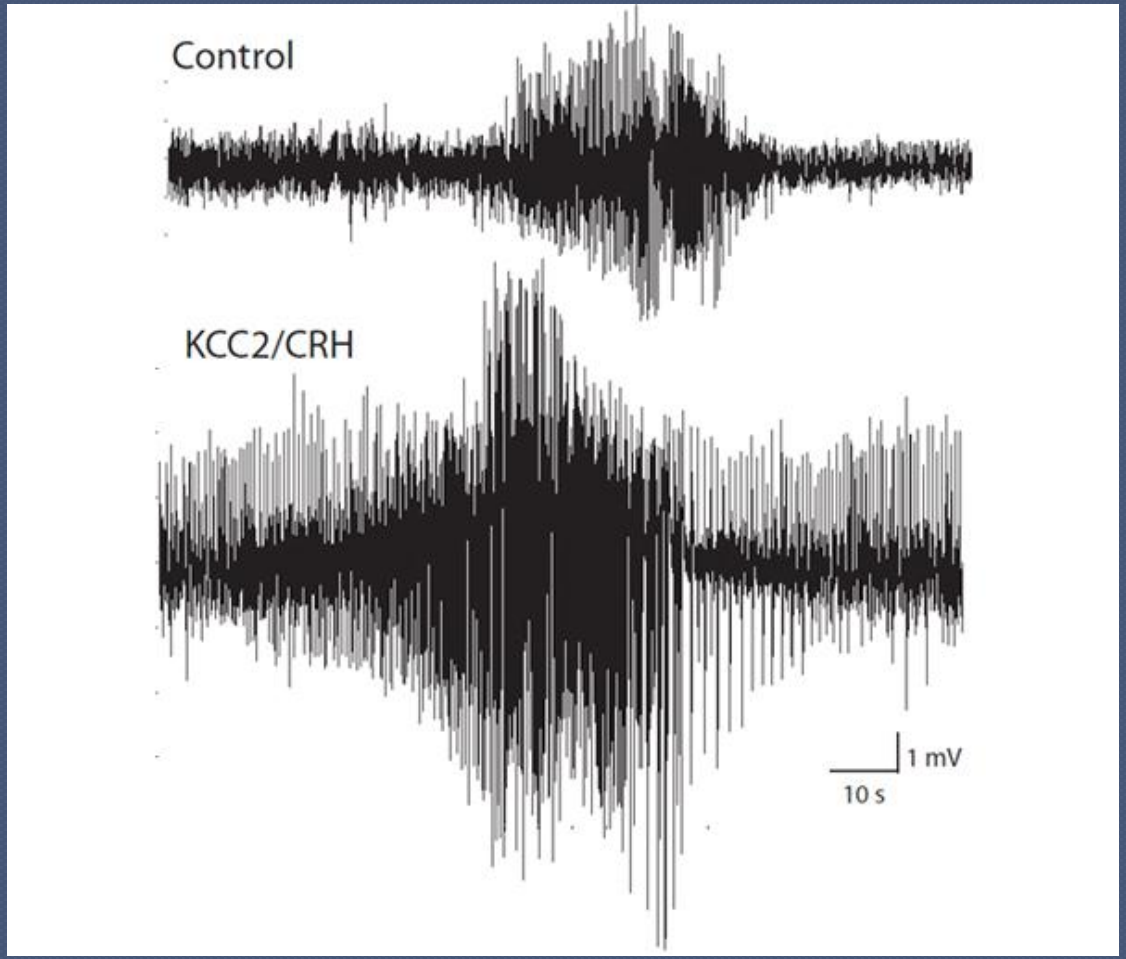


Image of HPA activated neural activity (KCC2/CRH) versus non-activated



Arousal and development

- When the HPA axis is highly activated in early development (up to age 2-3), it tends to be 'set' at a different level than for those who are not frequently activated.
- The brain achieves its set points for arousal as part of homeostasis-seeking.
- Thus, chronically disturbed arousal systems can arise from environmentally induced fear states.

Arousal and development

- Protracted and heightened arousal can result in one of two forms: (1) a chronically hyper-arousable type and (2) chronically hypo-arousable type.
- Both types also inherit temperamental contributions and perhaps even temperamental influence over which type arises from extended fear states.
- Extended periods of arousal lead to extended cortisol secretion and subsequent cell death in the hippocampus and amygdala.
- Also, overloaded burden on the arousal system is associated with allostatic load where the set point for arousal is modified and resource deployment from cortical areas is diminished.

Arousal

- One other factor to consider – the striatum, part of the basal ganglia, is comprised of nuclei that detect rank order of other persons.
- It receives afferents from the frontal lobes and the emotion system to ascertain social rank – dominance or submission patterns.

- Canines have this brain function, as do even more primitive animals such as reptiles (e.g., the adage about the 'reptilian brain').
- Detection of rank order can contribute to stress as evident among Sapolosky's baboons.
- Detection of rank order is a very primitive function and it plays a role in Marmot's study of social determinates of health and well-being.

Chronically disturbed arousal conditions

- Chronically disturbed arousal conditions become major risk factors for mental disorders and substance abuse.
- The brain is evolved to seek pleasure and avoid pain.
- Disturbed arousal conditions (either type) lead to are anhedonic states that people try to modify.

Arousal and depression

- Heightened or sustained arousal states are associated with depression.
- About 50% of patients with anxiety disorders also have depression.
- Has correlates with ego depletion.

- The serotonin and norepinephrine systems are most involved with depressive states and the Raphe nuclei and locus coeruleus are two critical nuclei for this.
- Prolonged depression is associated with changes in gene expression and in decreased volume and functionality of the frontal lobes.
- Depression is a major risk factor for substance abuse.

Brain anatomy and addiction

- All intoxicating substances are made of molecules that are shaped much like the brain's natural neurotransmitter molecules.
- Several neurotransmitters are affected by addictive substances. Sometimes the initial effect is on one neurotransmitter, but this activation can kick off something like a cascade of other events.
- The end result is dopamine activation of the:
  - Ventral tegmental area (VTA) and
  - The nucleus accumbens (NAc)

Brain structures and addiction

- The human brain has reward centers that mediate the experience of pleasure.
- The ventral tegmental area (VTA) and the nucleus accumbens (NAc) are the primary locations for core pleasure experiences.
  - These are the regions where **pleasure is mediated**.
- When a person experiences pleasure from chocolate, a ride in a fast car, a buzz off a drug, the NAc has been activated.

The reward system

Reward, pleasure, memory

- The brain regions responsible for mediating pleasure are located very close to memory centers and other key emotion sensing areas –
  - The hippocampus – memory encoding and retrieving and short-term memory
  - The amygdala – emotion-tagging system
  - Raphe nuclei – the serotonin system
- They are also closely related to centers that mediate intentional actions.
  - Striatum –mediated by dopamine and to some extent by serotonin

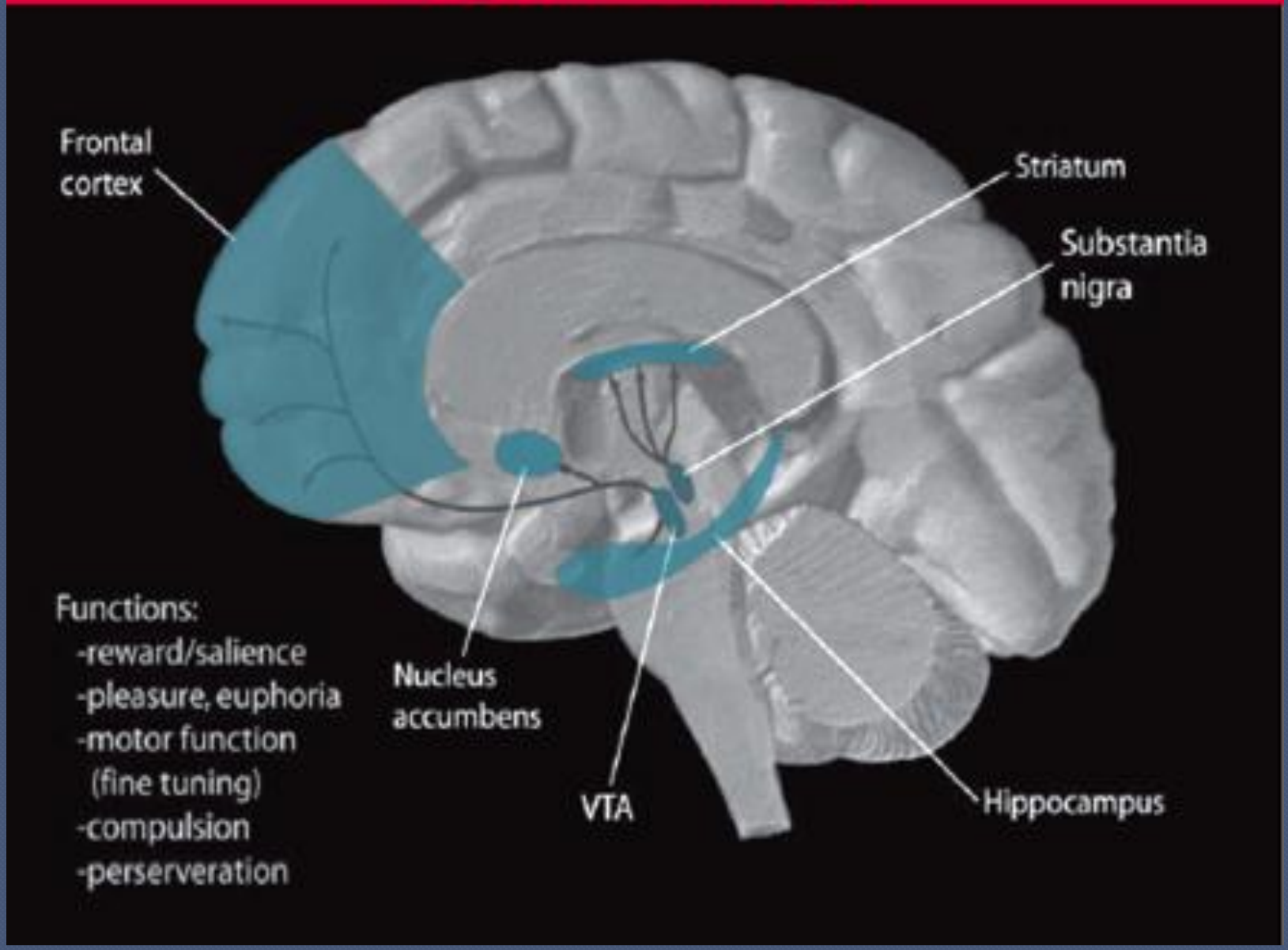
VTA and NAc

- Reward-seeking is facilitated by the release of the neurotransmitter dopamine in the nucleus accumbens (NAc),
- Subpopulations of NAc neurons even respond to predictive cues to promote reward-seeking behavior.
- Even cues about a drug (such as talking about it, or even thinking about incidents related to drug use) can mobilize brain centers to begin pleasure expectations.

Also,

- The orbitofrontal cortex is also involved.
  - This region is the center for socioemotional reasoning.
  - It is also anatomically thinner among individuals with severe depression, and who have been exposed to nicotine during fetal development.
  - It responds to cues associated with reward stimuli.
- The anterior cingulate gyrus is also involved – a mediating area between the frontal lobes and emotion centers of the brain.
  - This is also a brain region that mediates the emotions relating to pain.

Dopamine Pathways



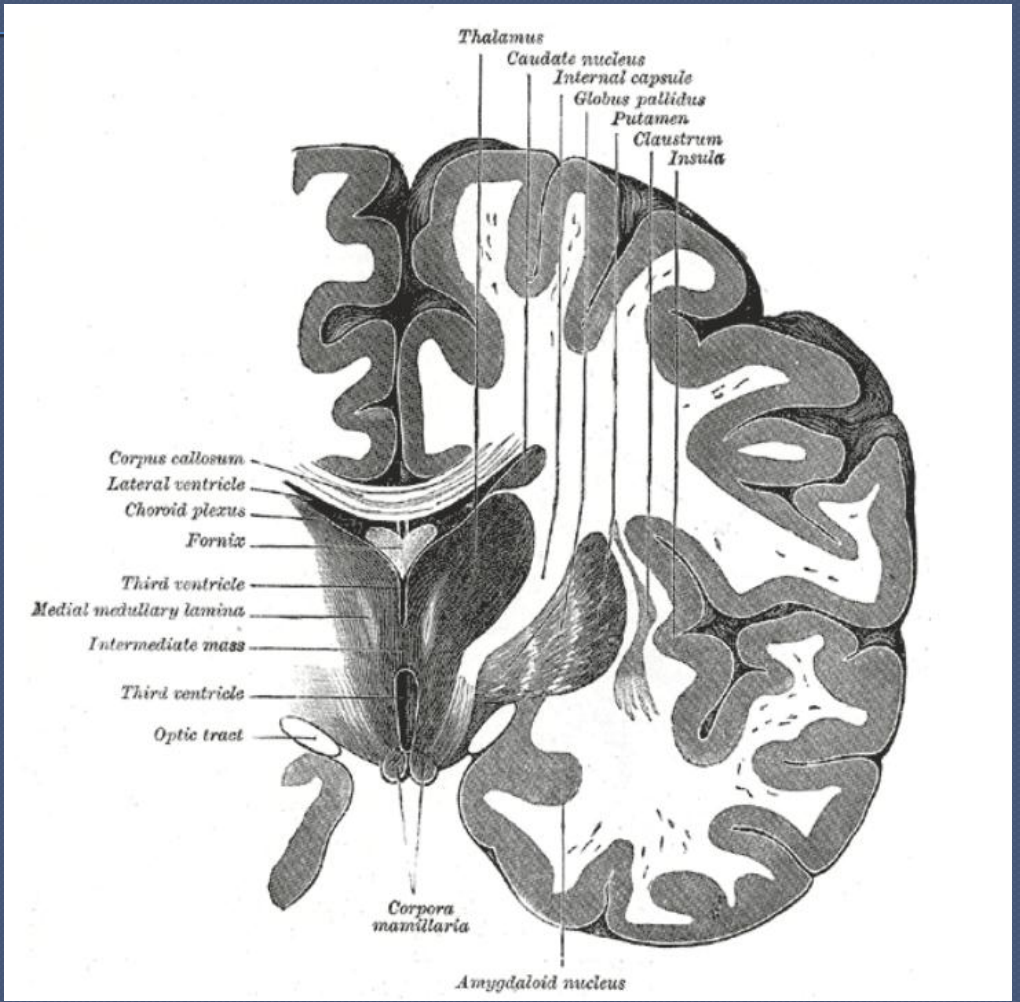
The insula

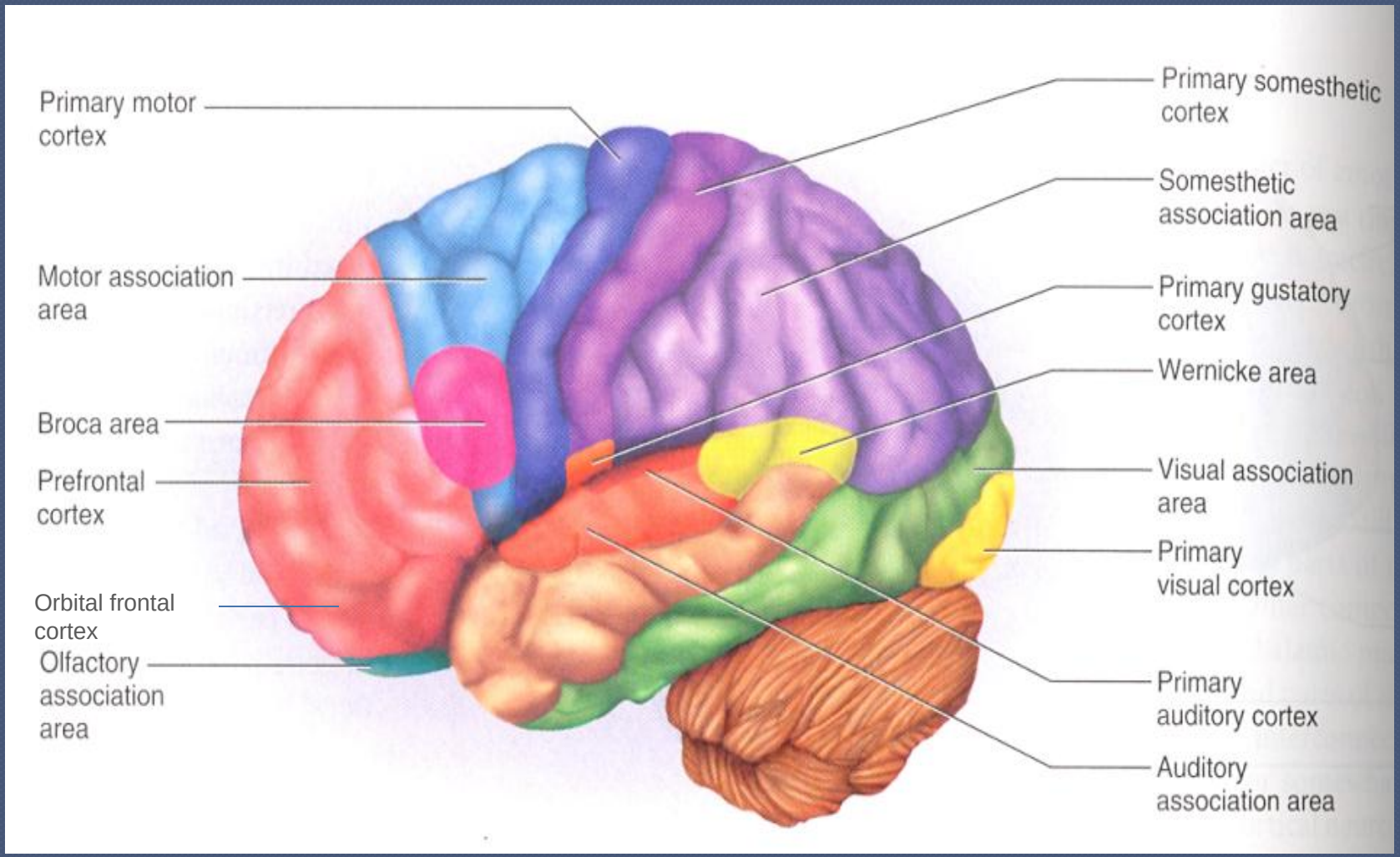
The insula is a tuft of cortex that helps mediate emotional tone and cognitive/emotional functions.

It also helps coordinate hand-eye movement, relays sensory information from the olfactory nerve into the frontal lobes and other regions.

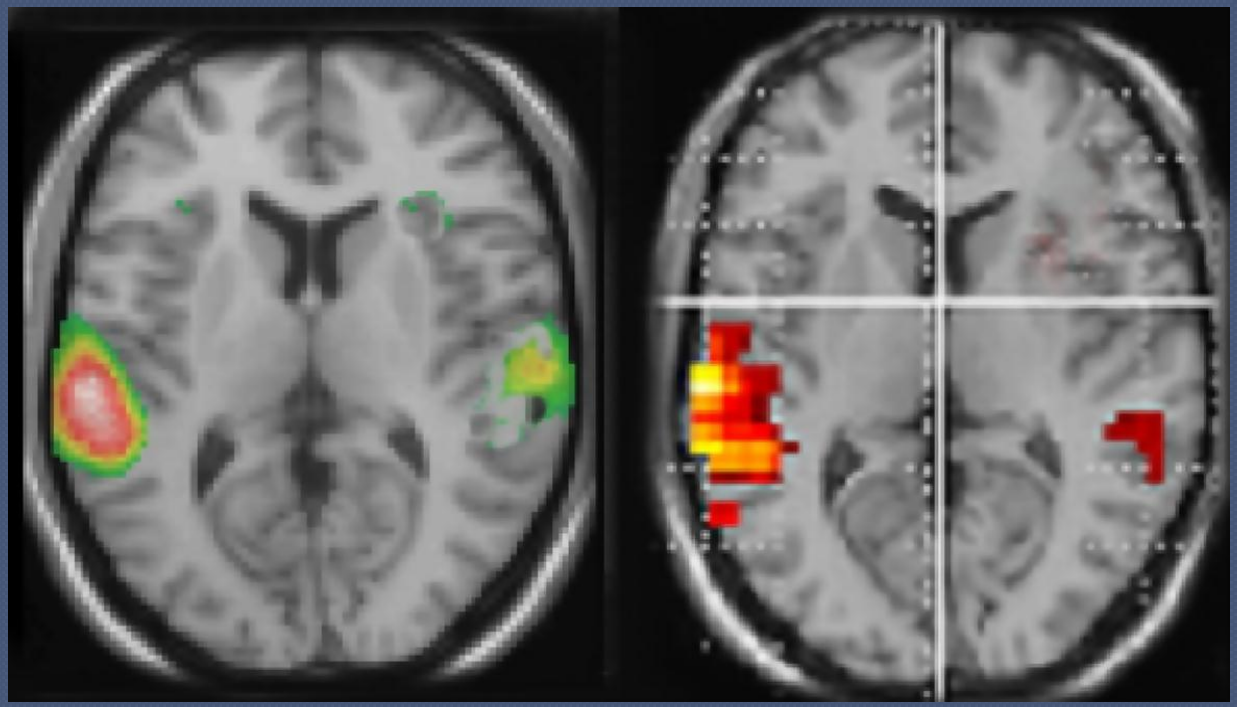
It, too, is part of the limbic system.

It has been recently identified as playing a major role in craving for nicotine.




Primary motor cortex
Motor association area
Broca area
Prefrontal cortex
Orbital frontal cortex
Olfactory association area
Primary somesthetic cortex
Somesthetic association area
Primary gustatory cortex
Wernicke area
Visual association area
Primary visual cortex
Primary auditory cortex
Auditory association area

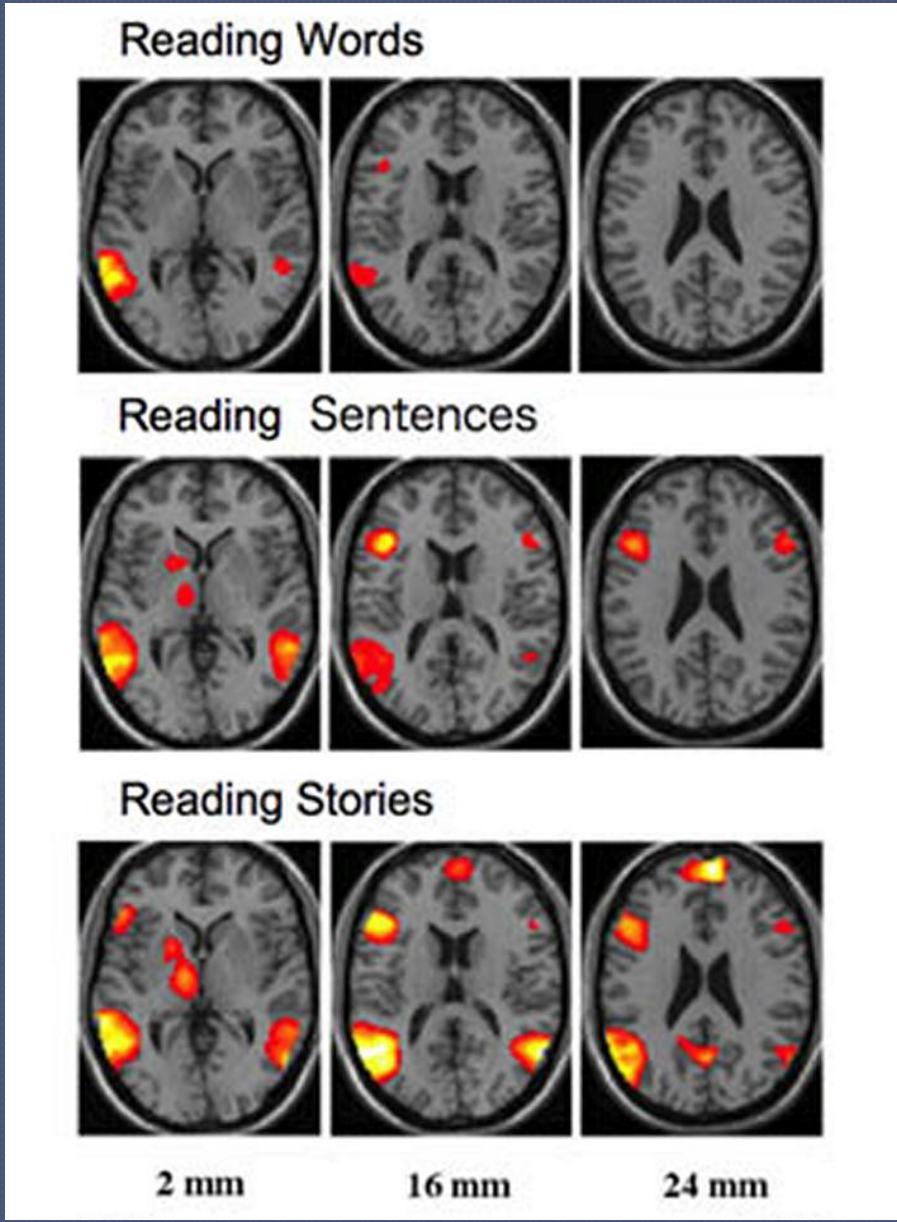
Pet scan (left) and fMRI of listening



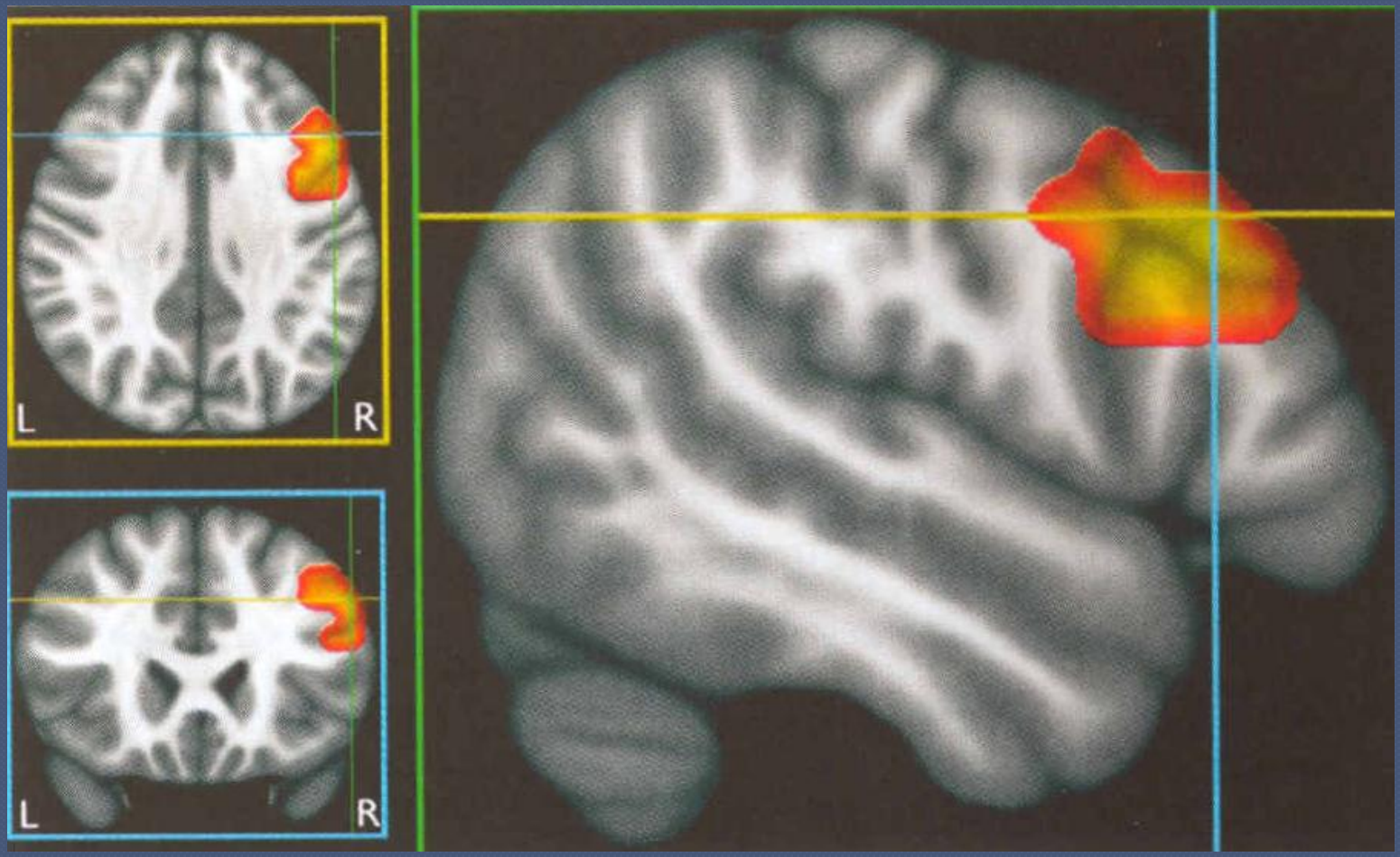
fMRI of brains during three sets of verbal activities. Note that as the complexity of language structure increases, the regional distribution of activity also increases.

The activation suggests greater use of associational areas.

The three columns are different slices through the brain.

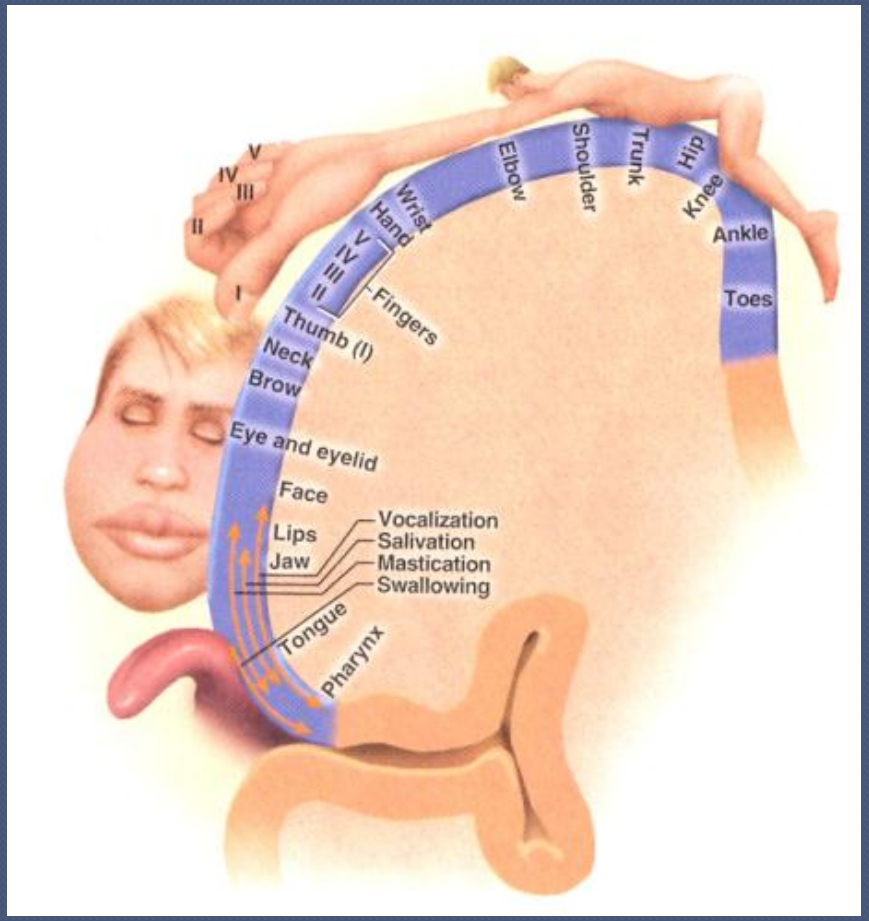


Inhibition appears to be associated with right dorsolateral frontal lobe activity – also may be a trigger area for greater anxiety

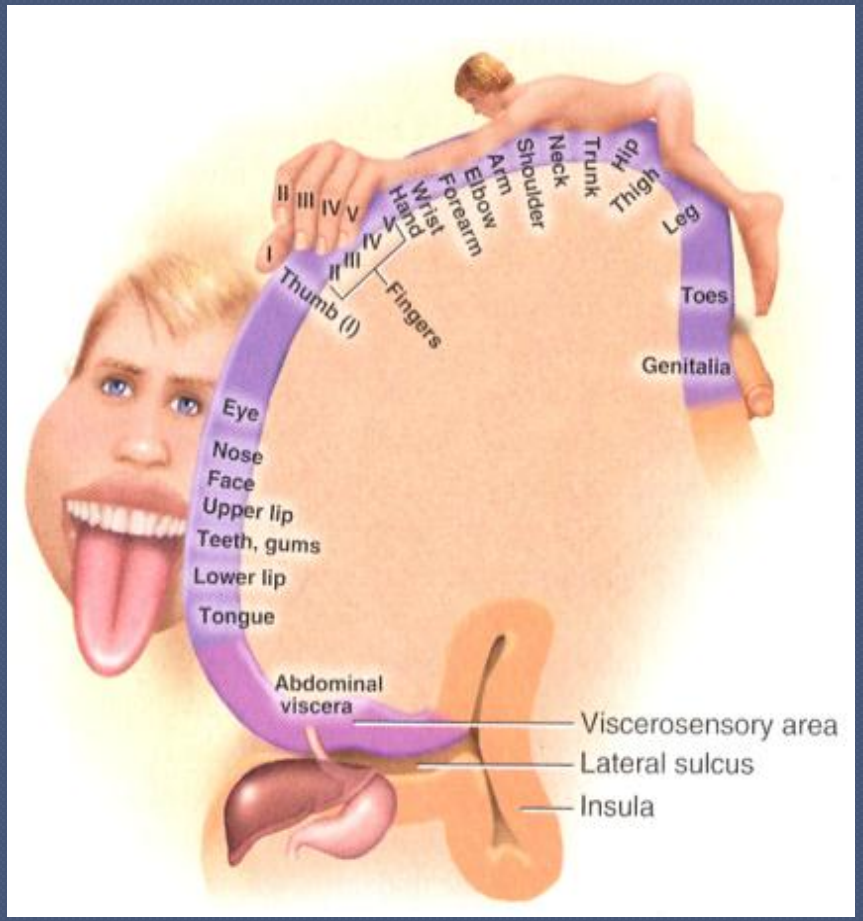


Shackman, McMenamen, Maxwell, Greicher & Davidson, 2009. *Psy.Science, 20*, *1500-1506.*

Primary motor areas (precentral gyrus)



Primary sensory areas (postcentral gyrus)

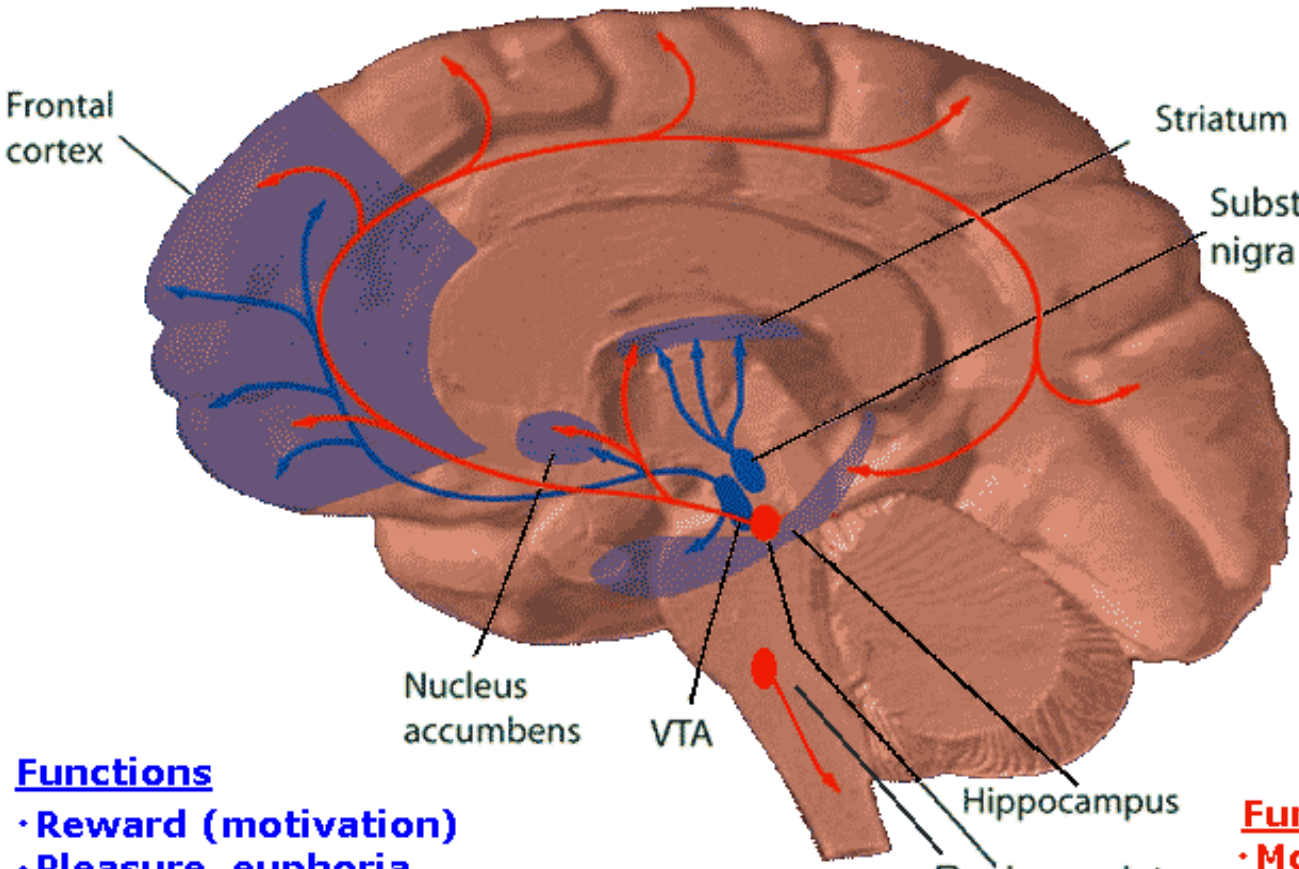


It's not simple

- While certain pathways are activated by designated neurotransmitters, the activation of one pathway can trigger others.
- Thus, a region or network that is activated by the neurotransmitter dopamine can, further down the line, activate another pathway that relies on encephalin.
- Here are the major neurotransmitters we are concerned about:
  - Dopamine
  - Serotonin
  - Encephalin – endorphin
  - GABA (γ-aminobutyric acid)
  - Norepinephrine

Dopamine Pathways

Serotonin Pathways



Functions

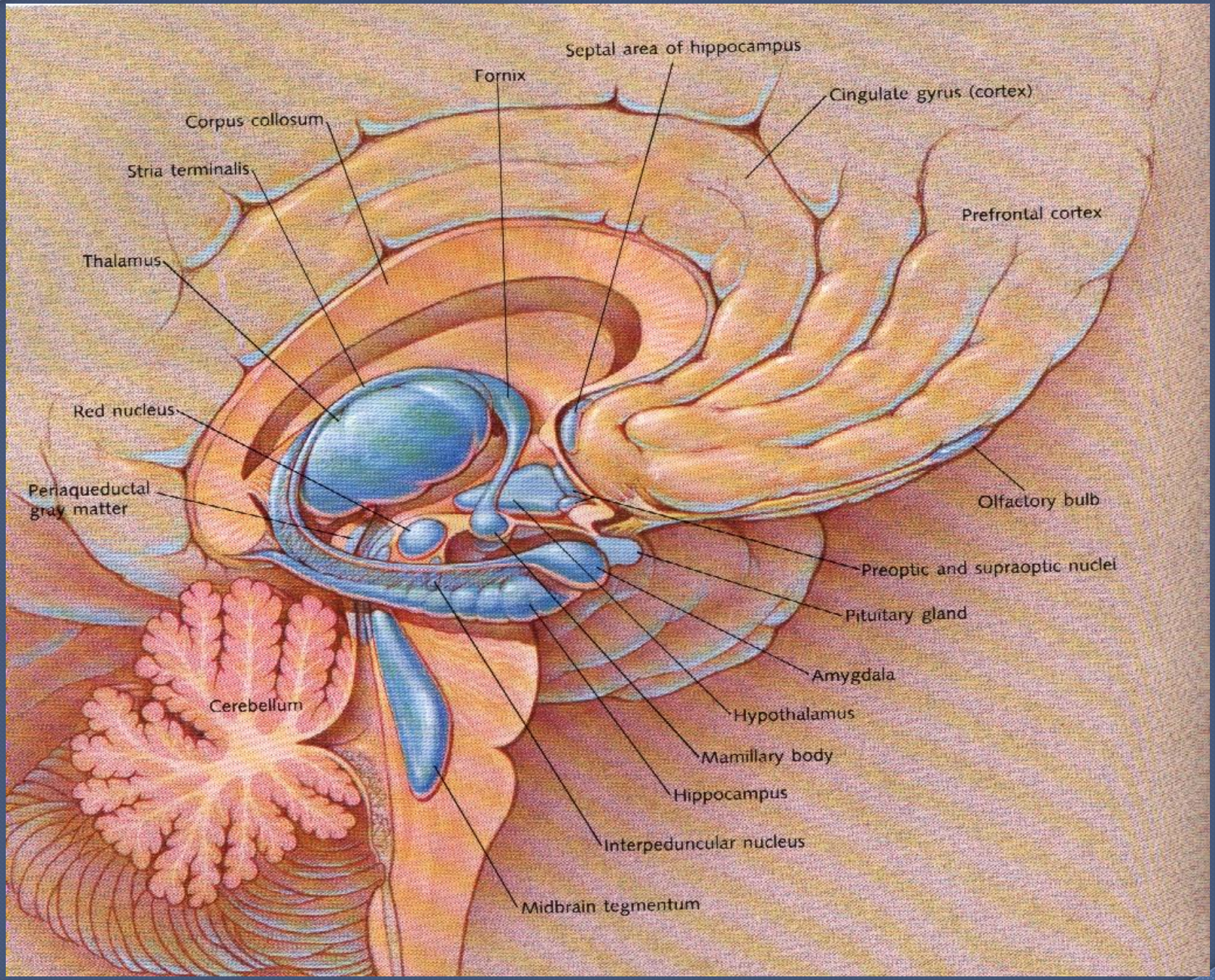
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Functions

- Mood
- Memory processing
- Sleep
- Cognition

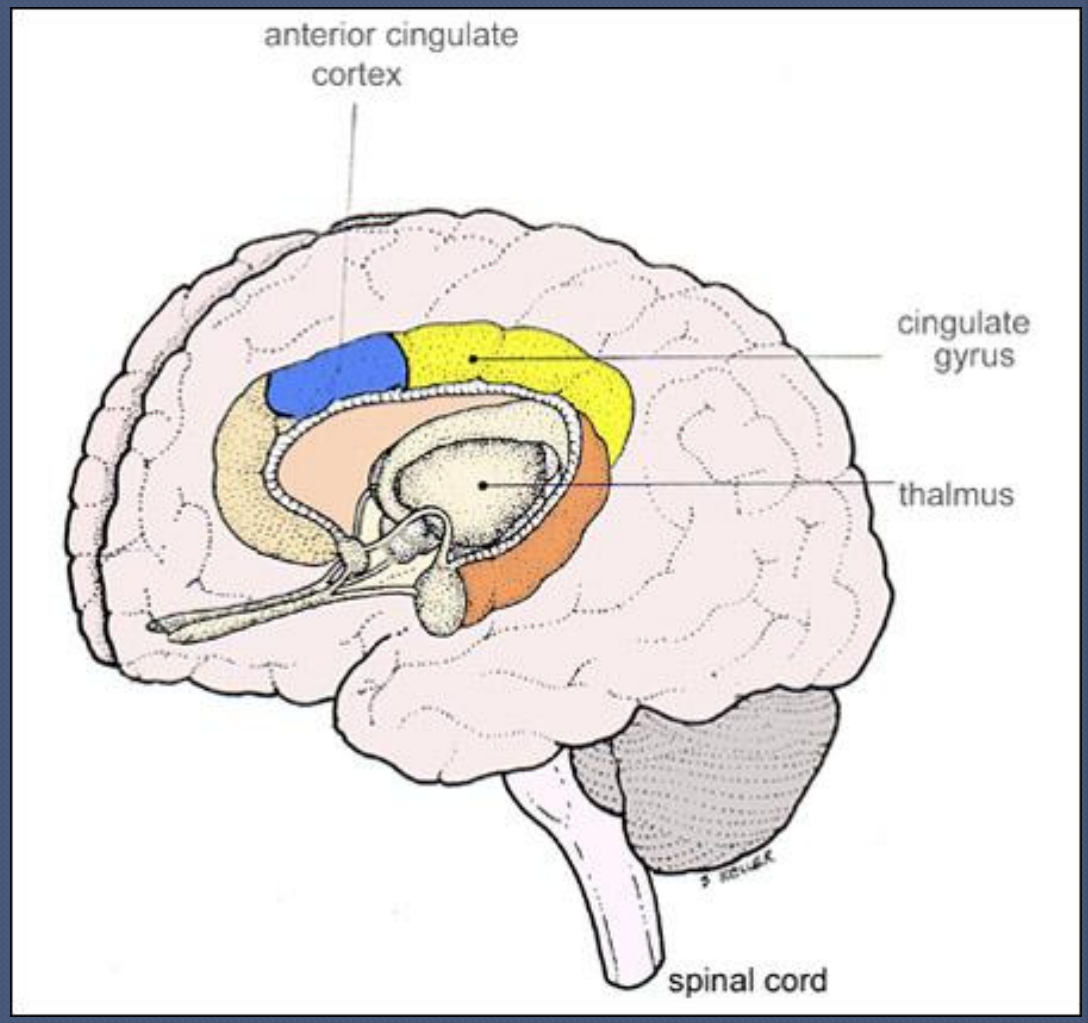
Reward, pleasure, memory

- The brain regions responsible for mediating pleasure are located very close to memory centers and other key emotion sensing areas –
  - The hippocampus – memory encoding and retrieving
  - The amygdala – emotion-tagging system
- They are also closely related to centers that mediate intentional actions.
  - striatum


Septal area of hippocampus
Fornix
Cingulate gyrus (cortex)
Corpus collosum
Stria terminalis
Prefrontal cortex
Thalamus
Red nucleus
Periaqueductal gray matter
Olfactory bulb
Preoptic and supraoptic nuclei
Pituitary gland
Amygdala
Cerebellum
Hypothalamus
Mamillary body
Hippocampus
Interpeduncular nucleus
Midbrain tegmentum

In addition to the internal structures that mediate reward experiences, the anterior cingulate cortex (ACC) along with the orbito-frontal cortex **basically navigates among reward and consequences expectations**.

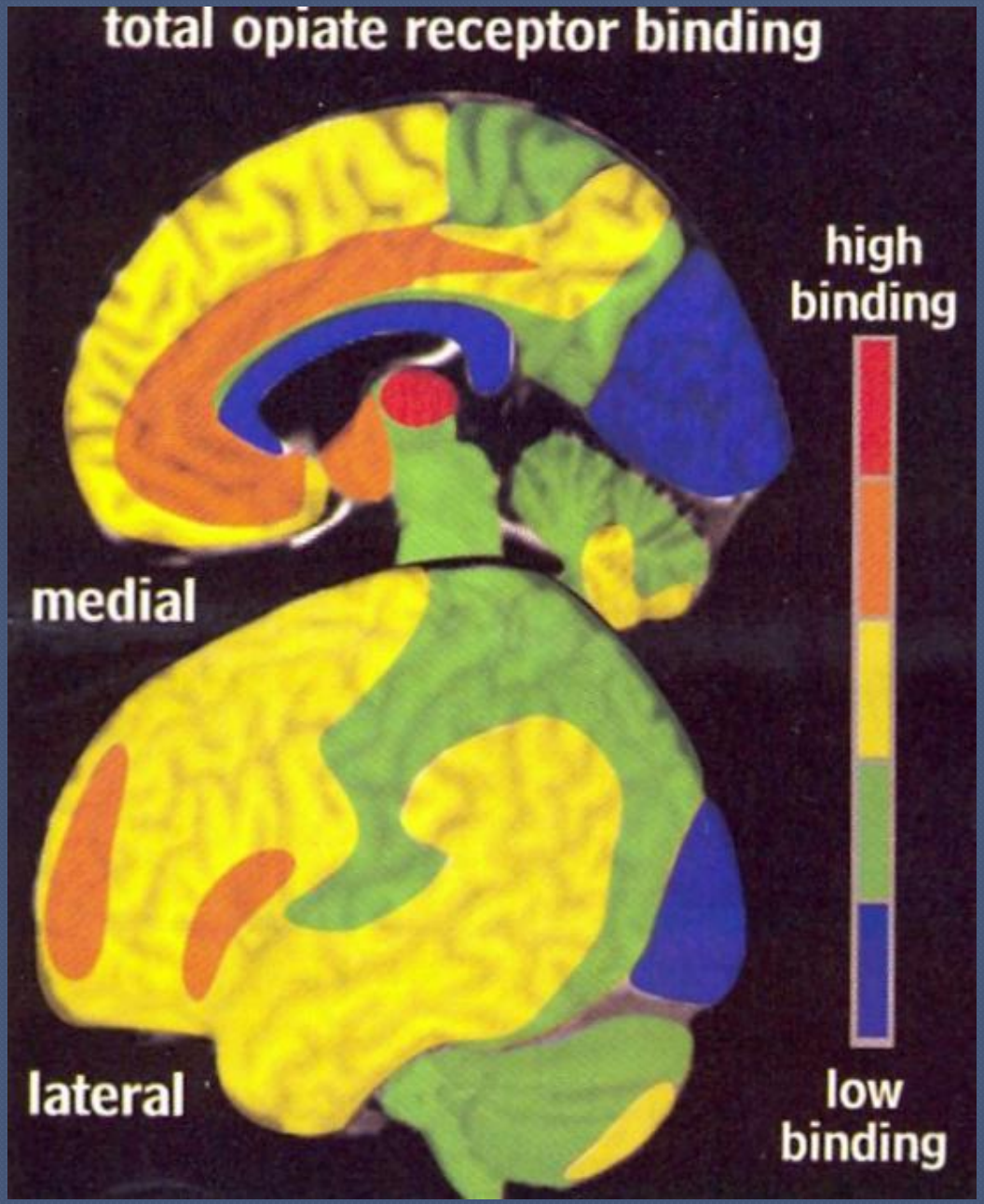
Among individuals with addictions, the ACC is naturally hypoactive, suggesting diminished capacity to do the kind of sorting out among rewards and punishments that could be expected from using drugs.



This slide shows the specific regions in the brain where opiate receptors are particularly prevalent.

Receptors in the inner areas show activation of pleasure mediation,

In the frontal areas, a different story.



NATURAL BRAIN MEDIATION OF REWARDS

Food

Water

Sex

Nurture

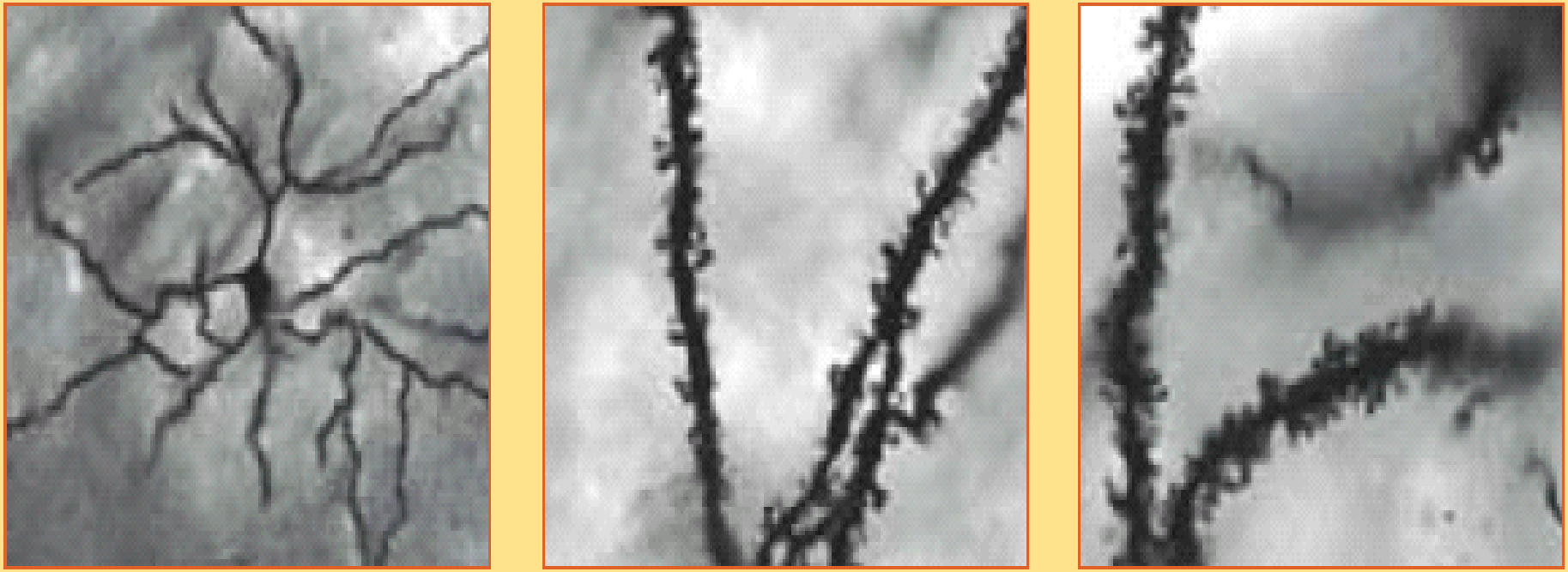
Synthetic Rewards

- The use of specific substances can be highly rewarding.
- In some individuals use of such substances can lead to uncontrolled use, displacement of more normal activity, and continued use despite painful and even life threatening consequences.
- All reward activities generate dopamine release to the NAc – natural AND synthetic rewards do this.

Brain and Habituation

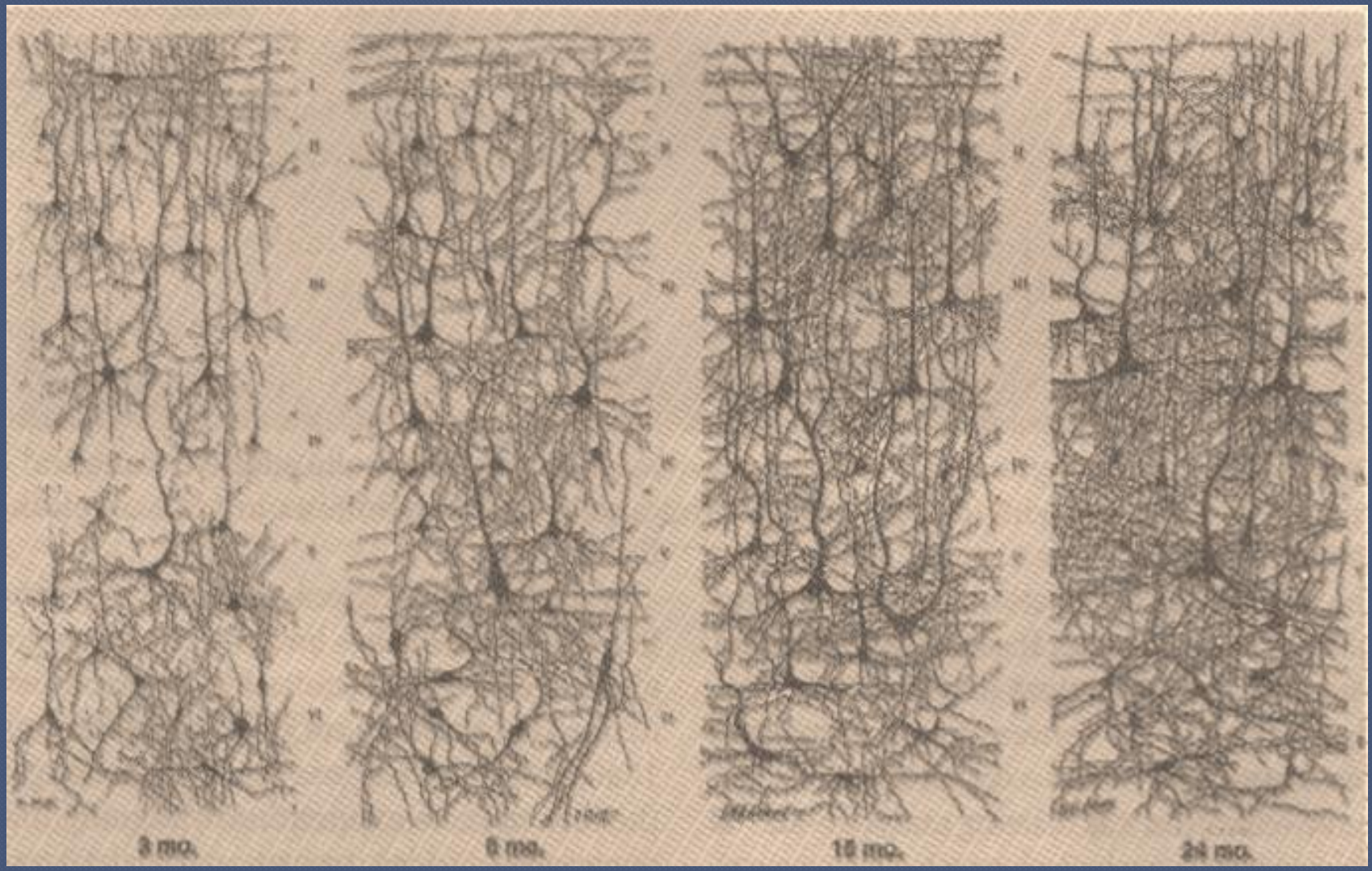
- The brain consists of millions of "circuits" and pathways.
- The more a particular pathway is "exercised", the greater the "strength" of that pathway and the more it begins to dominate mental space.
- Likewise, unstimulated pathways deteriorate and become less densely arborized.
- Also, the brain accommodates changes from one moment to another by maintaining a dynamic equilibrium or homeostasis –
  - That is, for every increase of one thing, the brain generally has a way to compensate and moderate the increase.

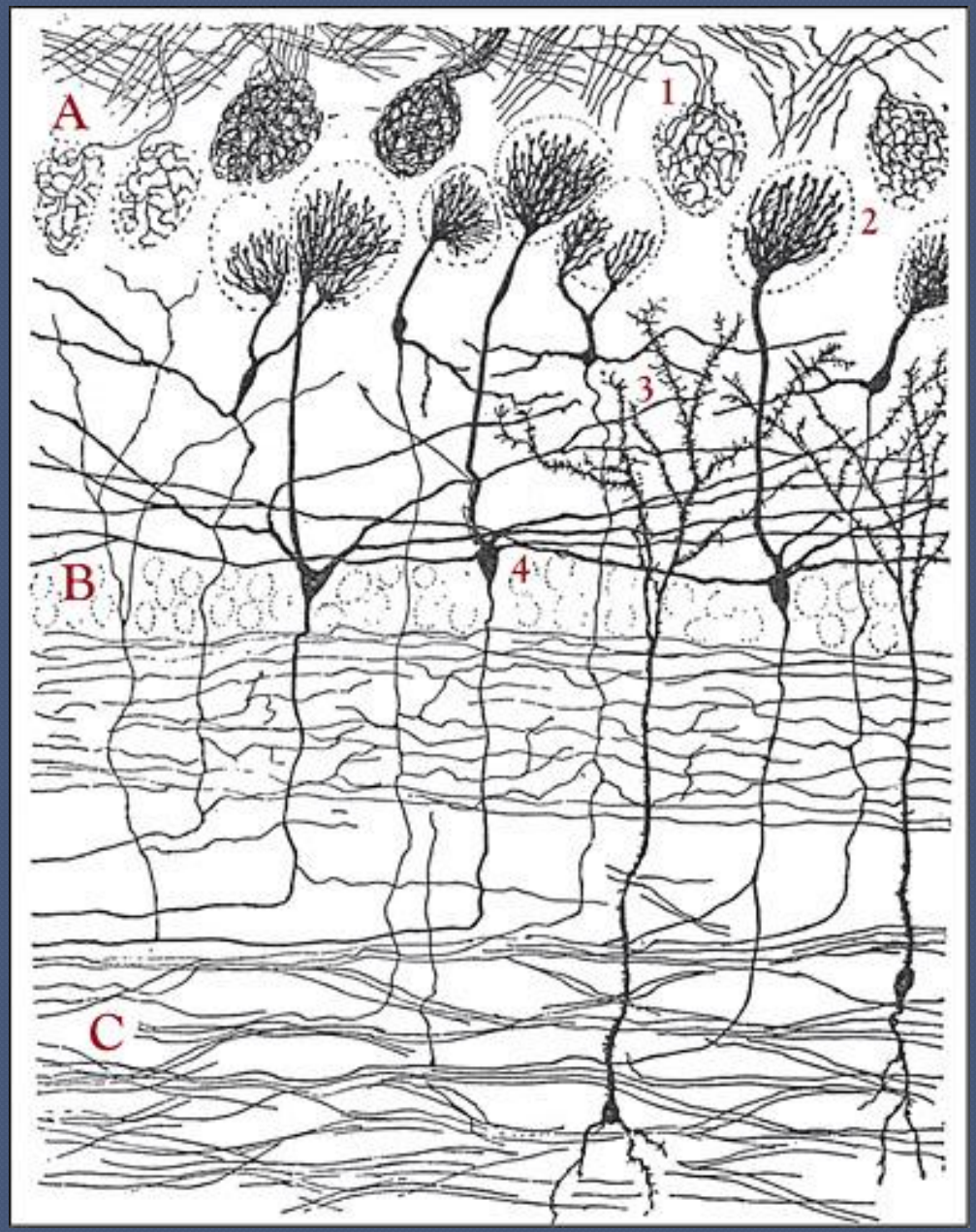
- With neurotransmitters, when an excess is added to the brain system, the brain tries to compensate by getting rid of the excess. So, the more you import, say a dopaminergic drug, the harder the brain works to get rid of the excess of dopamine.
  - One way that it does this is by decreasing its own natural production of neurotransmitter
  - Another way is by developing more receptor sites to draw up the excess OR,
  - Increasing the sensitivity of receptor sites, which happens in the striatum following cocaine addiction.
- Over time, the whole distribution of neurotransmitters gets out of kilter and the person can only function when importing the desired neurotransmitters to activate the pleasure parts of the brain.



MICROGRAPHS of nucleus accumbens neurons in animals exposed to nonaddictive drugs display dendritic branches with normal numbers of signal-receiving projections called spines (*left* and *center*). But those who become addicted to cocaine sprout additional spines on the branches, which consequently look bushier (*right*). Presumably, such remodeling makes neurons more sensitive to signals from the VTA and elsewhere and thus contributes to drug sensitivity. Recent findings suggest that delta FosB plays a part in spine growth.

It’s actually a two-way street – arborization occurs with stimulation, declines with lack of stimulation

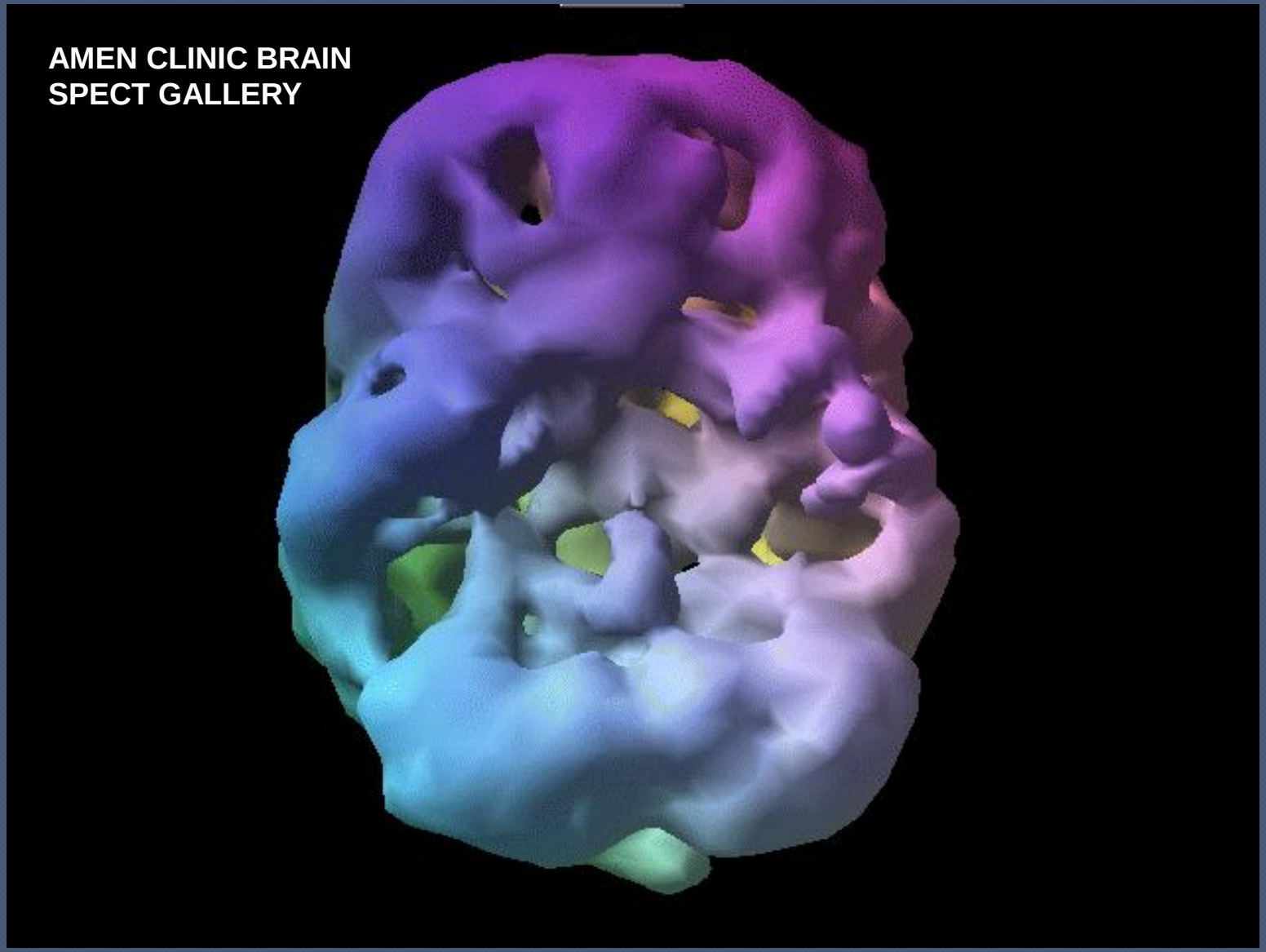



A
B
C
1
2
3
4

Effects on Brain Activity

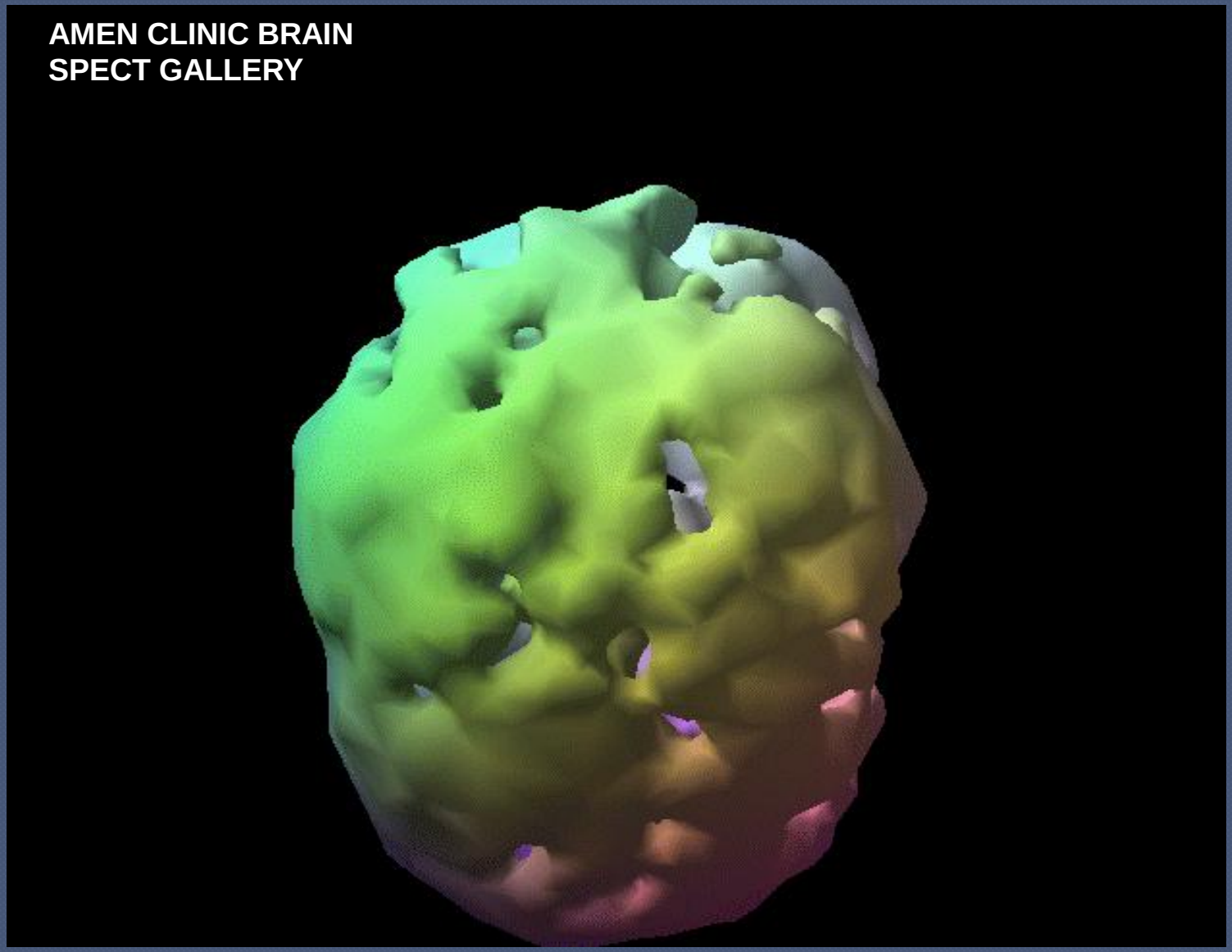
- Various approaches to functional brain imaging have been used to study specific areas of the brain in relation to the whole.
- Brain activity can be measured by examining how glucose is being metabolized by regions of the brain.
- It can also be studied by *fMRI* for functional anatomy and by SPECT to assess regional brain metabolism.
- These approaches allow one to examine specific areas affected by substance use.

Drug user's brain from the under side

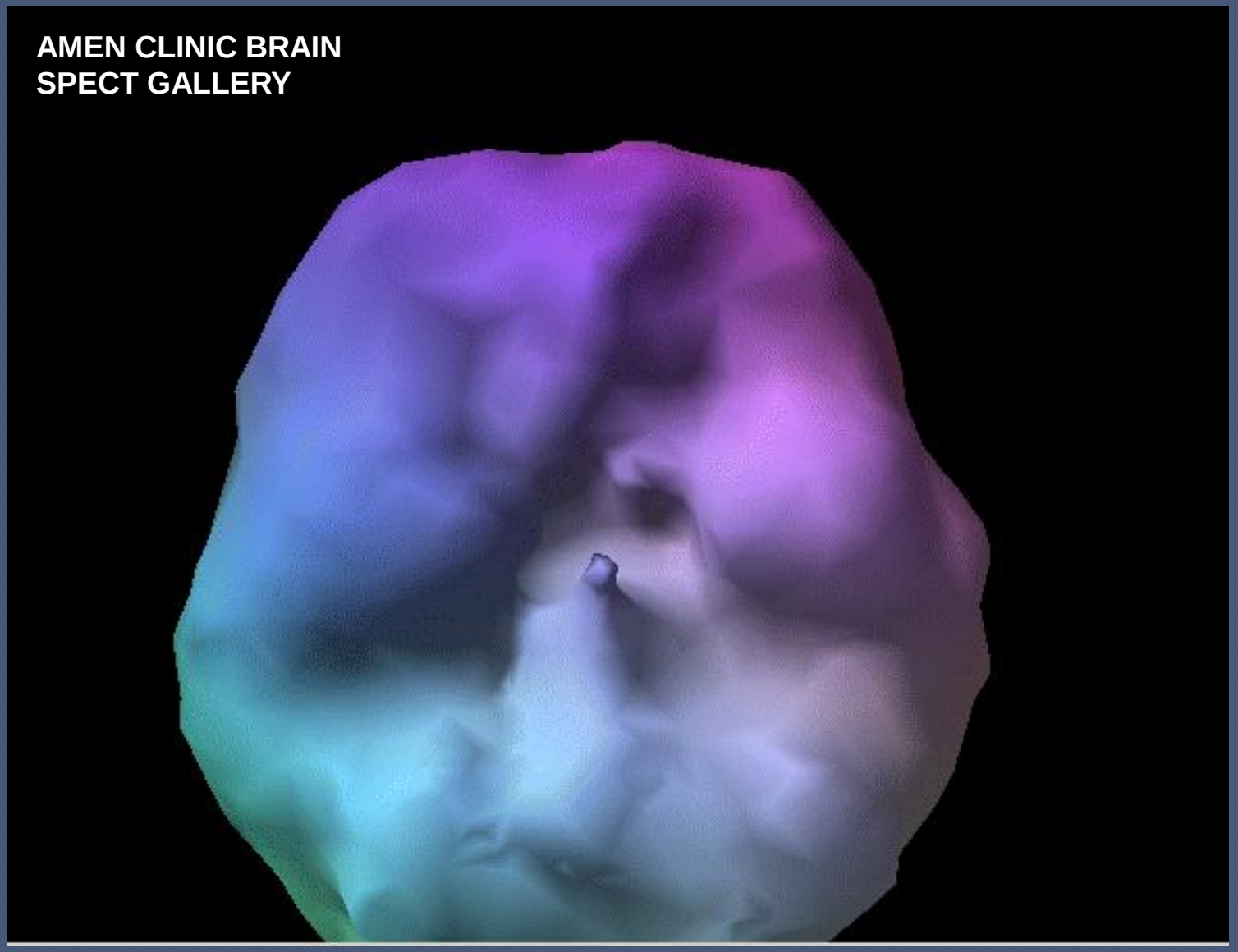


http://www.amenclinic.com/bp/spect_rotations/viewimage.php?img=da_CS.gif

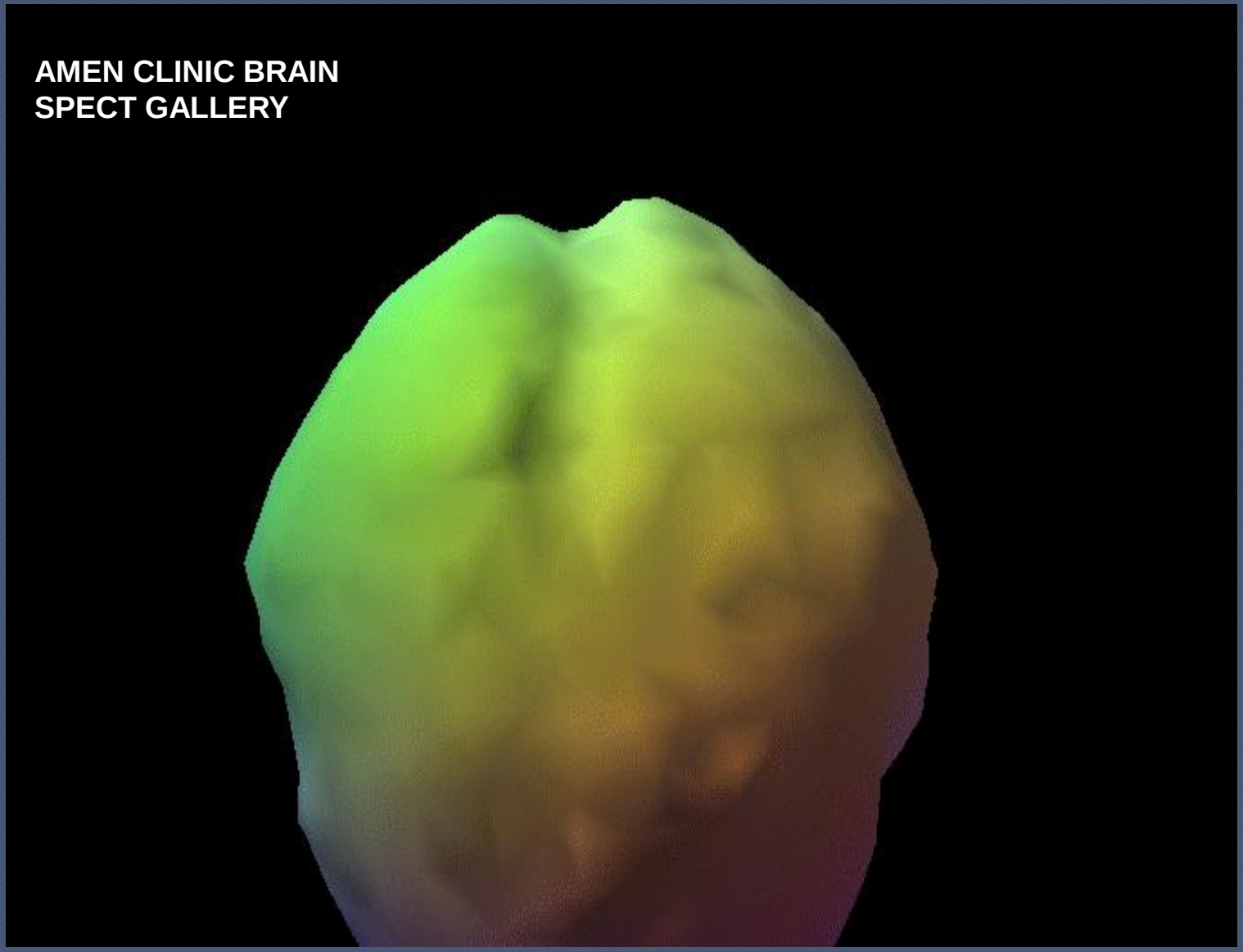
Drug user’s brain from the top



Healthy brain from the underside

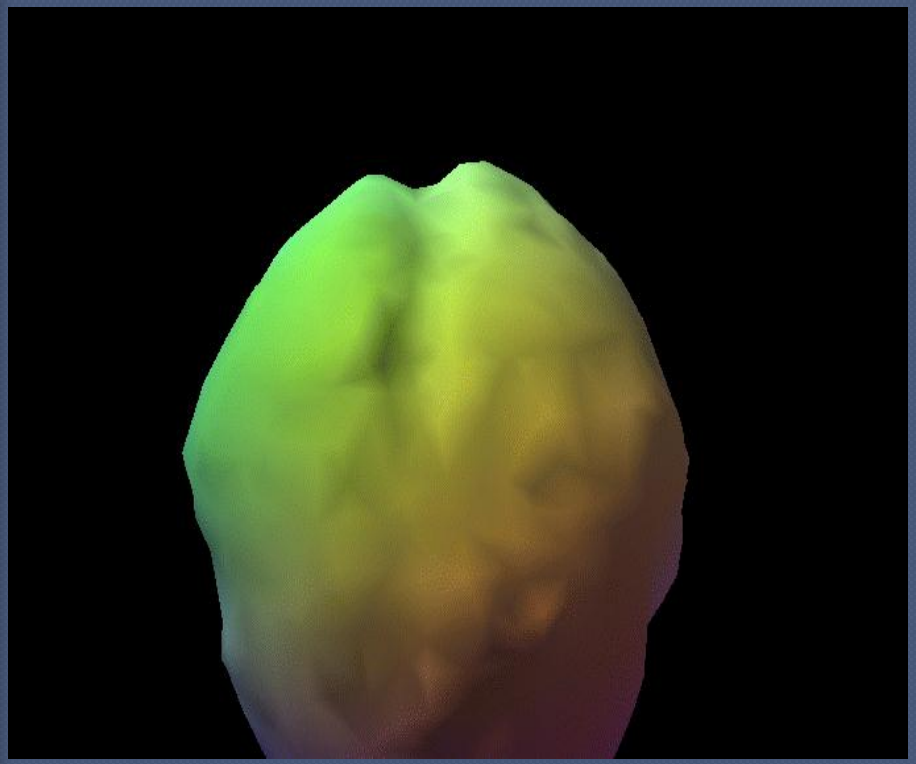


Healthy brain from the top

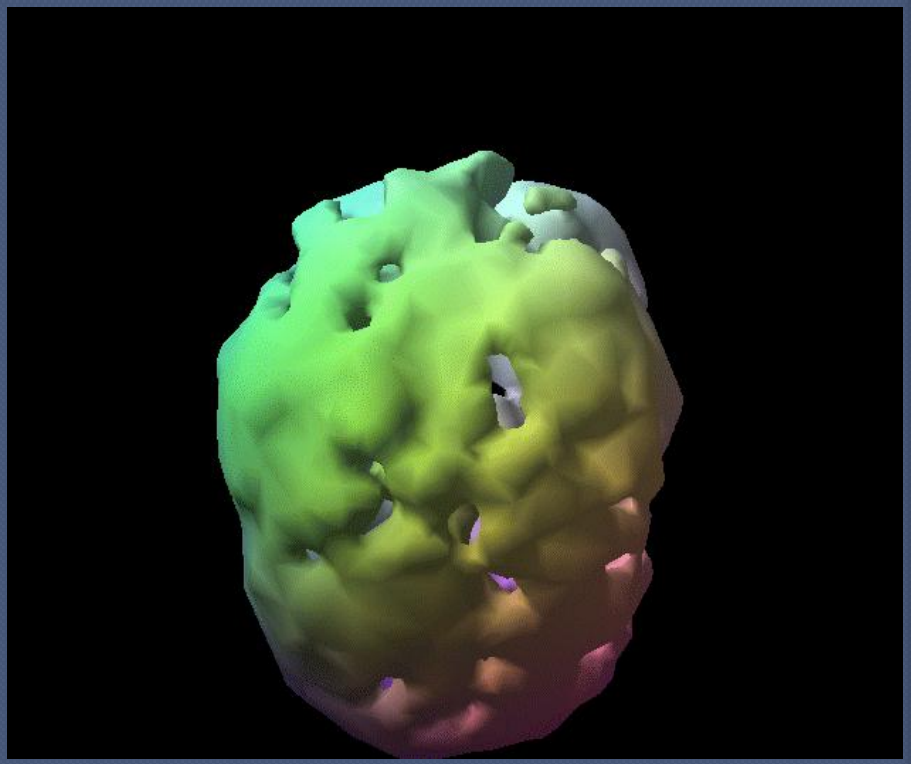


Side by Side

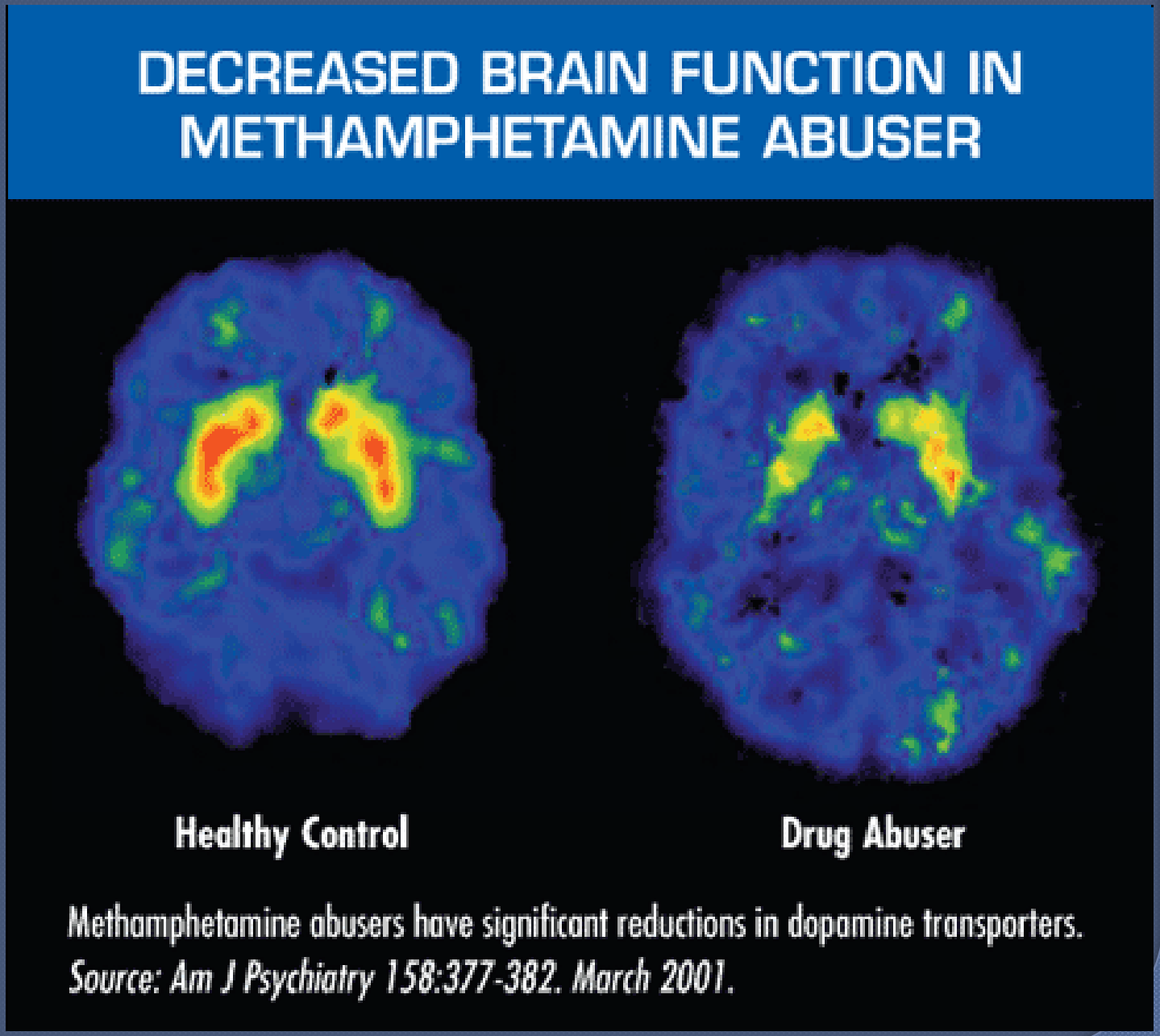
Healthy

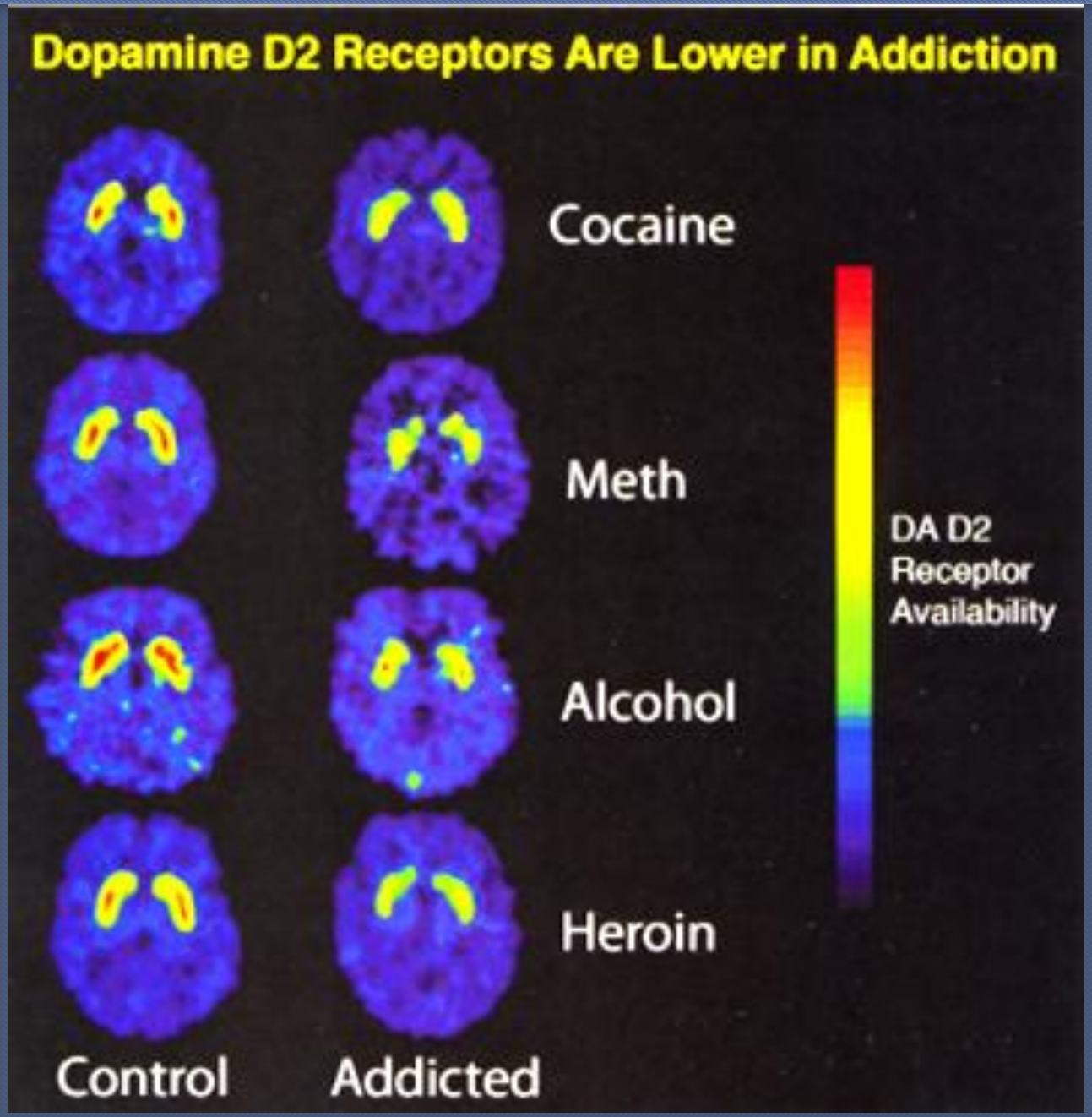


Drug User



The meth user's brain (drug free) shows lower levels of dopamine because the brain has learned how to accommodate the high levels of artificially induced dopamine.



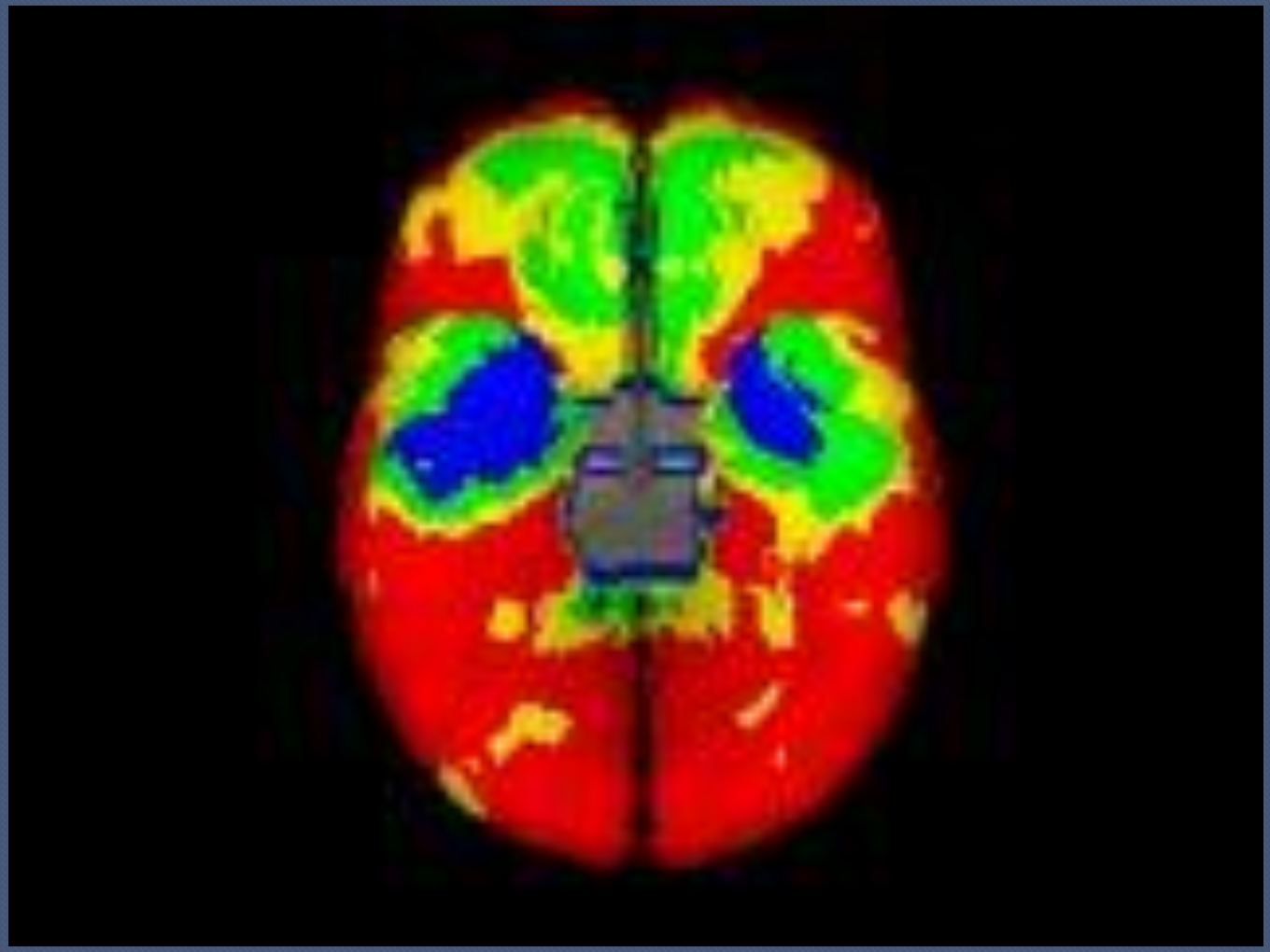


NIDA – Division of Clinical Neuroscience and Behavioral Research, NIDA NOTES, 21,(4), October, 2007

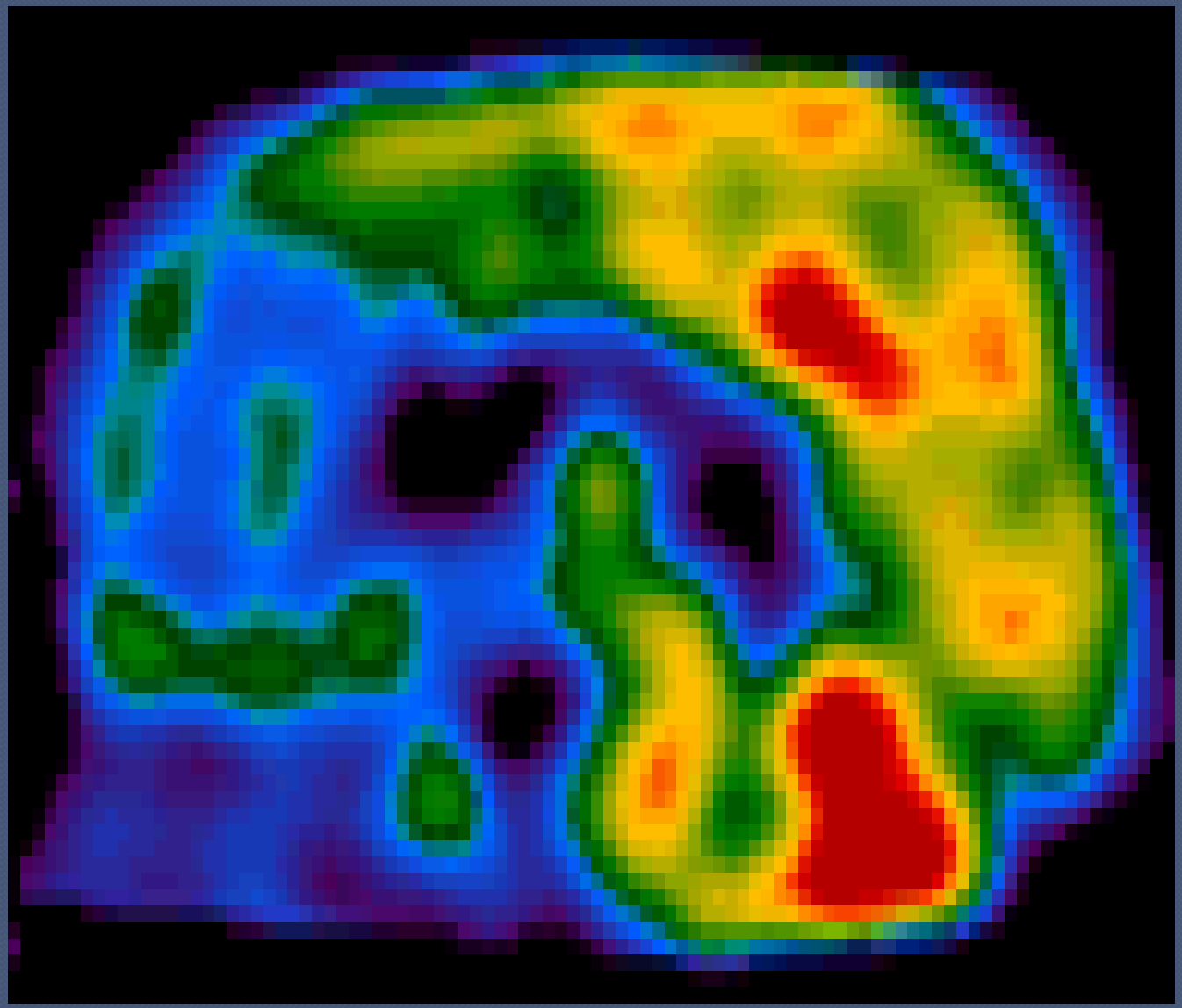
Brain functioning under other insults- similarity to addiction

- The long term effects of substance use and even long term untreated depression can reduce frontal lobe functioning in the human brain.
- The frontal lobes are where planning, executive functions, emotion management, and reasoning occurs – AND this is the area of the brain that *most needed for recovery activities*.
- In addition, head injuries can produce similar effects on the frontal lobes.

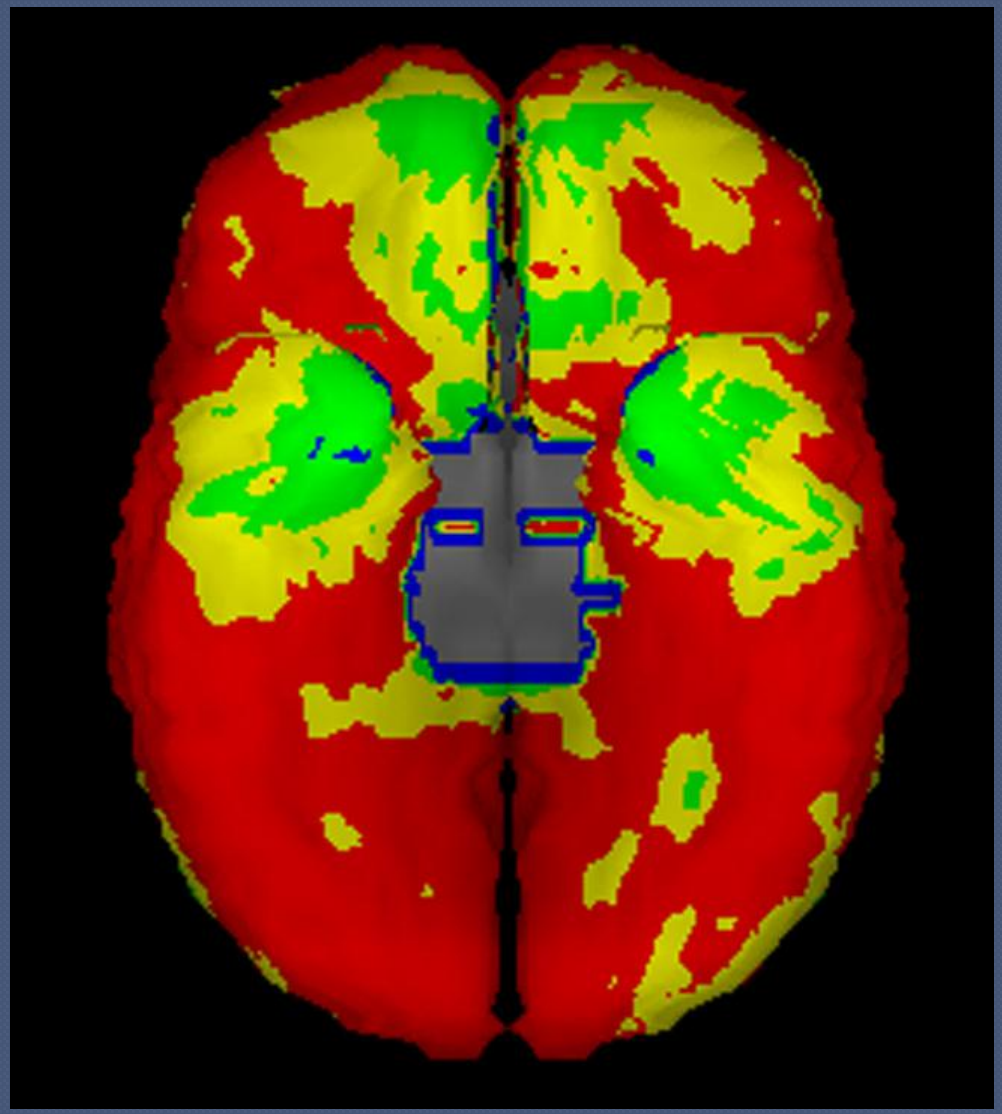
Underside view of a depressed brain – see the yellow and green areas at the frontal lobe area showing decreased activity there.



Picture courtesy of Dr. William Klindt of Silicon Valley Brain SPECT Imaging, San Jose, California www.braininspect.com



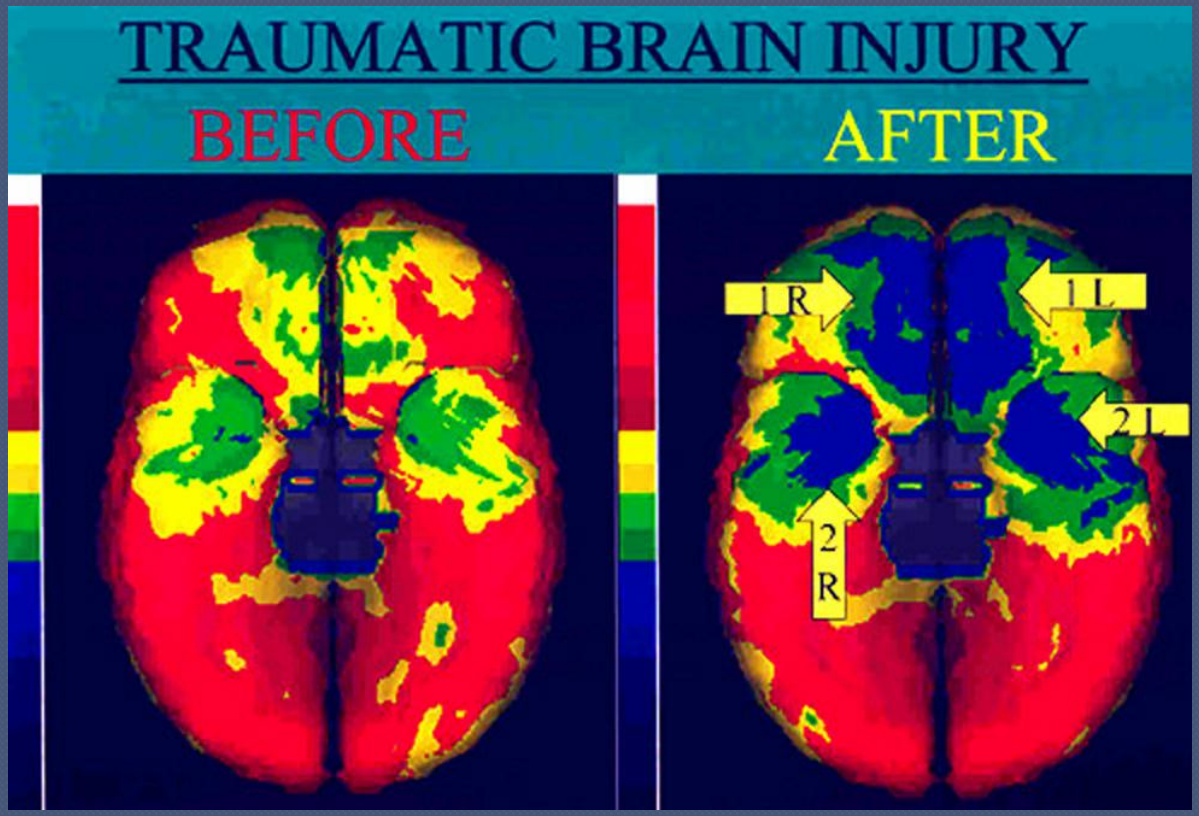
Now, for comparison, look at this same view from the underside of a brain that has had frontal lobe injury in an auto accident. The yellow and green colored areas are where there is less brain activity.



Picture courtesy of Dr. William Klindt of Silicon Valley Brain SPECT Imaging, San Jose, California www.braininspect.com

Brain injury and addiction can actually result in similar effects on brain activity – particularly in the frontal lobes where decisional thinking occurs

In this set of images, you can see a pre-injury and post injury difference in blood flow. The blue, yellow and green areas are where there is less brain activity – that is where the injury was.

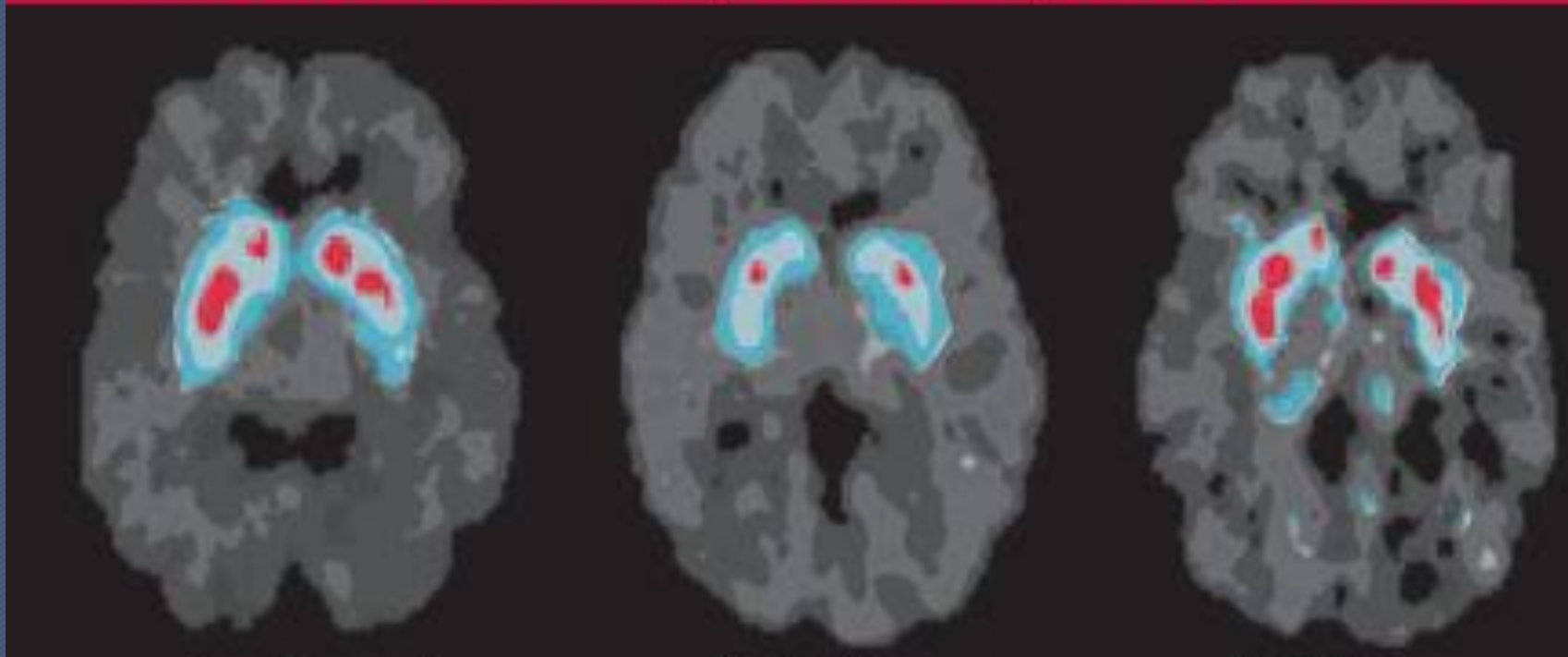


Picture courtesy of Dr. William Klindt of Silicon Valley Brain SPECT Imaging, San Jose, California
www.braininspect.com

Are the changes from drug use permanent?

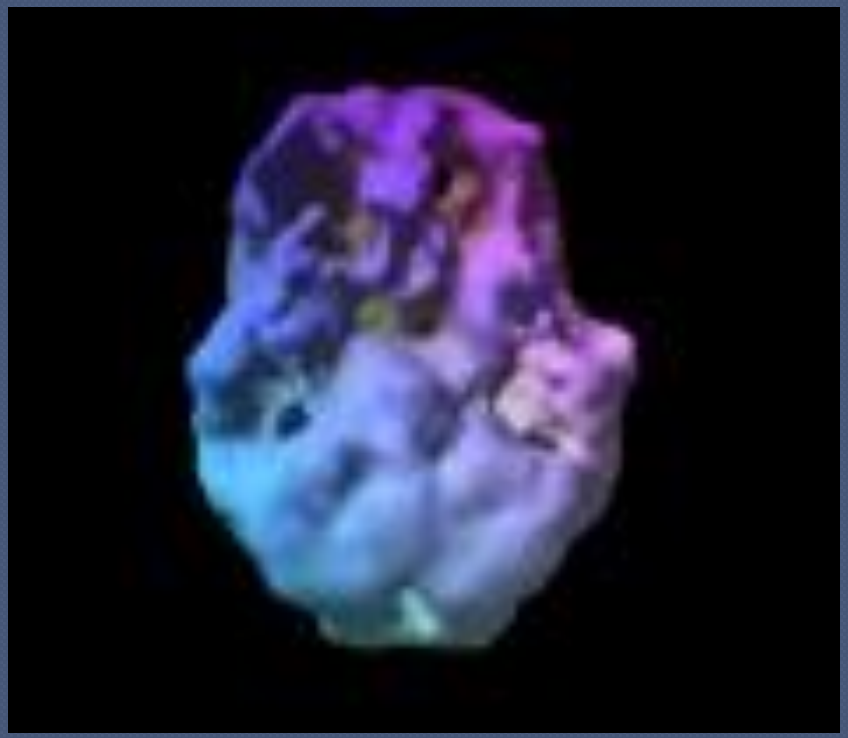
- Nope. Yep.
- There is increasing evidence of brain recovery from certain kinds of addiction.
- Long term heavy alcohol use results in some permanent damage and alcohol is perhaps the most harmful drug to the CNS.
- However, much of the damage done by alcohol use can be either restored or the brain can develop compensations for damaged areas.
- Even with methamphetamine, there is evidence of correcting earlier CNS damage.
- However, fundamental neurochemical "imbalances" that were there before the addiction, may still need attention.

Recovery of Brain Dopamine Transporters in Chronic Methamphetamine (METH) Abusers

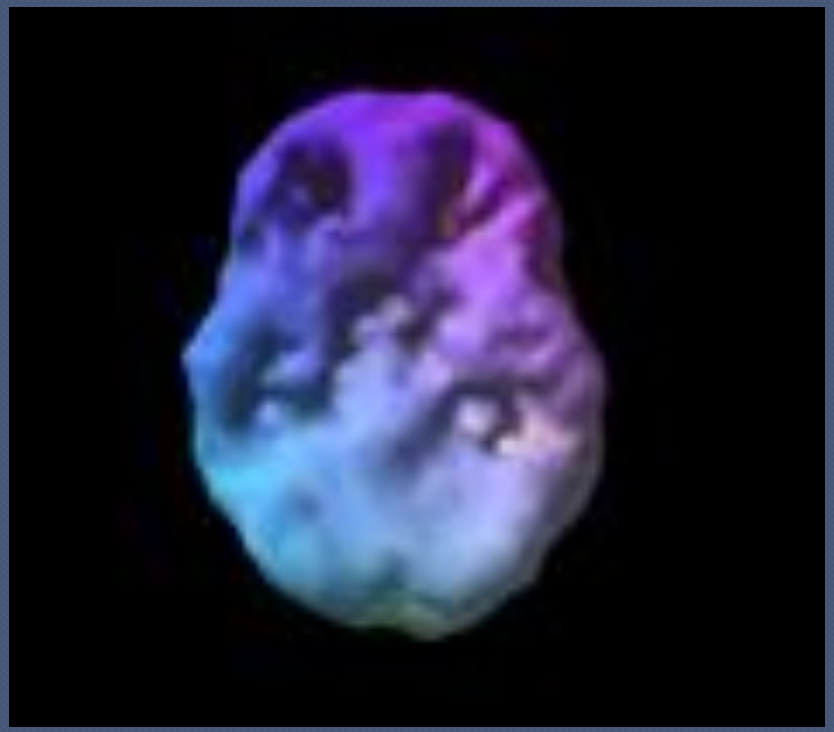


Source: Volkow ND et al., *Journal of Neuroscience* 21:9414–9418, 2001.

Imaging the underside: Extensive HX Alcohol and Cocaine – Before and After TX



Before



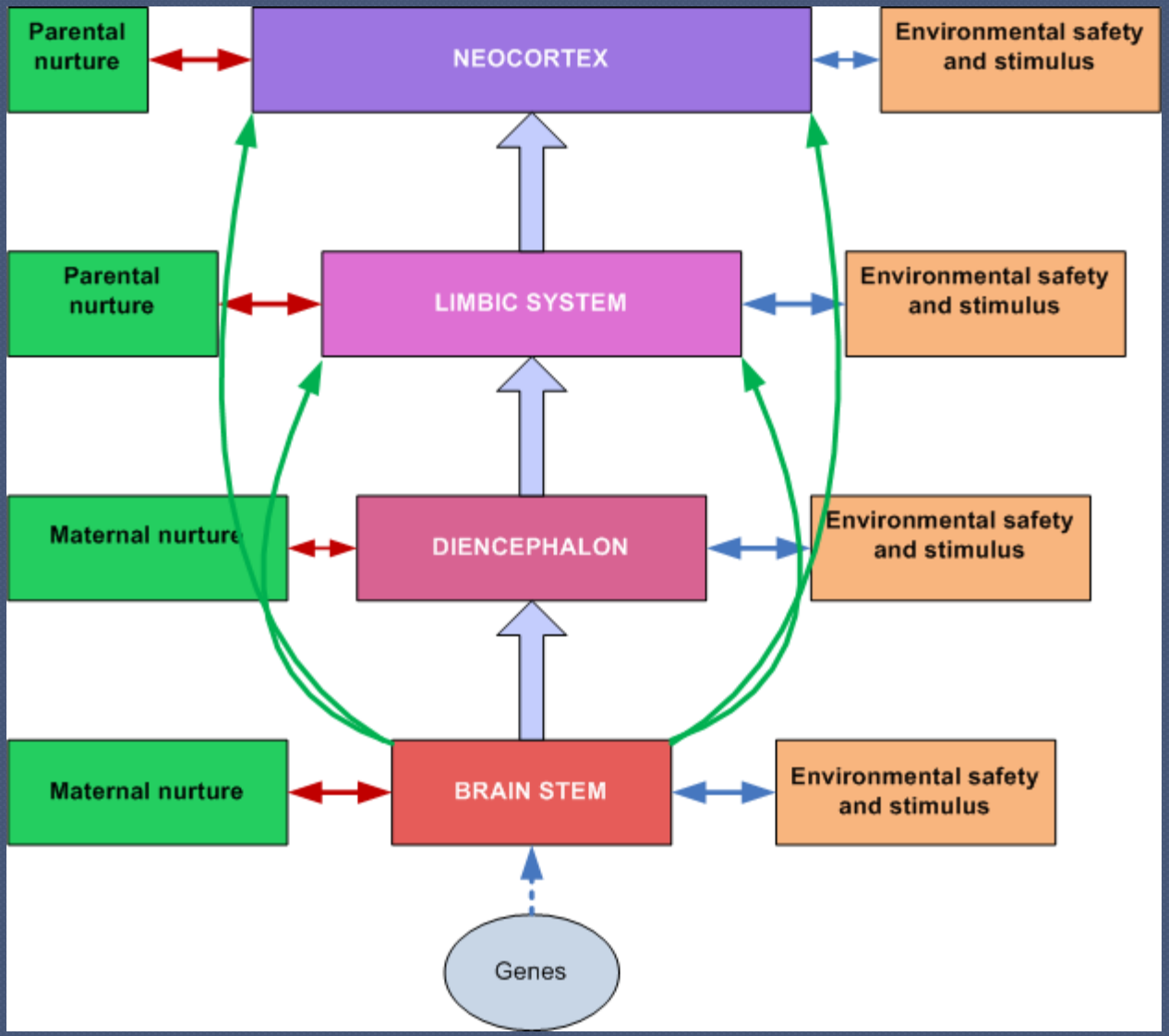
After

Do all drugs work the same?

- Nope. Yep.
- Each substance mimics a particular neurotransmitter, but in the end, each of these trigger a cascade of chemical events that results in activation of the VTA and NAc.
- If the event did not end up in the VTA/NAc, the substance would not be addicting.

The brain, drugs, and developmental stages

- The brain's capacity to adapt to substance use is also very different depending on the individual's age in the developmental cycle.
- The brain is constantly changing and even more so from birth to about age 20 or 21.
- There are major advances in development of the higher cortical areas during adolescence and substance use prior to this last stage of major brain development has serious consequences for continued development.


Parental nurture
NEOCORTEX
Environmental safety and stimulus
Parental nurture
LIMBIC SYSTEM
Environmental safety and stimulus
Maternal nurture
DIENCEPHALON
Environmental safety and stimulus
Maternal nurture
BRAIN STEM
Environmental safety and stimulus
Genes

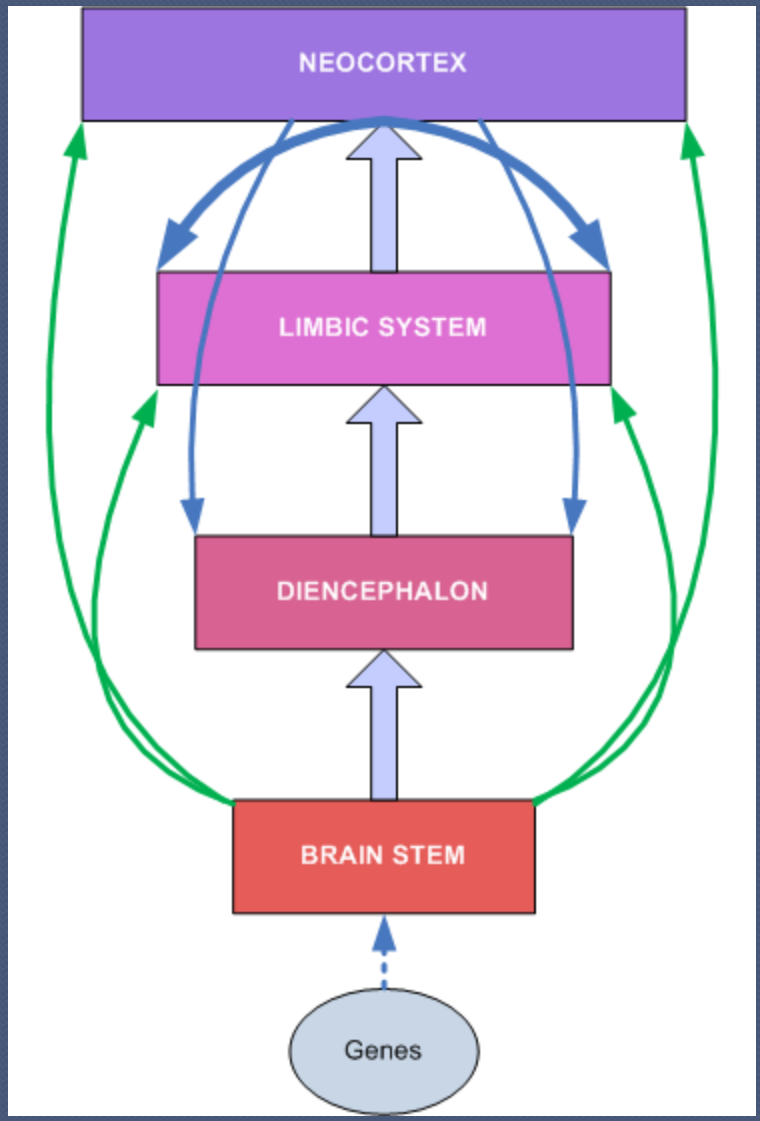
The processes by which interventions affect underlying structures in the brain are less well understood.

Essentially, trying to “undo” developments in lower levels of neurodevelopmental architecture is very challenging.

All therapies essentially focus on the neocortex. The capacity of the neocortex to reach down and changes ‘settings’ in the diencephalon is limited.

Verbal, rational processes will not get there.

Music, relaxation, meditation *might* get there.



Threats from the world

- Our environment provides cues and stimuli that trigger our responses and reactions.
- New input is "compared" to what the brain has stored in its automatic response library.
- Most of these automatic responses arise from the brain stem.
- The higher brain areas can modify and even dampen those automatic responses – IF the brain has developed these areas.

Trauma

- During early childhood threats to the organism lead to "state memories" – not content memories.
- These memories are like default settings in the brain so that when a threat occurs it triggers an automatic re-use of the response state.
- When the threat is sustained or severe, the higher brain areas may be unable to shut this system off.

Development

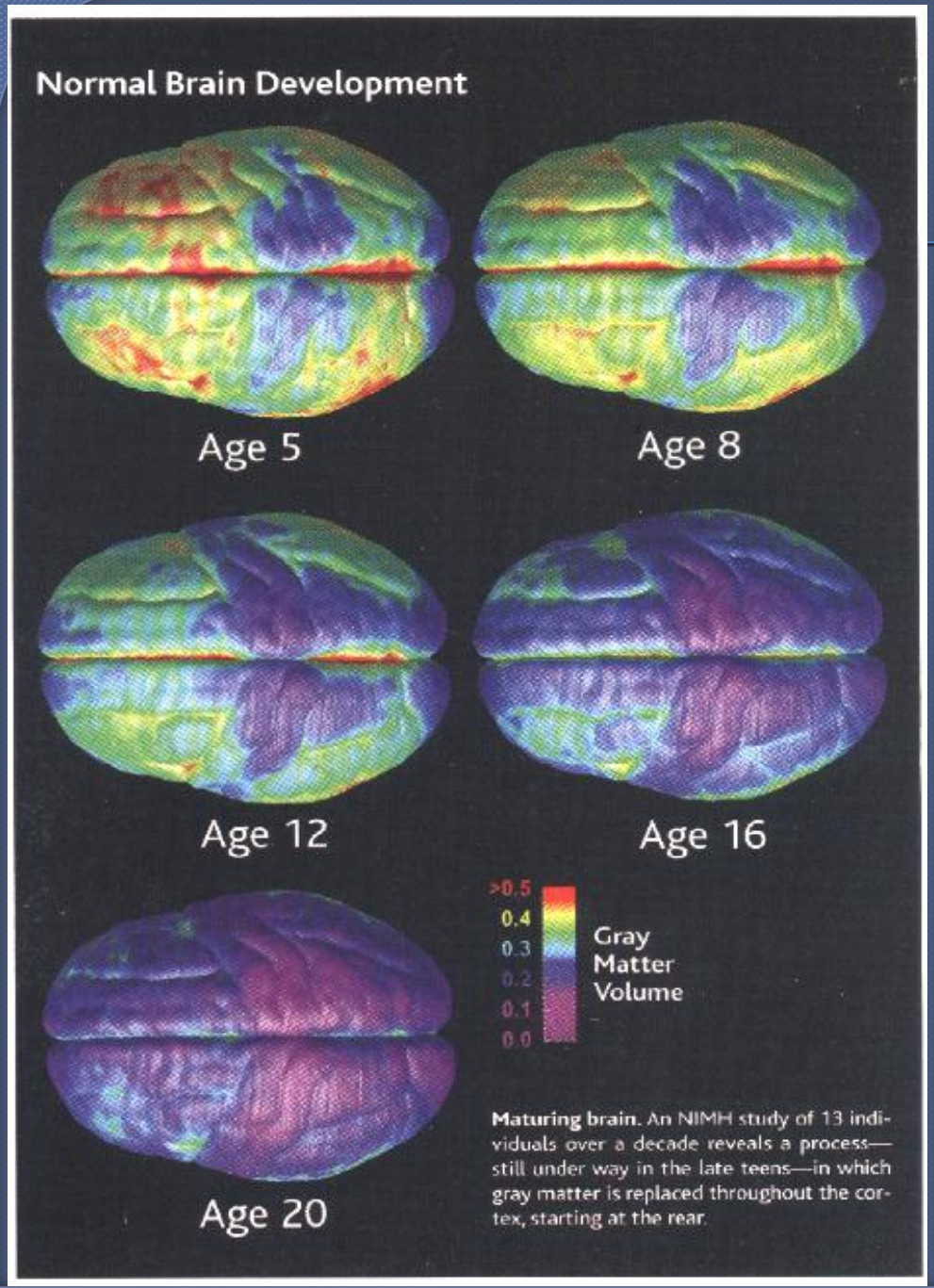
- Brain development occurs through stimulation and use.
- Development is also sequential with each successive stage dependent on successful development of the previous stage.
- Chaotic experiences interfere with and can arrest this stepwise developmental process.

Also,

- The brain develops most rapidly in early childhood. By age 2 the brain has its maximum of neurons.
- By age 4, the brain is 90% of its adult size.
- There are developmental windows for specific functions and if these are missed or are mal-stimulated, the damage is much harder to repair later on.

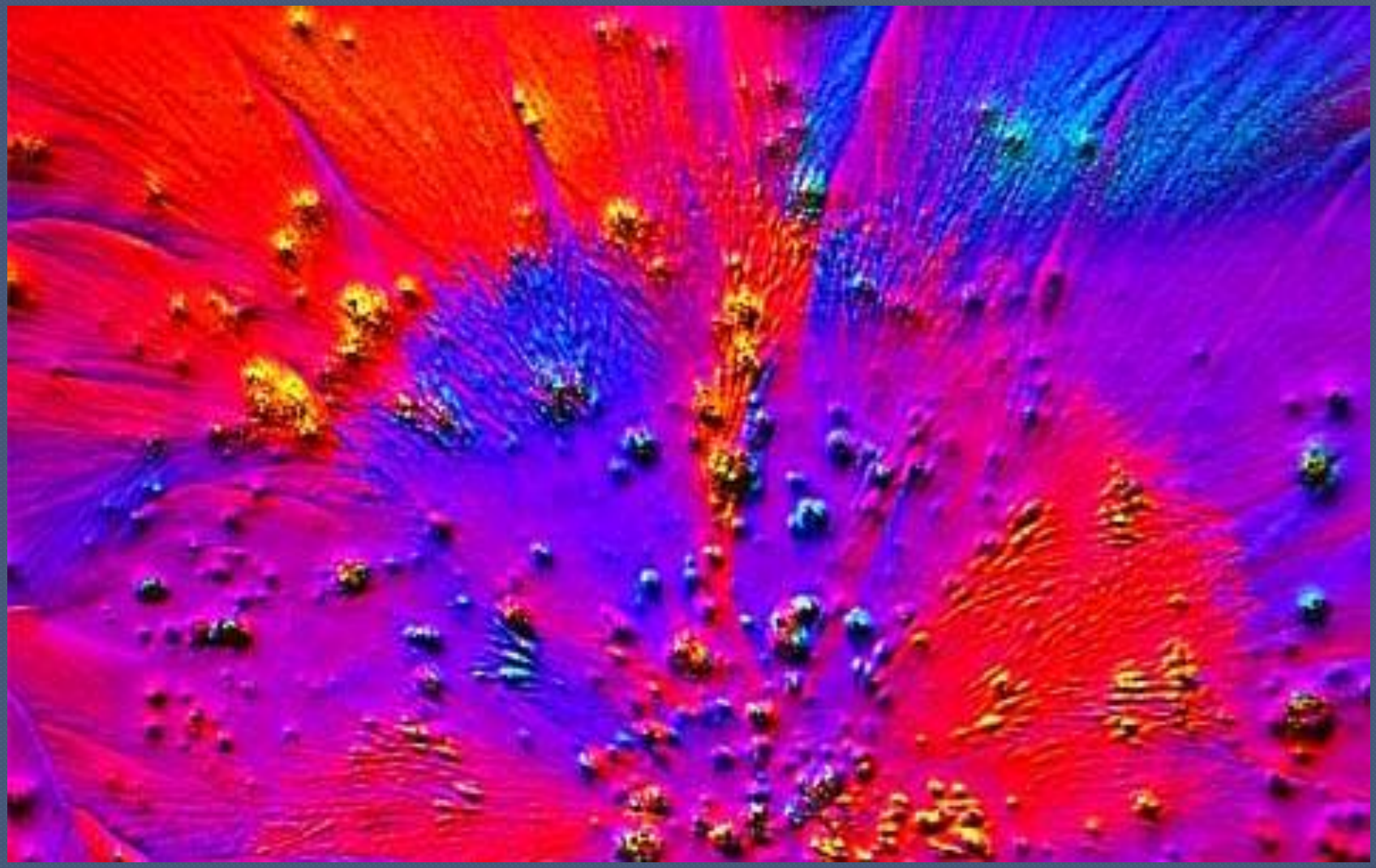
Early drug use

- The literature has long held that repeated drug use before age 14 is associated with far greater likelihood of adult addiction.
- The reward centers of the brain, being more primitive, develop before the frontal cortex.
- Thus, with early drug use, the brain gets stimulated intensely but does not yet have the ability to put the frontal lobe brakes on.



This set of images, a composite of 13 brains during development, shows how the cortex goes through changes during adolescence. The purple color shows the replacement of gray matter in the cortex throughout development. By age 20, the brain is essentially complete in cortical development.
(Science, 2002).

Interventions?



Always think of….

- The combined effects of the many factors that impair substance users' cognitive functioning and all treatment approaches call for increased use of cognitive processes.
  - The very brain center that is most impaired is the one we need the most in treatment.
- In most cases, we are looking at multiple insults to addicts' brains – developmentally, experientially, and psychologically.
  - Too often treatment fails to address all these areas of harm to functioning.

- Addicts lose the ability to invent solutions to problems – they tend to rely on tried and true coping tools - drug use.

- The frontal lobes are greatly affected by almost all substances – both short term and longer term.

- Thus, the very thing we are asking them to do (exercise control over impulsive and compulsive behavior) is the one thing they will have the greatest difficulty doing.

- It's like asking someone with sprained ankles to run.

Programs and treatment compliance

- Drug courts and many other treatment approaches to substance abuse develop stringent rules.
- Many programs have rigid phases and clients must comply with rules to move into higher phases.
- The very thing being asked for is what these brains are uniquely adapted to NOT do.

So, what might work?

- While cognitive approaches might have usefulness, interventions aimed at dampening arousal through non-verbal means may be useful.
- Meditation, focused relaxation, listening to calming music, dance therapy, drumming (usually thought of as arousing), massage therapy.
- If an individual is unable to dampen arousal long enough to listen to talk therapy, then the intervention is useless.

Why can't they just stop?

- Remember, each intoxicating substance ***mimics a natural chemical***.
- The more you introduce into a brain, the more the brain tries to compensate.
- So, for example, when using methamphetamine, the brain is deluged with dopamine and norepinephrine.
  - The brain tries to clear these chemicals out using enzymes that break them down and the brain develops ways to increase production of these enzymes.
  - Also, the nerve cells develop more receptor sites to handle the increases number of NE molecules.

- When addicts go "cold turkey" the mass of enzymes and the greatly increased number of receptor sites cause massive depletion of dopamine and norepinephrine – so much so that even basic capacity is seriously affected.

- This is what fuels craving in the brain.

- Craving, combined with a brain that is developmentally hyperaroused = high risk for relapse.
- Teaching management of arousal states plus relapse management is the critical activity.
- Addicted brains have very limited capacity to dampen negative or strong excitatory emotions.
  - Thus training brains how to do this can be critical.
  - The use of relaxation, meditation, music, calming imagery – all may be important early steps in teaching a brain how to cope with loss of drugs.

So, what about the implications of all this science?

- The neurobiology of addiction suggests a complex, genetically vulnerable condition.
- Brain habituation means that core vulnerabilities have also been increased due to the brain's compensatory processes.
- Therefore, to go cold turkey means the brain becomes like a fish on the beach.