

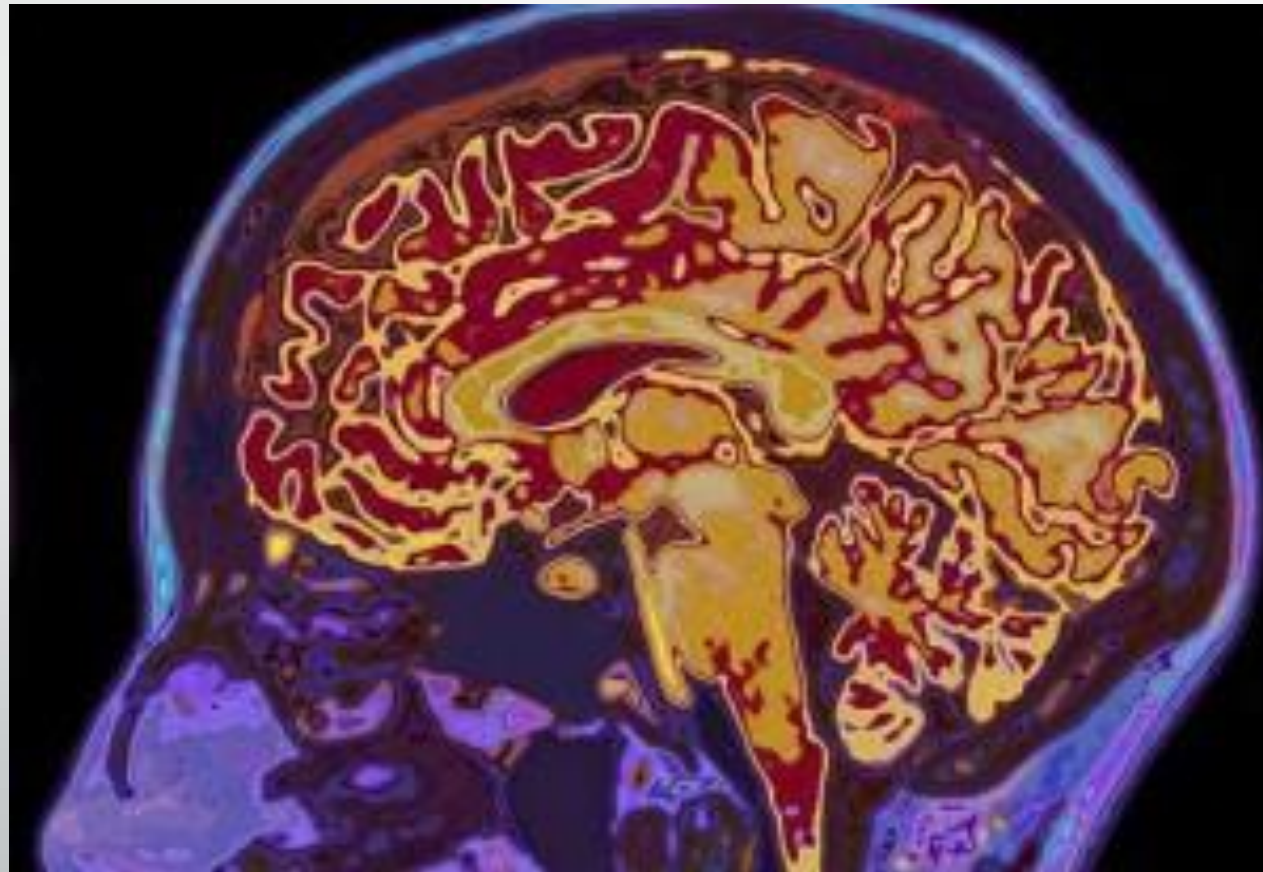
# Neuroscience of Mental Health Disorders Part 3

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# BIPOLAR DISORDER



# The Brain and Bipolar Disorder

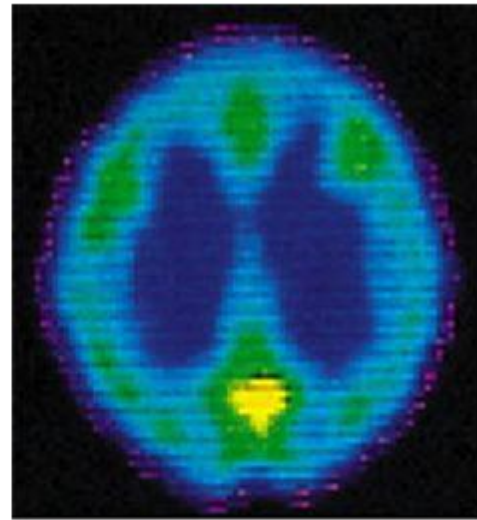
Experts believe bipolar disorder is partly caused by an underlying problem with specific brain circuits and the balance of brain chemicals called neurotransmitters.

Three neurotransmitter (brain chemicals) identified with Bipolar Disorder are:

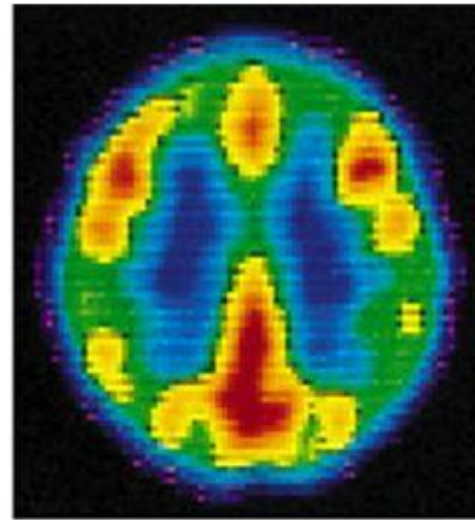
- Noradrenaline (norepinephrine)
  - Serotonin
  - Dopamine
- Serotonin is connected to many body functions such as sleep, wakefulness, eating, sexual activity, impulsivity, learning, and memory. Researchers believe that abnormal functioning of brain circuits that involve serotonin as a chemical messenger contribute to mood disorders (depression and bipolar disorder).
  - Dopamine is commonly linked with the pleasure system of the brain. Disruption to the dopamine system is connected to psychosis and schizophrenia, a severe mental disorder characterized by distortions in reality and illogical thought patterns and behaviors, thus the reason for confusion in gaining an accurate diagnosis of an individual with Bipolar who is also psychotic and/or delusional

# The Depressed Brain

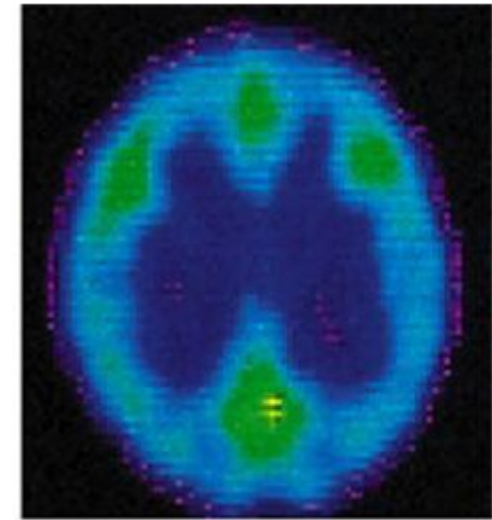
PET scans show that brain energy consumption rises and falls with manic and depressive episodes.



**Depressed state**  
(May 17)

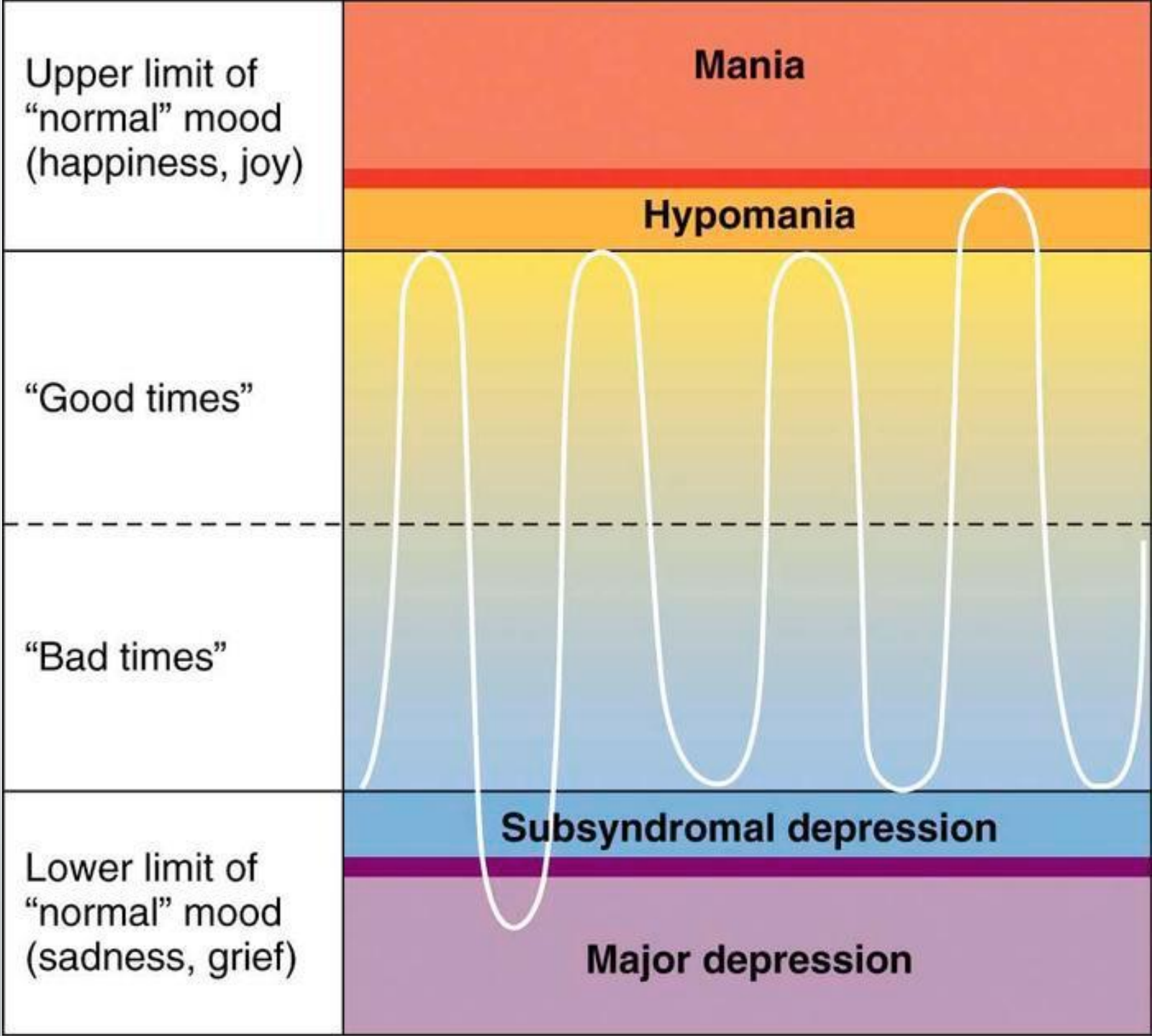


**Manic state**  
(May 18)



**Depressed state**  
(May 27)

Courtesy of Lewis Baxter, an Michael E. Phelps, UCLA School of Medicine



Upper limit of "normal" mood (happiness, joy)

**Mania**

**Hypomania**

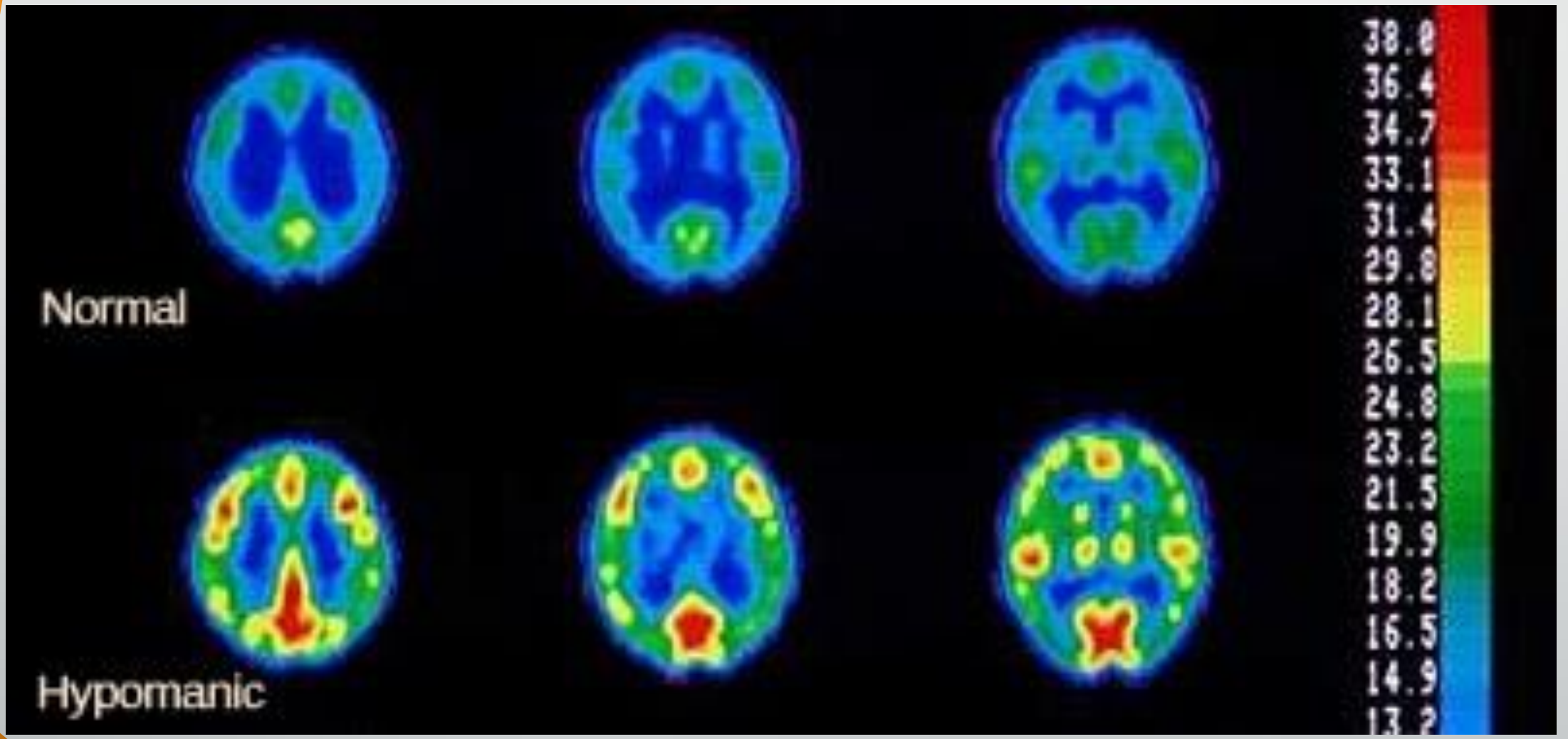
"Good times"

"Bad times"

Lower limit of "normal" mood (sadness, grief)

**Subsyndromal depression**

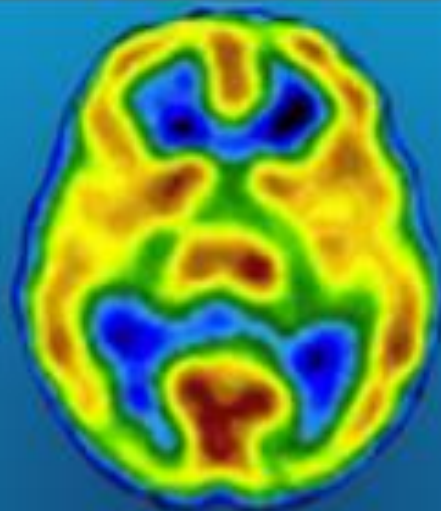
**Major depression**



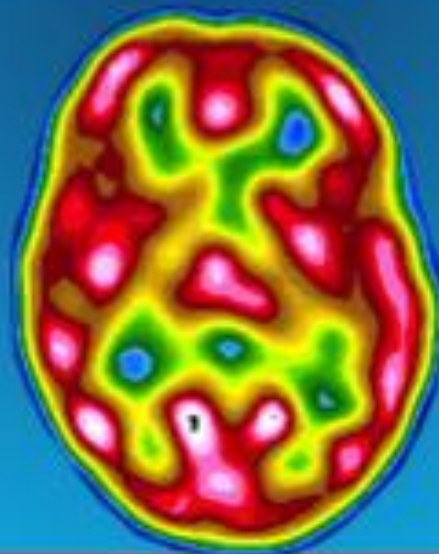
Normal

Hypomanic

NORMAL BRAIN



BIPOLAR DISORDER



# DEPRESSION



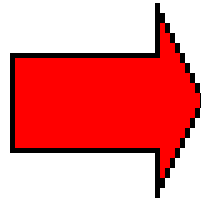


# Neurobiology of Depression – Depression Is In the Brain

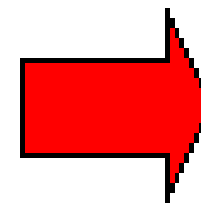
The neurobiology (biology of the brain) of major depression research areas include:

- Psychosocial stress and stress hormones
- Neurotransmitters such as serotonin, norepinephrine, dopamine, glutamate and gamma-aminobutyric acid (GABA)
- Neurocircuitry (neuroimaging)
- Neurotrophic factors
- Circadian rhythms

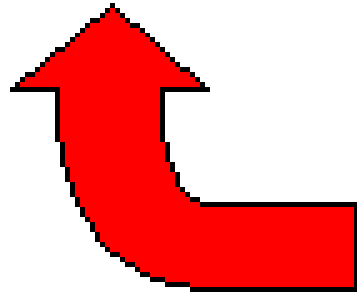
**Emotionally  
arousing  
rumination**



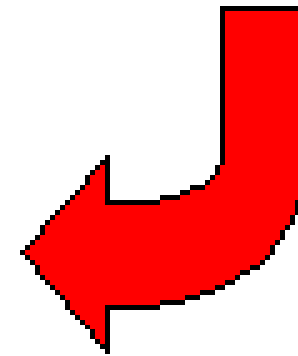
**Over  
dreaming  
(REM) and less  
deep sleep  
(recuperation)**



**Tiredness or  
exhaustion by  
morning**



**Depressive  
thinking styles**

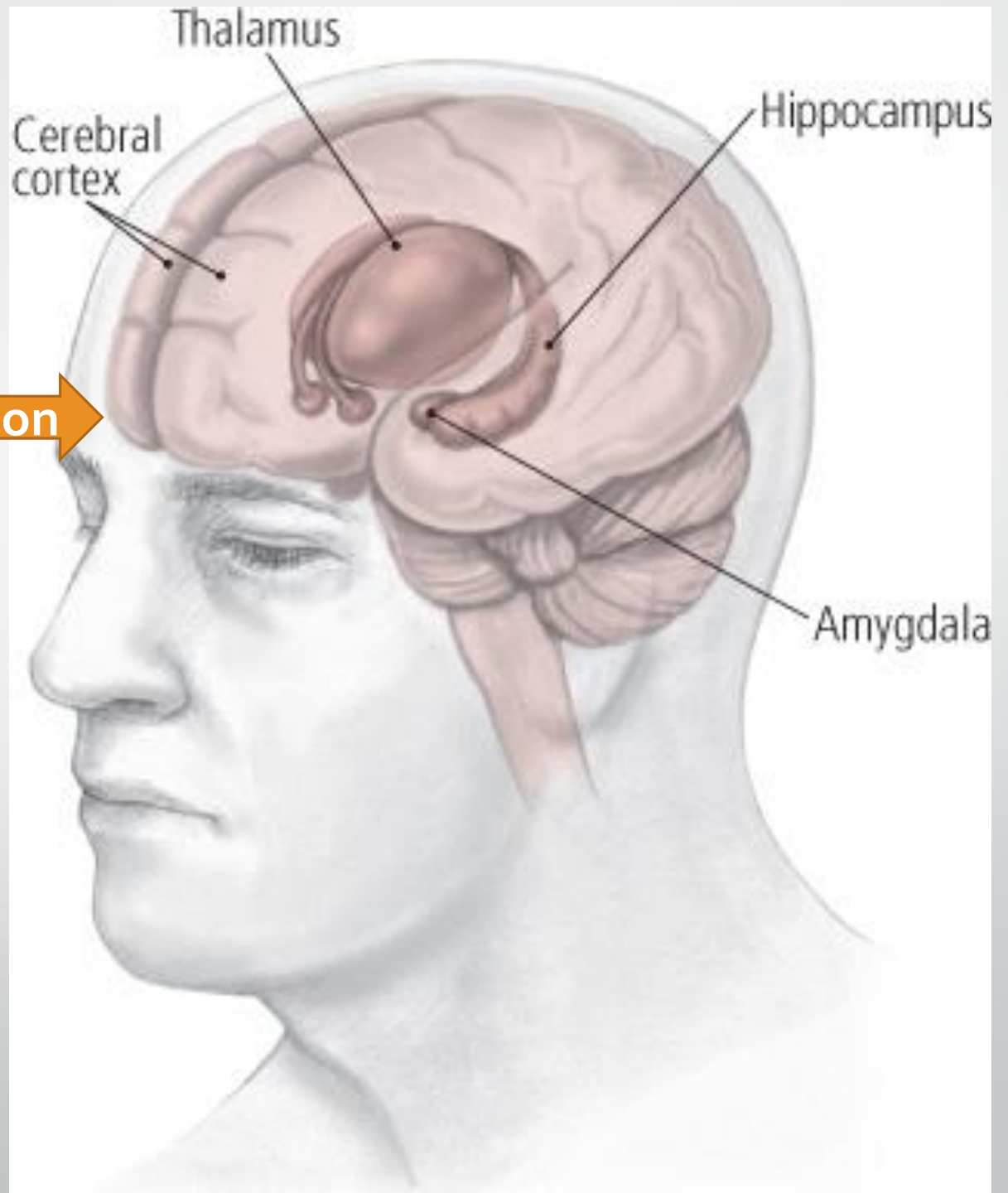


(c) Clinical-Depression.co.uk

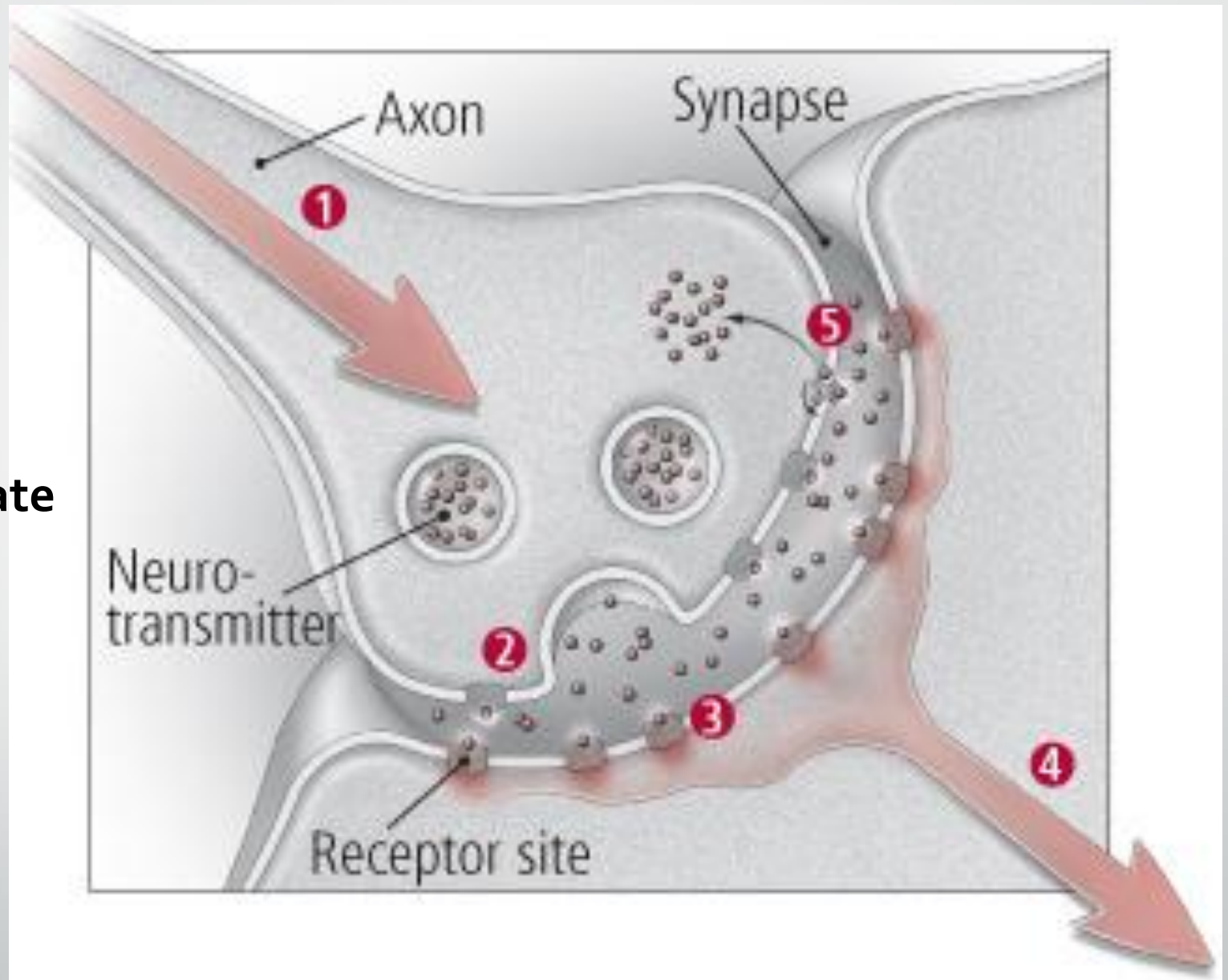
# CAUSES AND TREATMENT



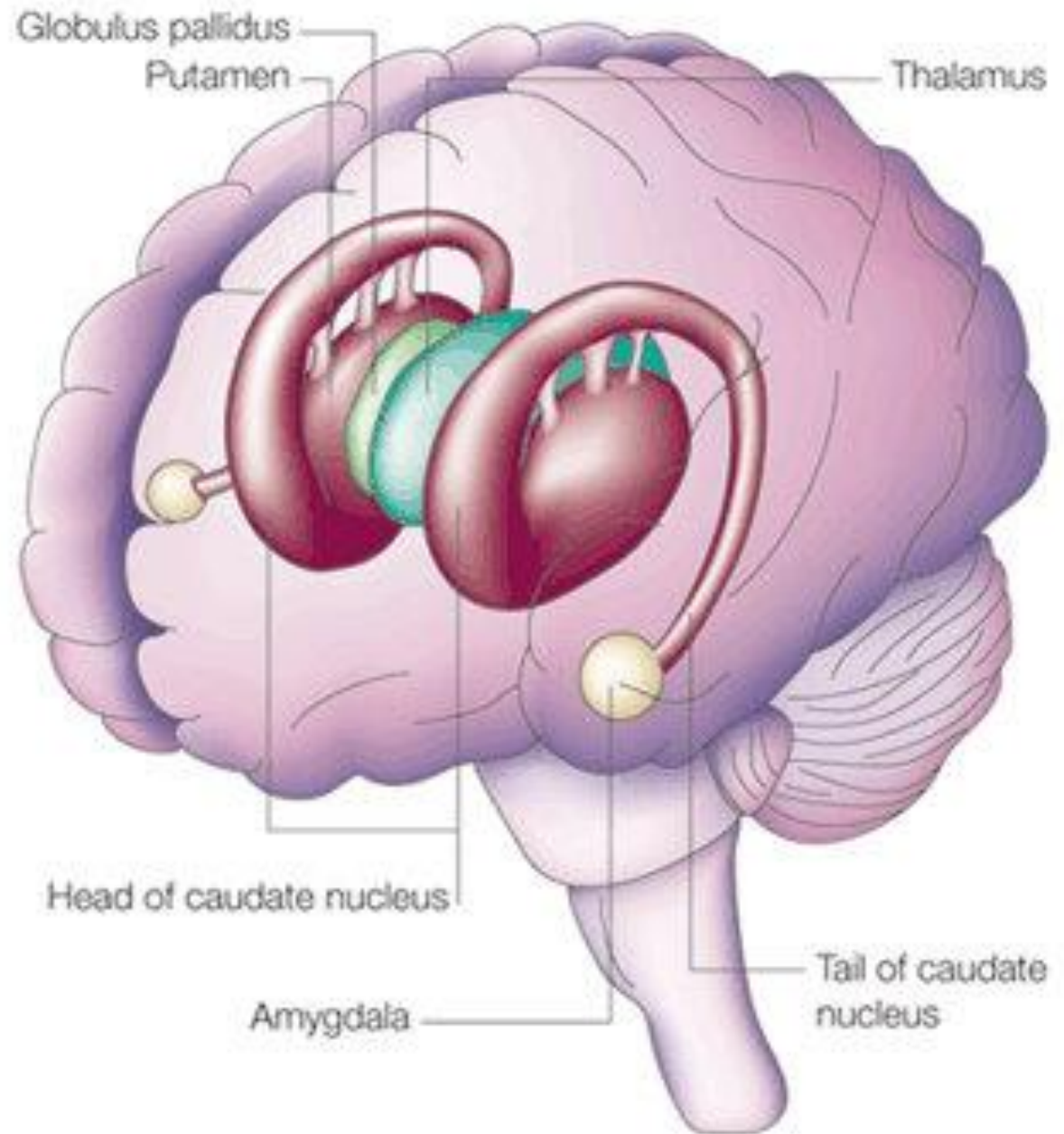
Areas of the brain affected by Depression



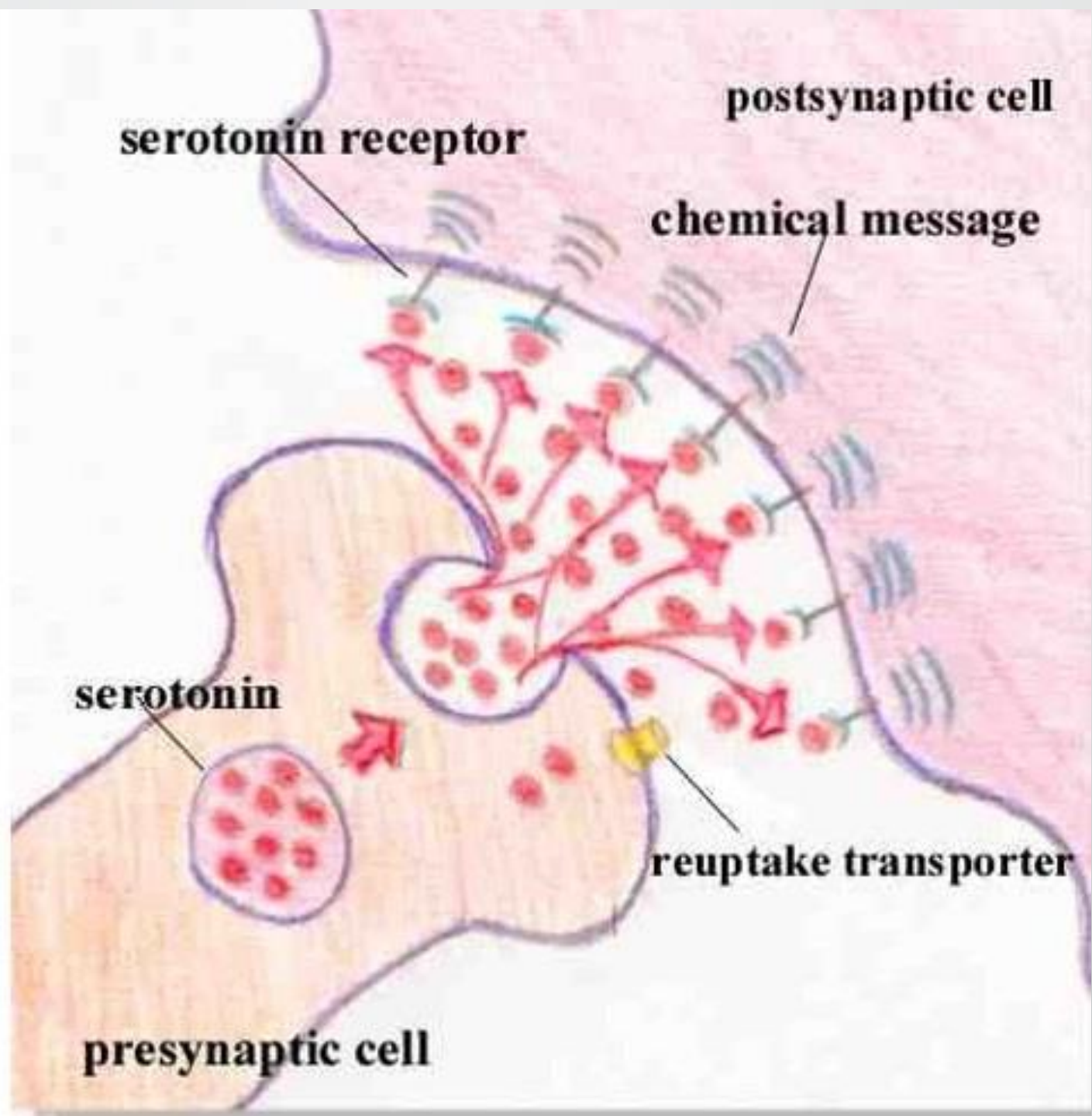
# How neurons communicate



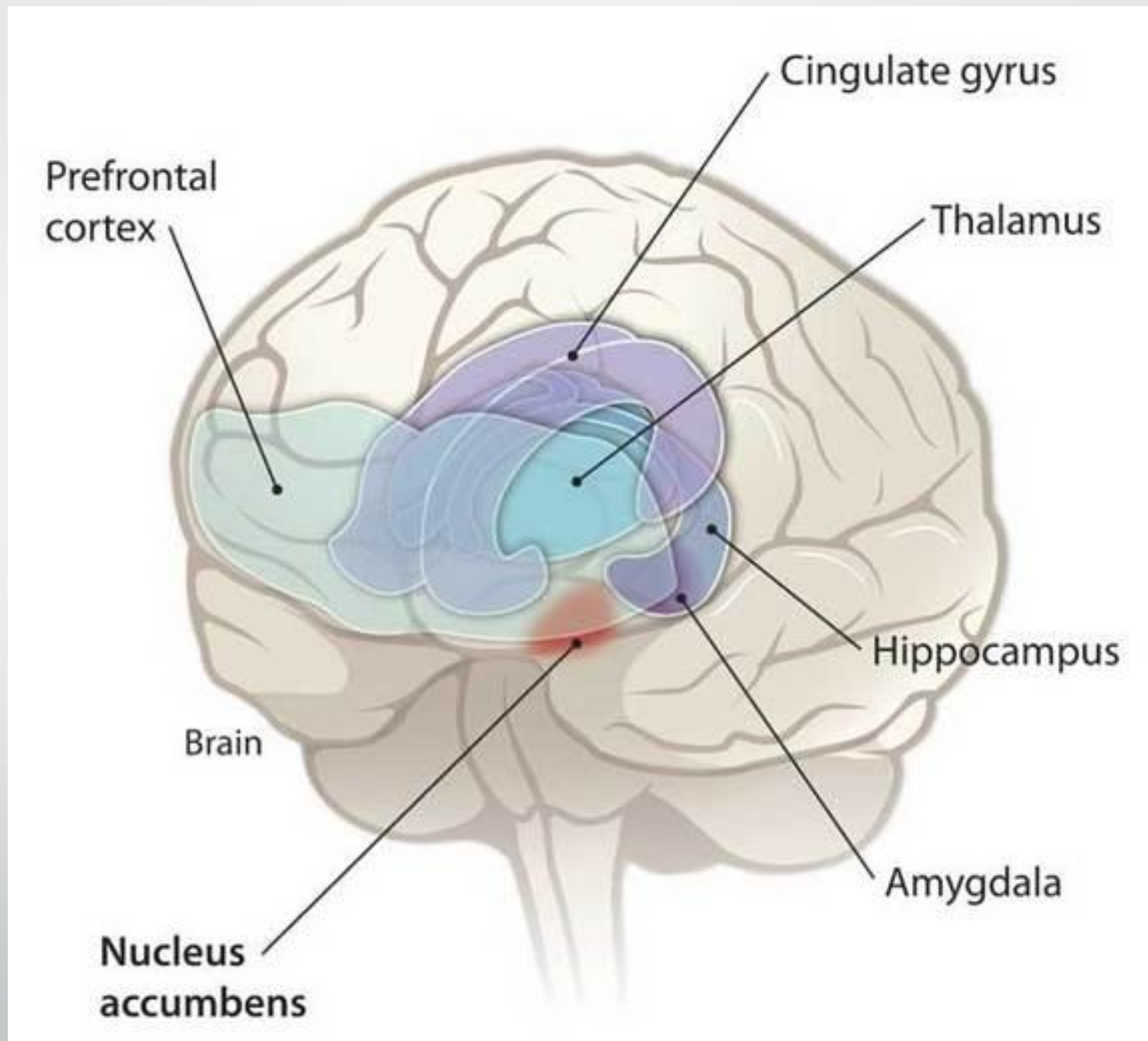
## Brain Diagram with Amygdala



“Neurotransmitter” what does this really mean? Neurotransmitters are chemical messengers within the brain that facilitate communication between nerve cells. Here’s an illustration of serotonin.



**Another view of the components of the Brain's Limbic System involved in Depression**





## Depression Manifestations

```
graph LR; A[Depression Manifestations] --- B[Major or Clinical Depression: Sever and disrupts ability perform daily tasks]; A --- C[Dysthymia: Milder than major depression but persists for at least 2 years]; A --- D[Double Depression: = Major + Dysthymia]; A --- E[Atypical Depression: Can temporarily put on a brave face and can appear OK to others]; A --- F[Melancholia: Unable to even temporarily feel any lift, easy to see in someone]; A --- G[Depression coupled with Anxiety]; A --- H[Postpartum Depression]; A --- I[SAD Winter Blues];
```

**Major or Clinical Depression:**  
Sever and disrupts ability perform daily tasks

**Dysthymia:**  
Milder than major depression but persists for at least 2 years

**Double Depression:**  
= Major + Dysthymia

**Atypical Depression:**  
Can temporarily put on a brave face and can appear OK to others

**Melancholia:**  
Unable to even temporarily feel any lift, easy to see in someone

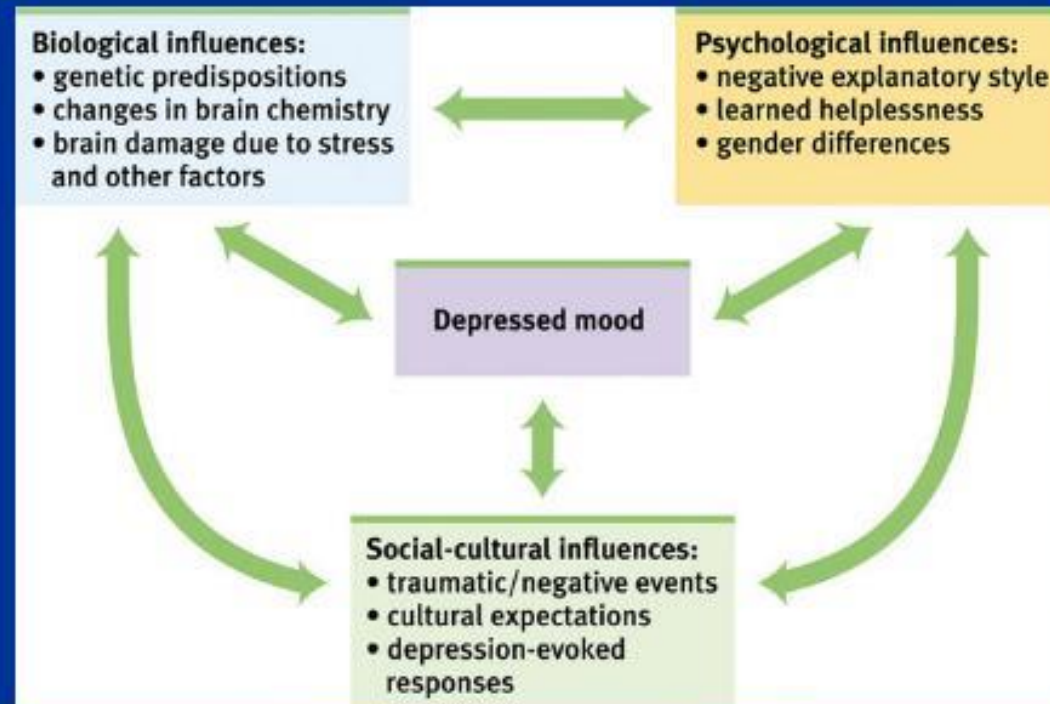
**Depression coupled with Anxiety**

**Postpartum Depression**

**SAD**  
Winter Blues

# Social-Cognitive Perspective

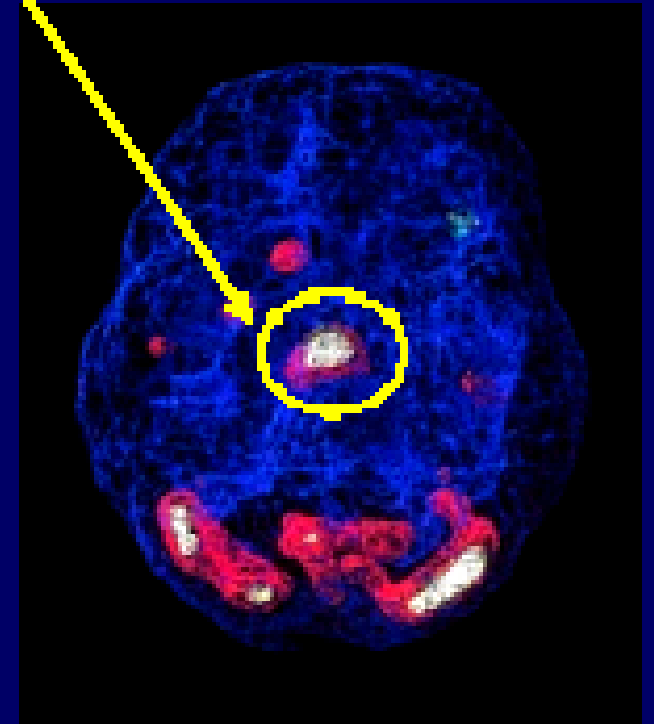
The social-cognitive perspective suggests that depression arises partly from self-defeating beliefs and negative explanatory styles.



# Diminished Serotonin Activity

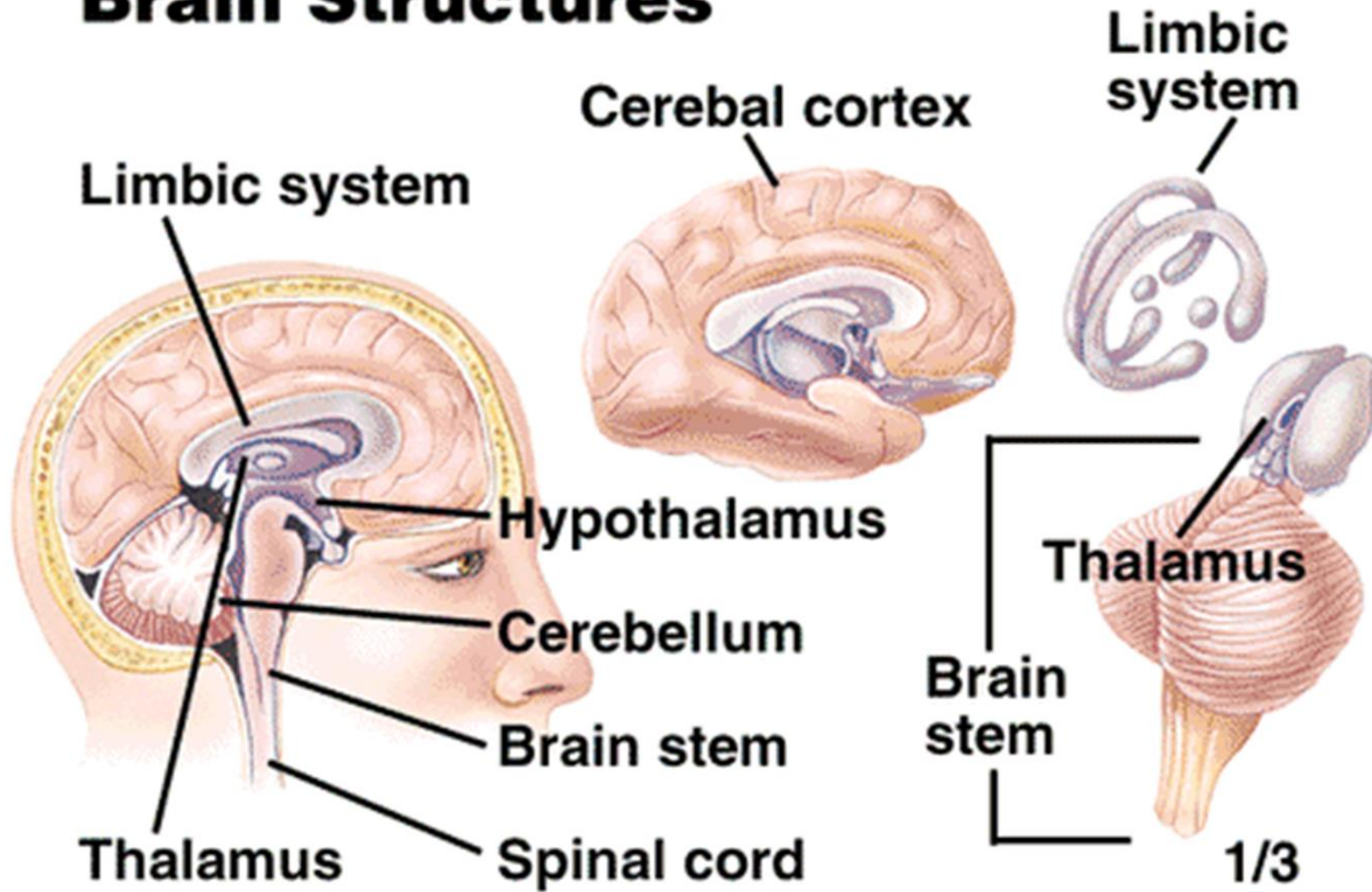
## Overactive Deep Limbic System

- Depression
- Negativity
- Moodiness
- Irritability
- Social isolation
- Hopelessness
- Excessive guilt
- Easily offended



The Limbic System  
& Brain Structures  
related to it

## Brain Structures

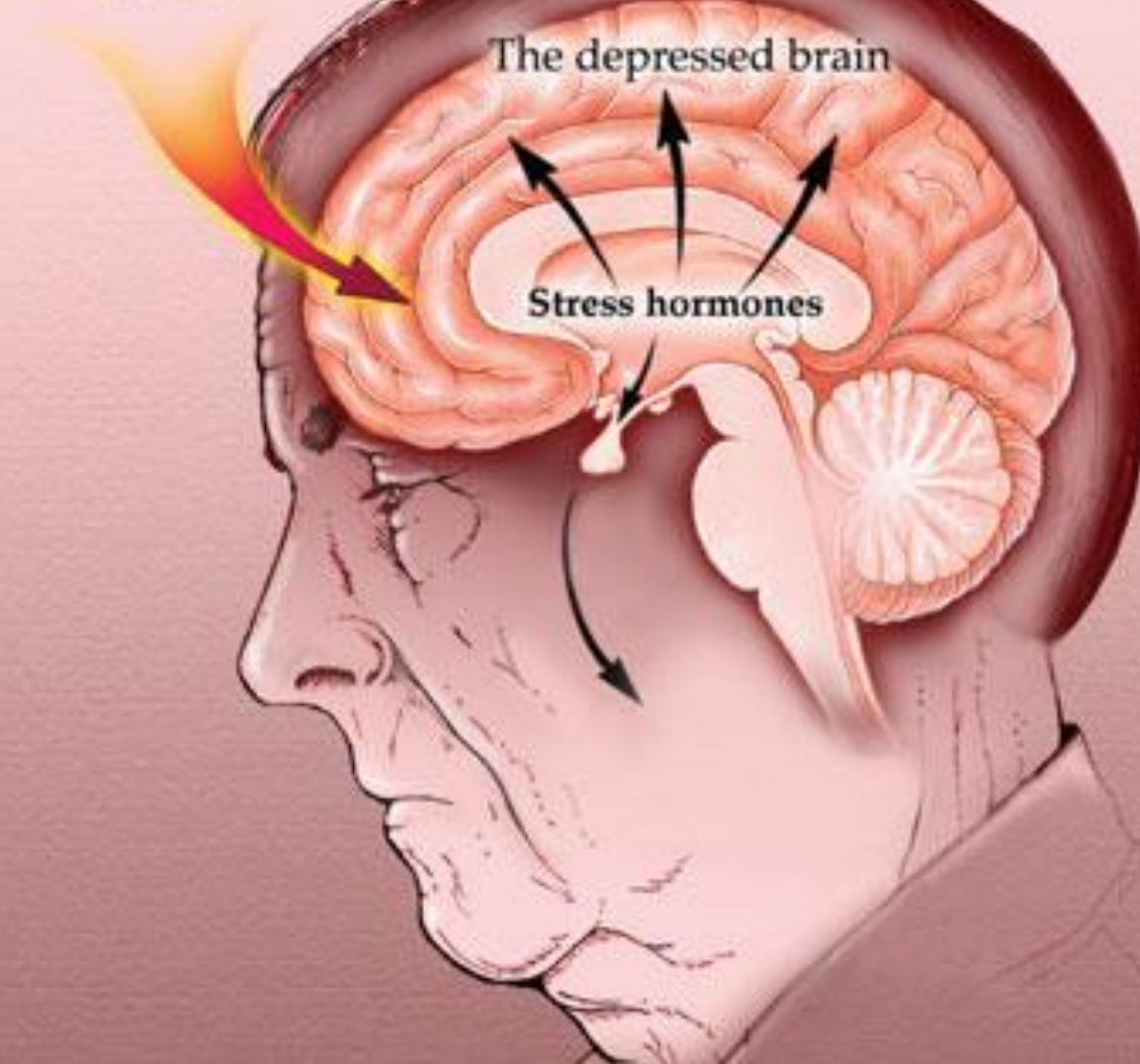


# Brain Circuits and Symptoms in Depression

- More than just a mood circuit for MDD
  - Monoamine pathways hypothetically relate to all symptoms of MDD
- Separate branches of monoamine pathways may independently modulate various malfunctioning brain areas that create a unique portfolio of symptoms
- Modulating separate branches of monoamine pathways with treatment may cause some but not all symptoms to be resolved

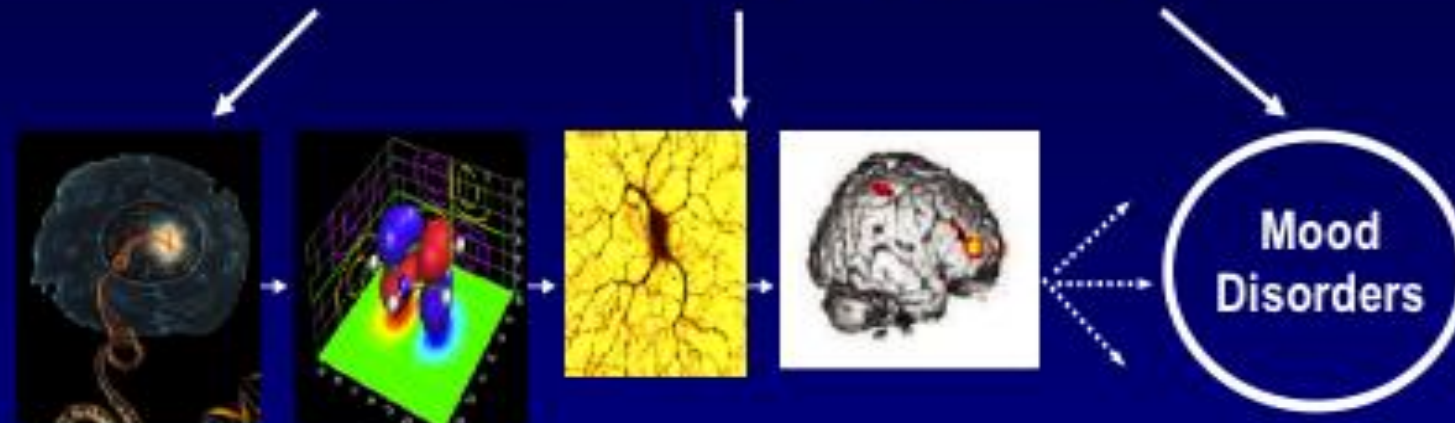


# STRESS



# Depression and Anxiety are Ultimately About How the Brain Responds to the Environment

“Stressors” (psychological, nutritional, hormonal, medication, drug/alcohol “kindling”)



Genes  
Multiple susceptibility alleles each of small effect; Promoters bind RNA polymerase; Suppressors block phenotypic expression  
BDNF, Bcl-2

Epigenetics  
Gene and Protein Expression, e.g., BDNF\* levels reduced during depression, mania

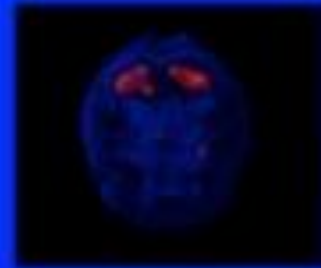
Cells:  
Glial and neuronal abnormalities; mitochondrial dysfunction

Systems:  
Abnormal function and information processing in multiple, interacting circuits

Behavior:  
Complex interactions affecting emotional, psychomotor, cognitive, visceromotor function

\*BDNF promotes the growth and survival of brain cells, promotes learning, memory, higher thinking; Bcl-2 exerts pro-and anti-apoptosis via mitochondria membrane

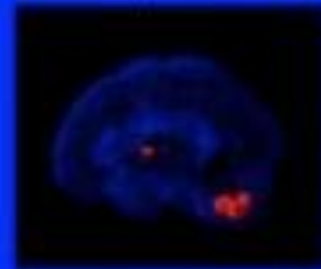
# 3-D Active SPECT Healthy Brain vs Anxiety and Depression



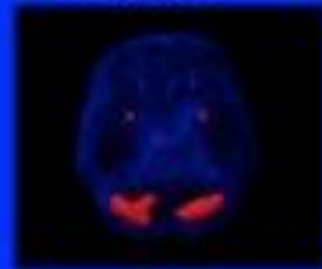
Top-down



Front-on



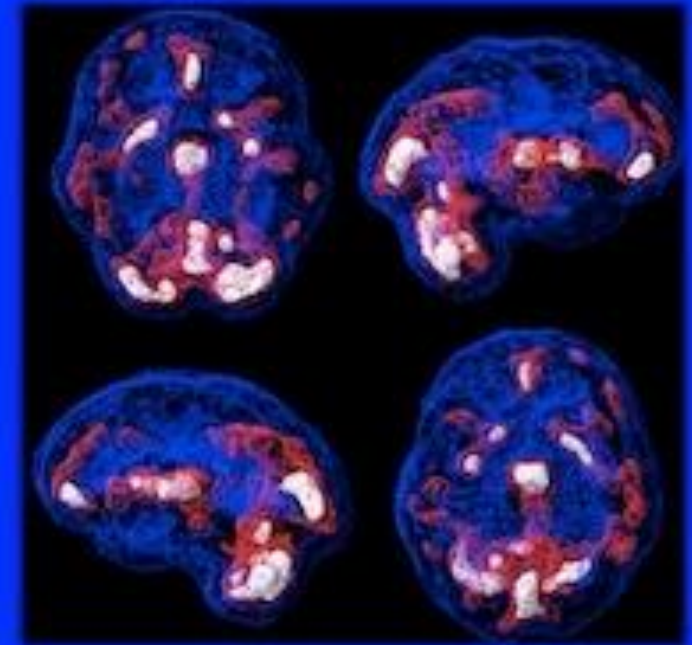
Side View



Underside

3-D Active SPECT of a Healthy Brain

Image: Amen Clinics,  
Reprinted with permission from Amen Clinics.



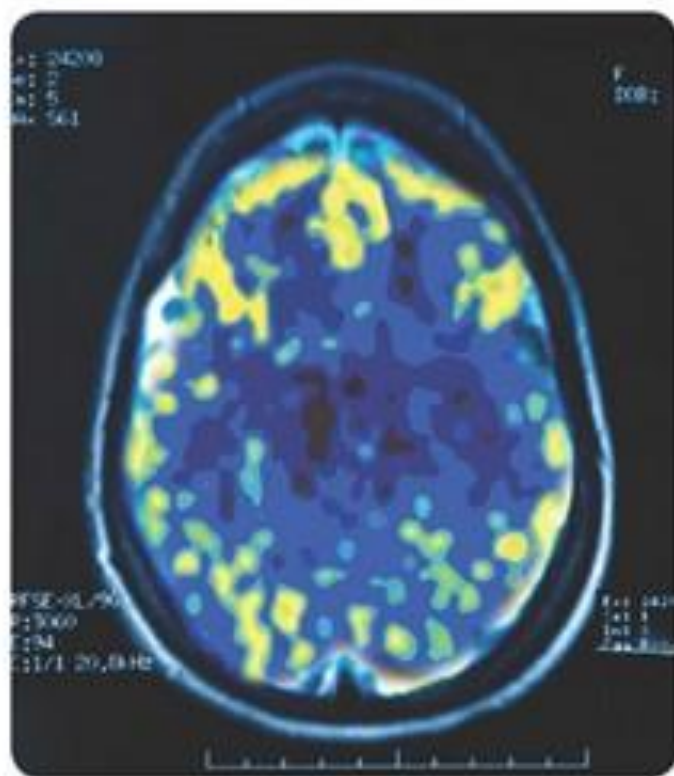
3-D Active SPECT of Brain With Anxiety and Depression – increased anterior cingulate and deep limbic activity.

Image: Amen Clinics,  
Reprinted with permission from Amen Clinics.

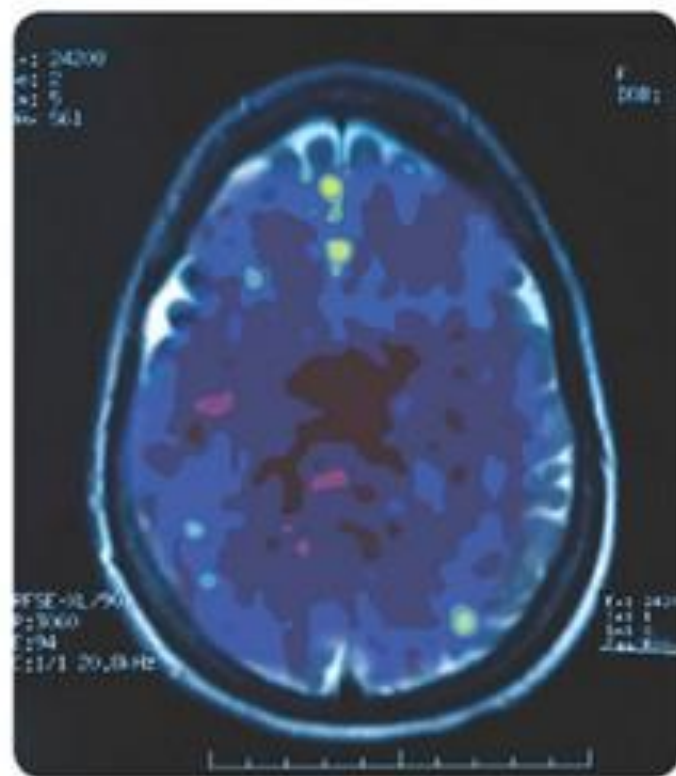


# Depression is a real, biochemical brain dysfunction

**NON-DEPRESSED**



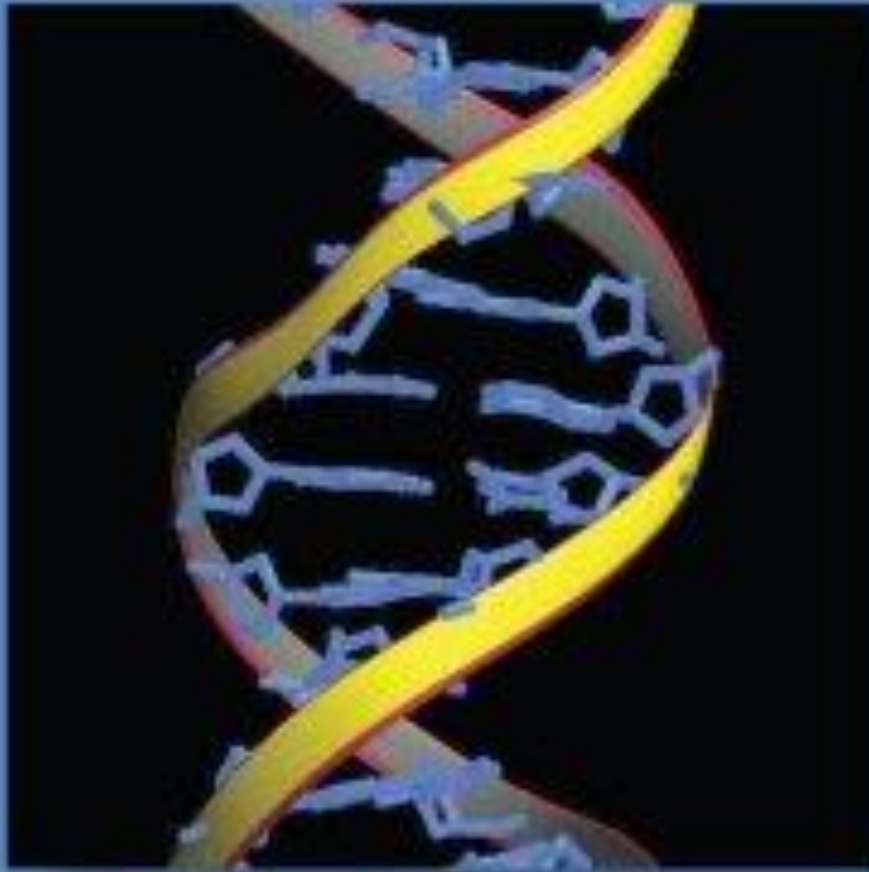
**DEPRESSED**



**A PET Scan measures vital functions such as blood flow, oxygen use, and blood sugar (glucose) metabolism**

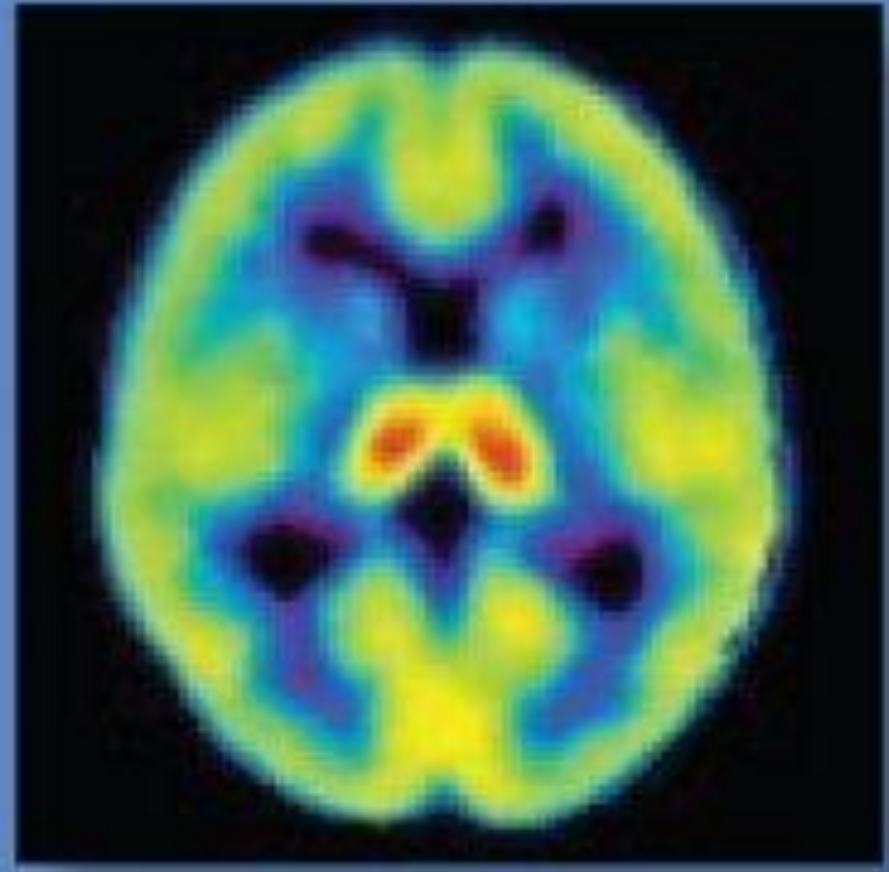


Color PET scan of brain showing depression



## Genes

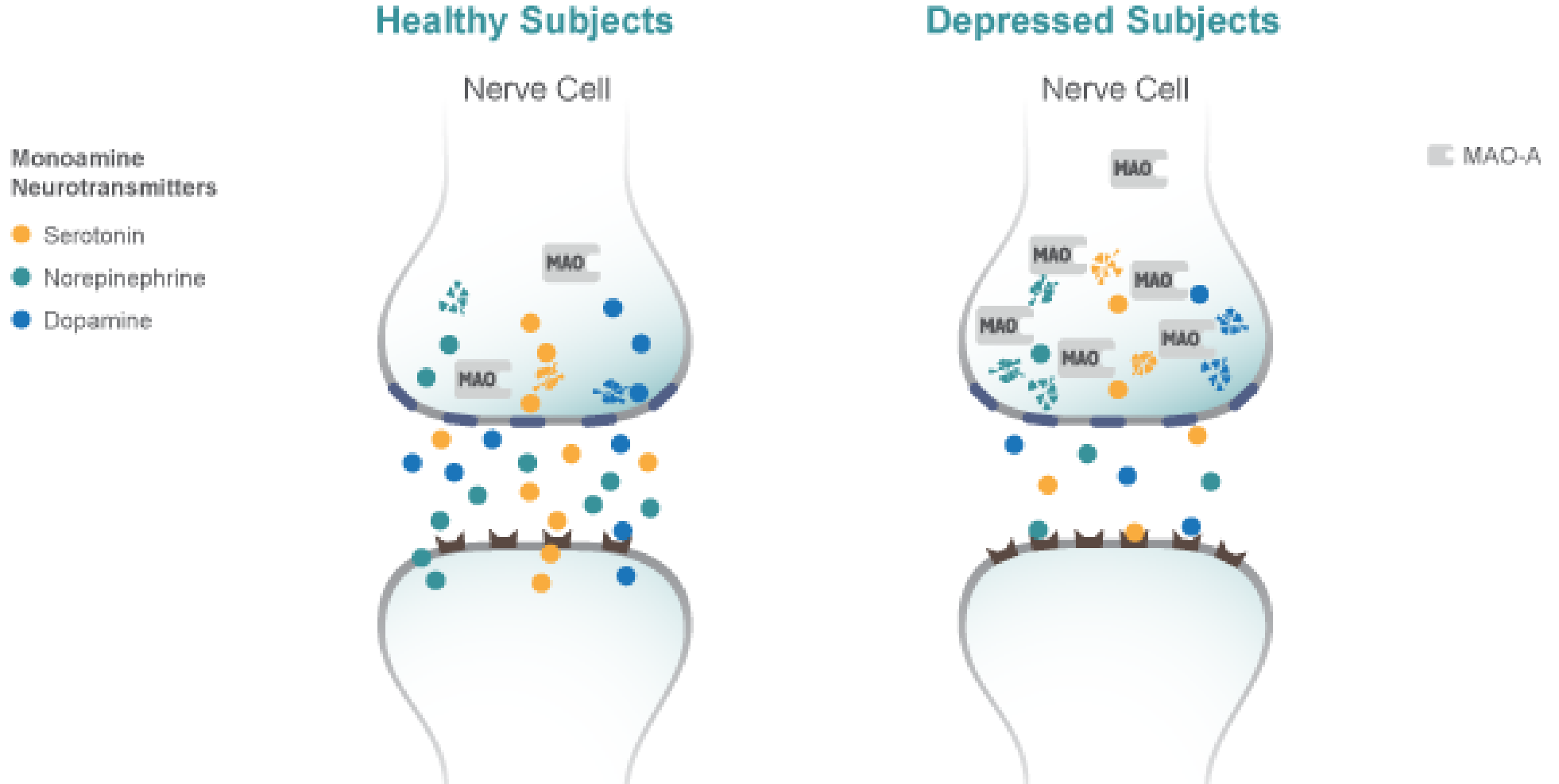
MAO A, low/high



## Brain MAO A

PET, [ $^{11}\text{C}$ ]clorgyline

## Elevated Levels of MAO in Depression<sup>2</sup>



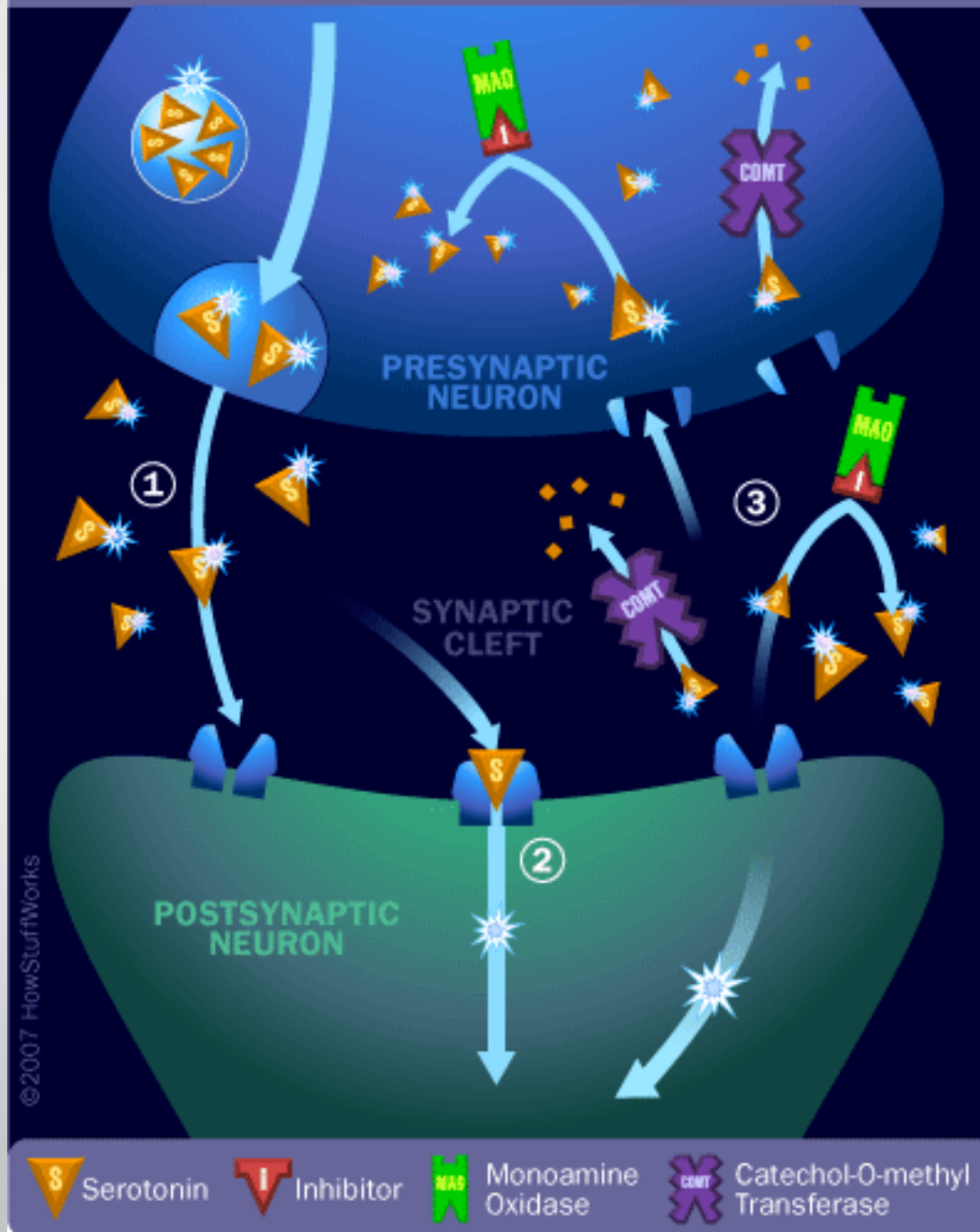
Elevated levels of MAO-A may be the primary monoamine lowering process in MDD.<sup>2</sup>

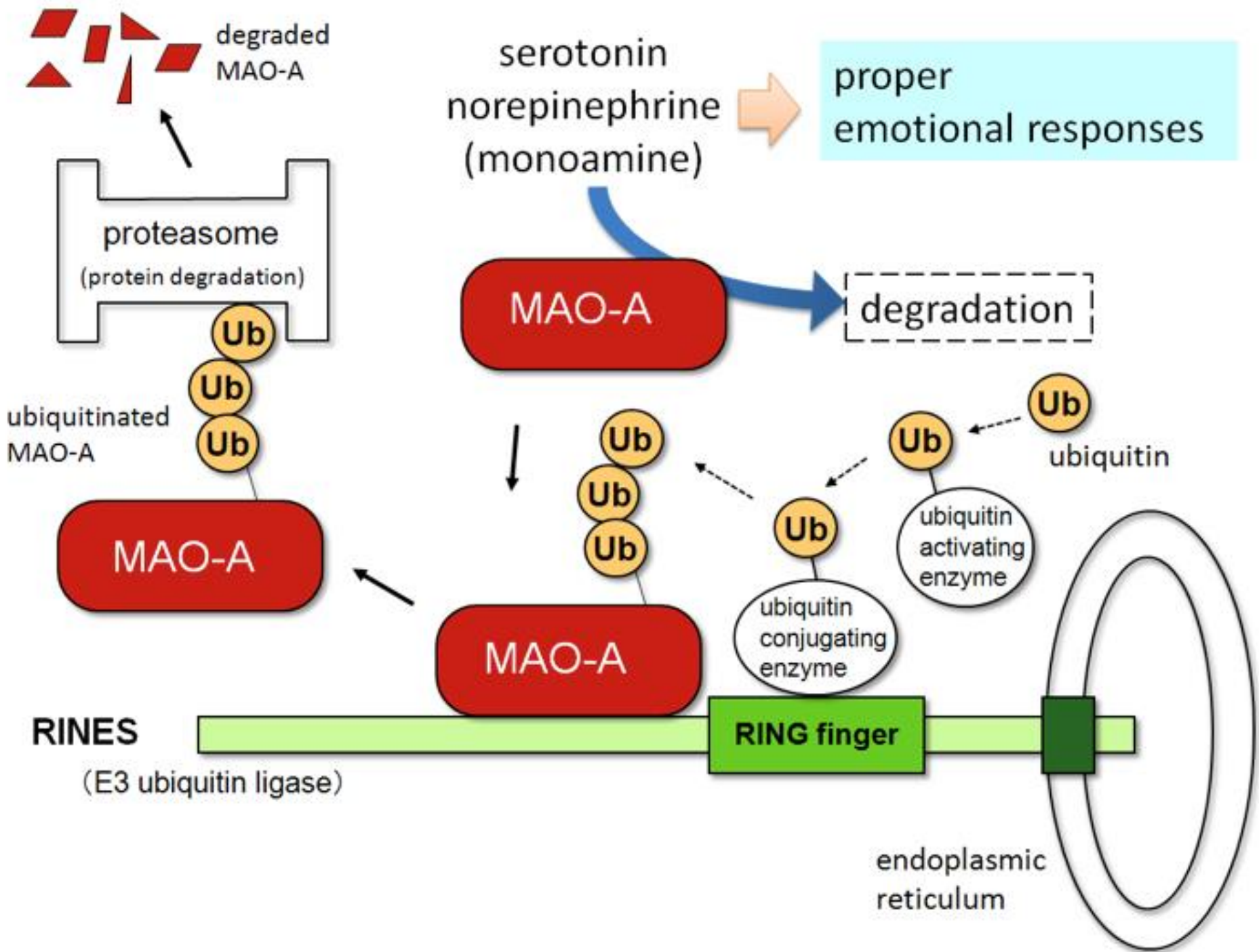
MAO=monoamine oxidase.

MDD=major depressive disorder.

\*MAO exists as 2 forms: MAO-A and MAO-B.

# How Antidepressants Work MAO Inhibitors

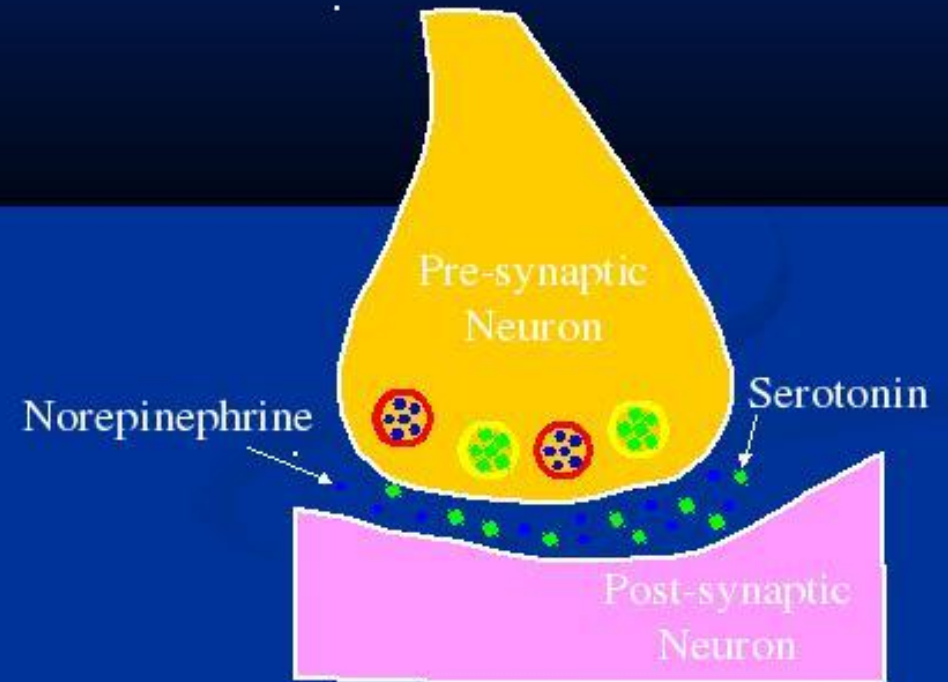




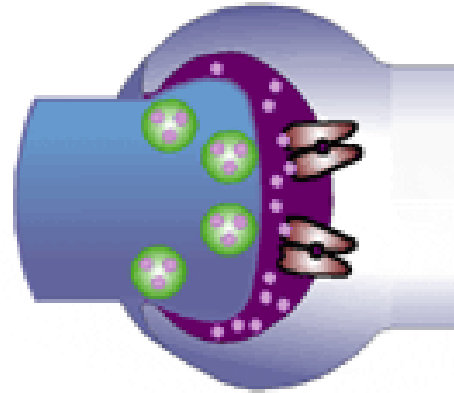
# Neurotransmitters & Depression

A reduction of norepinephrine and serotonin has been found in depression.

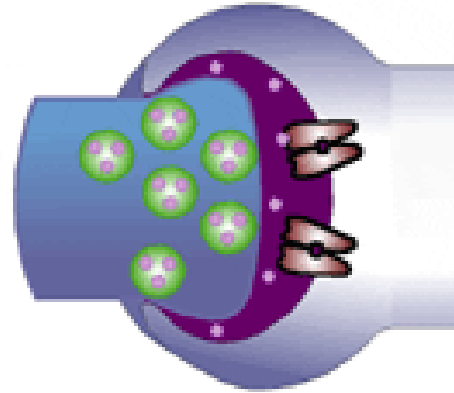
Drugs that alleviate mania reduce norepinephrine.



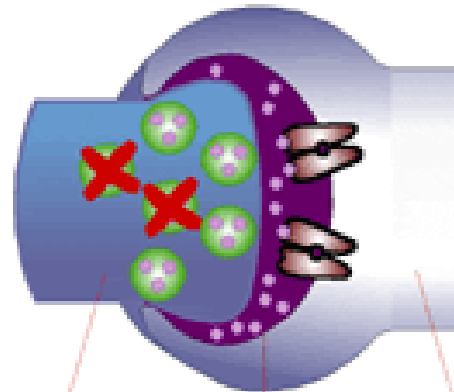
## Prozac: How It Works



**Normal:**  
Serotonin is released into the synapse to aid in the transmission of nerve impulses.



**Depressed:**  
The pre-synaptic nerve reabsorbs the serotonin from the synapse too quickly. The low concentration of serotonin in the synapse prevents the traveling of the impulse to the post-synaptic nerve.

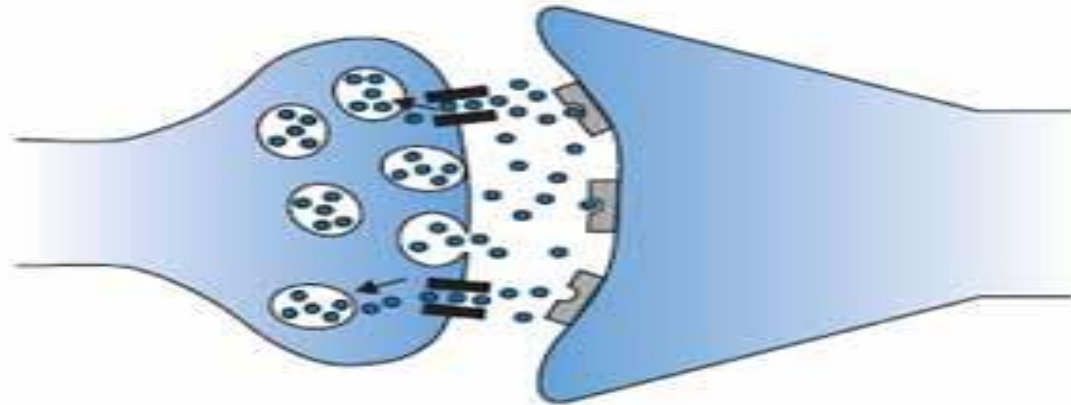


**On Prozac:**  
Prozac blocks serotonin reuptake receptors, keeping the concentration of serotonin in the synapse high enough to carry nerve impulses across the synapse.

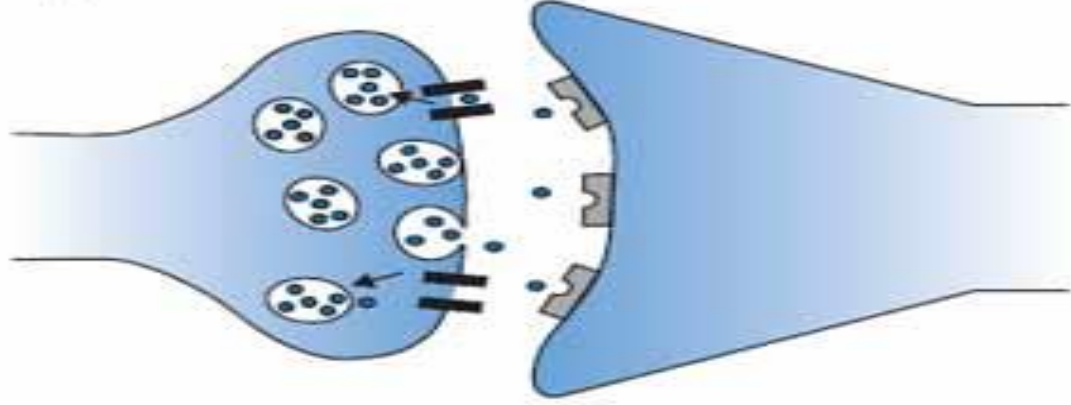
Pre-synaptic nerve      Synapse      Post-synaptic nerve



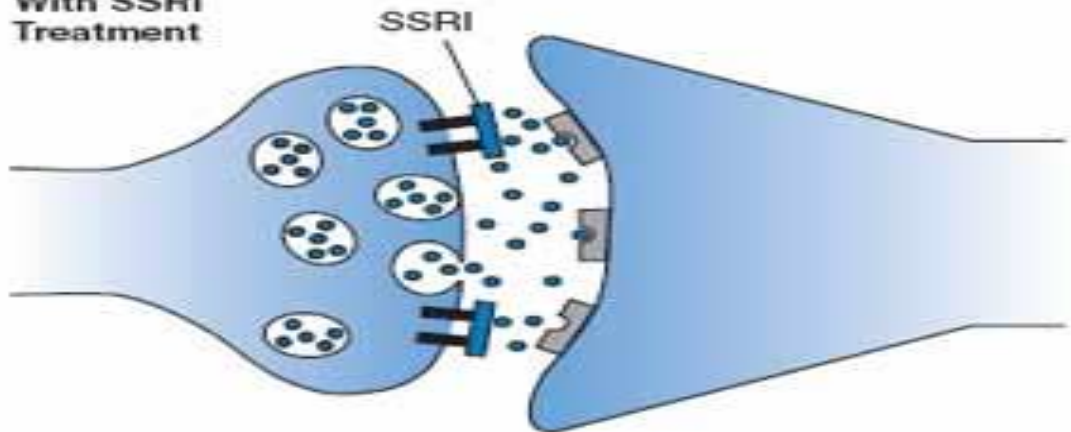
Normal

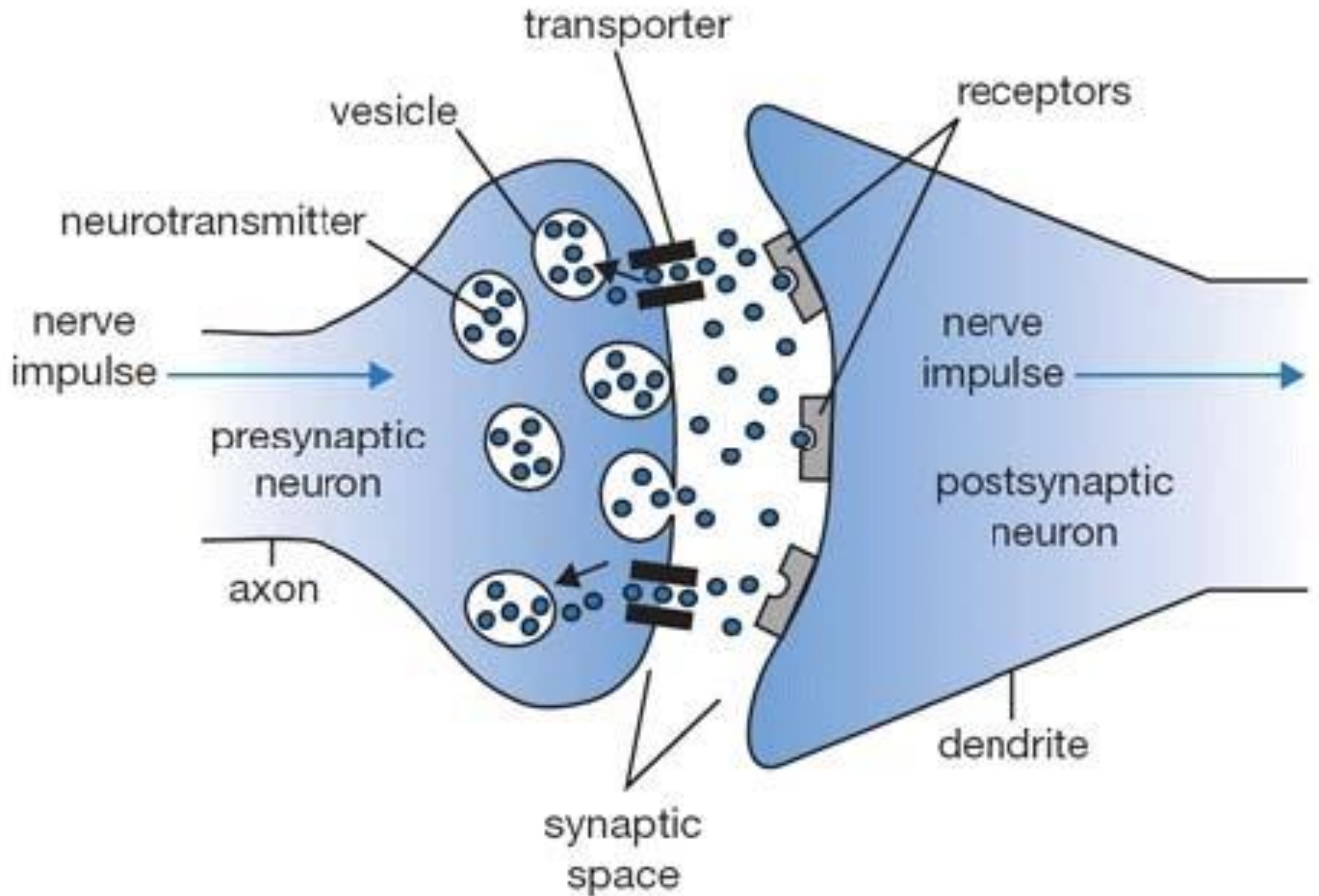


Depression



With SSRI Treatment





**THOUGHTS**



**BEHAVIORS**

**EMOTIONS**

**or**



# DEPRESSION

## Selenium

Integral part of regulatory proteins (selenoproteins) in the brain; Supplementation trials are promising; May alleviate postpartum depression.<sup>18,19</sup>

## Magnesium

Deficiency damages NMDA (N-methyl-D-aspartate) receptors in the brain, which regulate mood; Well-documented anti-depressant effects.<sup>1,2,4,4</sup>

## Chromium

Elevates serotonin (feel-good neurotransmitter) levels in the brain; May be particularly effective on eating symptoms of depression such as carbohydrate craving and increased appetite, due to its effect on blood sugar regulation.<sup>11,18,20</sup>

## Vitamin B12

Depression may be a manifestation of B12 deficiency; Repletion of B12 to adequate levels can improve treatment response; B12 deficiency common in psychiatric disorders.<sup>11,12,19</sup>

## Zinc

Improves efficacy of antidepressant drugs; Particularly useful for treatment resistant patients; Regulates neurotransmitters.<sup>18,19,20,21</sup>

## Serine

Regulates brain chemistry; Involved in NMDA receptor function; Acts as a neurotransmitter; Low levels correlate with severity of depression.<sup>17,22</sup>

## Vitamin B6

Cofactor for serotonin and dopamine production (feel good chemicals); Studies indicate that low levels may predispose people to depression.<sup>14,15,19</sup>

## Antioxidants

Oxidative stress in the brain alters neurotransmitter function; Antioxidants protect our brain, which is very sensitive to oxidation; Several antioxidants – Vitamins A, C and E, Lipoic Acid, CoQ10, Glutathione and Cysteine – play a key role in prevention and treatment of depression.<sup>23,24,25</sup>

## Vitamin B2

Low B2 has been implicated in depression due to its role in methylation reactions in the brain.<sup>17,18</sup>

## Vitamin D

Clinical trials suggest increasing blood levels of vitamin D, which is actually a hormone precursor, may improve symptoms of depression.<sup>13,26,27</sup>

## Biotin

Part of the B-vitamin complex, biotin deficiency has induced depression in animal and human studies.<sup>28,29</sup>

## Inositol

Influences signaling pathways in the brain; Particularly effective in SSRI (selective serotonin reuptake inhibitor) sensitive disorders.<sup>30,31</sup>

## Carnitine

Increases serotonin and norepinephrine which lift mood; In trials, carnitine alleviates depression with few, if any, side effects.<sup>32,33</sup>



# How talk therapy and antidepressant medications add up

