



# Pathophysiology of Depression and the Role of Neuroplasticity

Disease State Education

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# Suicide Prevention Hotline/Lifeline

**1-800-273-TALK(8255)**

Or text:

# Crisis Text Line

**741-741**

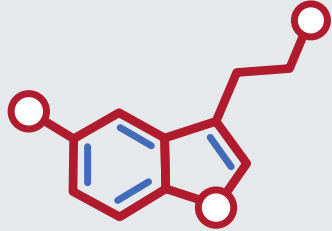
**Dial 988**

# Objectives

**Discuss the theories of Major Depressive Disorder (MDD)**

**Explore the roles of neurocircuitry and neuroplasticity in the pathophysiology of depression**

# The Pathophysiology of Depression Is Multifactorial



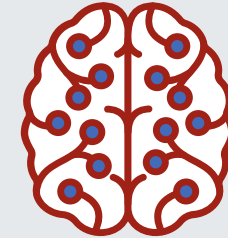
## Monoamine hypothesis<sup>1</sup>

Depression is caused by a deficiency of certain chemicals in the brain



## Cognitive theory<sup>2</sup>

A cognitive bias toward negativity leads to the symptoms of depression



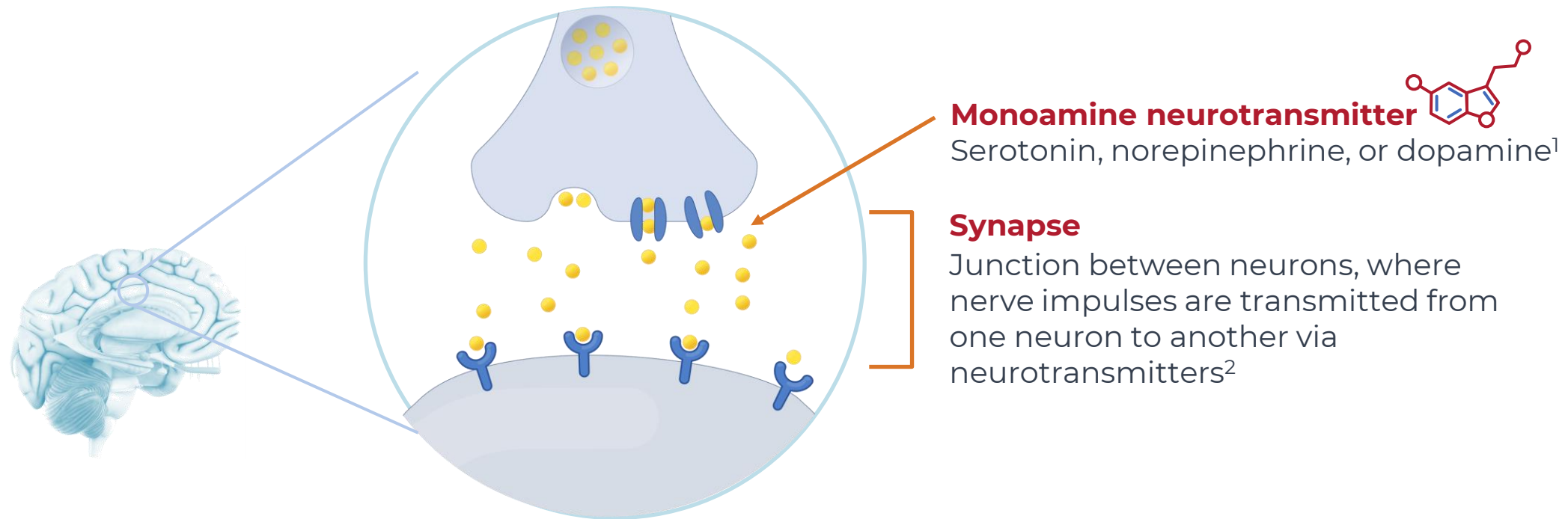
## Neuroplasticity model<sup>3</sup>

Symptoms of depression stem from changes in the brain's structure, function, or connections

**Our understanding of depression has evolved over the years**

1. APA Dictionary of Psychology. Accessed September 8, 2022. <https://dictionary.apa.org/monoamine-hypothesis>.
2. Beck AT. Am J Psychiatry. 2008;165(8):969-977.
3. Price RB, Duman R. Mol Psychiatry. 2020;25(3):530-543.

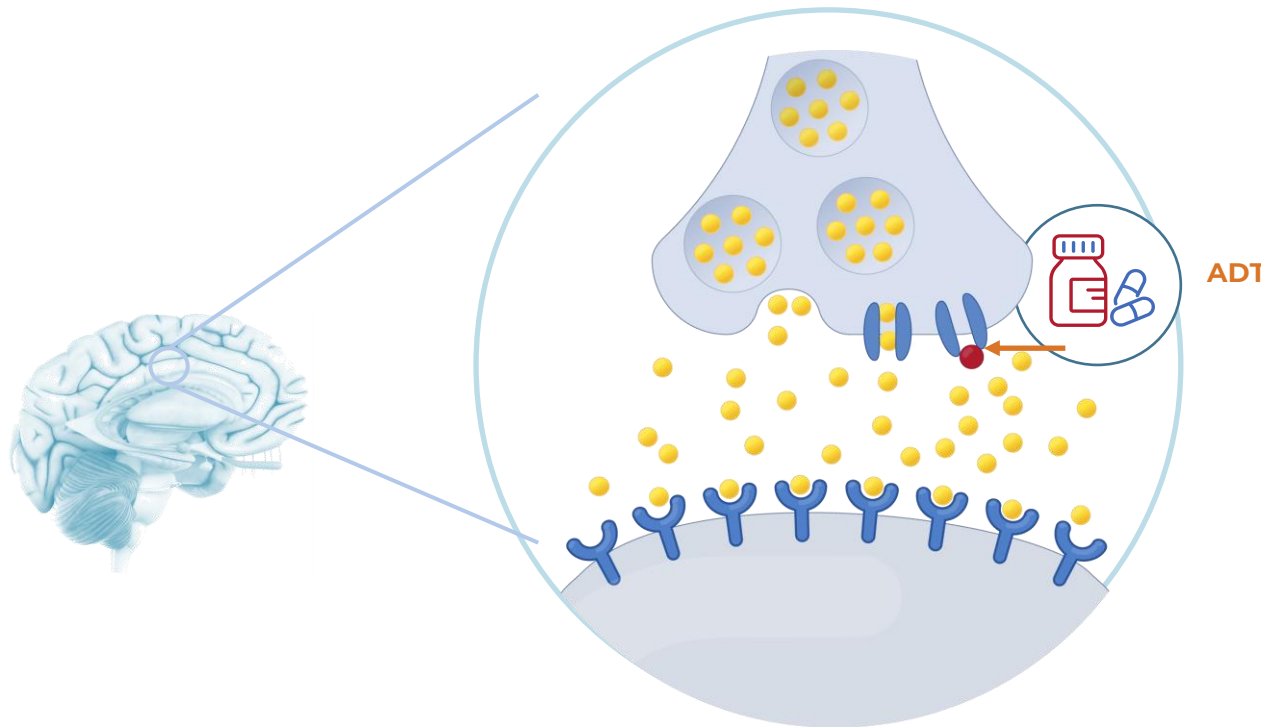
# 1950s: The Monoamine Hypothesis Was Proposed



According to the monoamine hypothesis, depression is caused by **deficiencies in serotonin, norepinephrine, and dopamine**<sup>1</sup>

1. APA Dictionary of Psychology. Accessed September 8, 2022. <https://dictionary.apa.org/monoamine-hypothesis>.
2. Taber's Medical Dictionary. Accessed December 12, 2022. <https://www.tabers.com/tabersonline/view/Tabers-Dictionary/740939/all/synapse>.

# The Monoamine Hypothesis Drove the Development of ADT



ADT was thought to treat depression by blocking reuptake of monoamine neurotransmitters, thus increasing their availability in the synapse,<sup>1</sup> and/or modulating serotonin receptors<sup>2</sup>

**BUT**

Even though ADT reaches the synapse within hours, there may be a delay of several weeks before symptoms improve<sup>3</sup>

**AND**

Many individuals do not respond to ADT<sup>4</sup>

These observations suggest that there may be **other pathways underlying depression**

ADT, antidepressant therapy.

1. APA Dictionary of Psychology. Accessed September 8, 2022. <https://dictionary.apa.org/catecholamine-hypothesis>.
2. Ruberto VL, et al. *Pharmaceuticals (Basel)*. 2020;13(6):116.
3. Uher R, et al. *J Clin Psychiatry*. 2011;72(11):1478-1484.
4. Cipriani A, et al. *Lancet*. 2018;391(10128):1357-1366.

# 1970s: Aaron Beck Proposed a Cognitive Theory of Depression<sup>1,2</sup>



## Theory

Dysfunctional attitudes and beliefs create a **cognitive bias that magnifies the effects of negative events compared with positive events**, leading to the symptoms of depression

- The vulnerability-stress model provides an example of how this theory works



**Traumatic experiences lead to dysfunctional attitudes** (eg, “I need other people’s approval to be happy”), making an individual vulnerable to depression

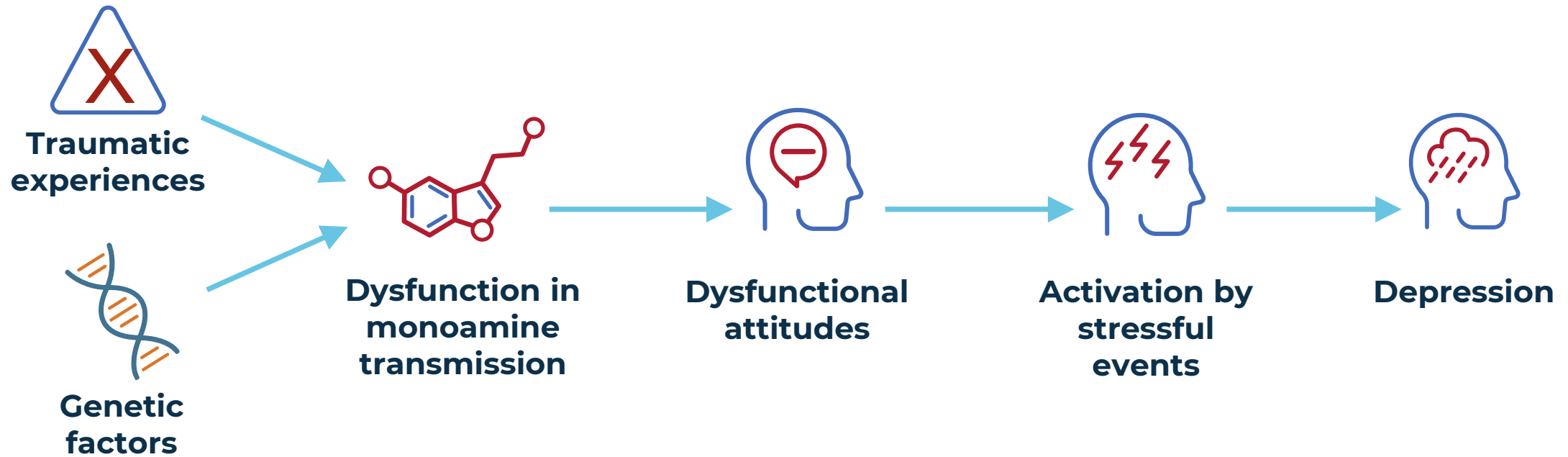
**Repeated activation by stressful events** (eg, job loss, rejection) solidifies these dysfunctional attitudes into a **consistent negative bias** that triggers the development of depression

1. Beck AT. Am J Psychiatry. 2008;165(8):969-977.

2. Kwak YT, et al. Dement Neurocogn Disord. 2016;15(4):103-109.



# The Current Cognitive Theory of Depression Integrates Monoamines<sup>1,2</sup>



In the current cognitive model, individuals are vulnerable to depression due to a **dysfunction in monoamine transmission that stems from traumatic experiences and/or a genetic predisposition**

1. Beck AT. Am J Psychiatry. 2008;165(8):969-977.
2. Kwak YT, et al. Dement Neurocogn Disord. 2016;15(4):103-109

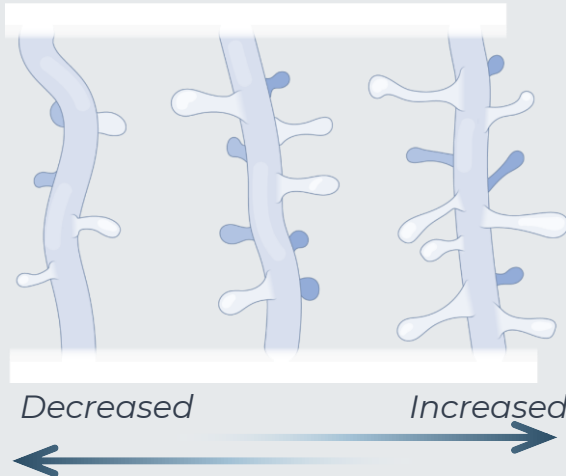
# An Integrative Understanding of Depression Involves a Look at the Brain



## Neuroplasticity Definition<sup>1</sup>

Ability of the nervous system to reorganize its structure, functions, or connections in response to internal or external stimuli

## Synaptic Density<sup>2</sup>

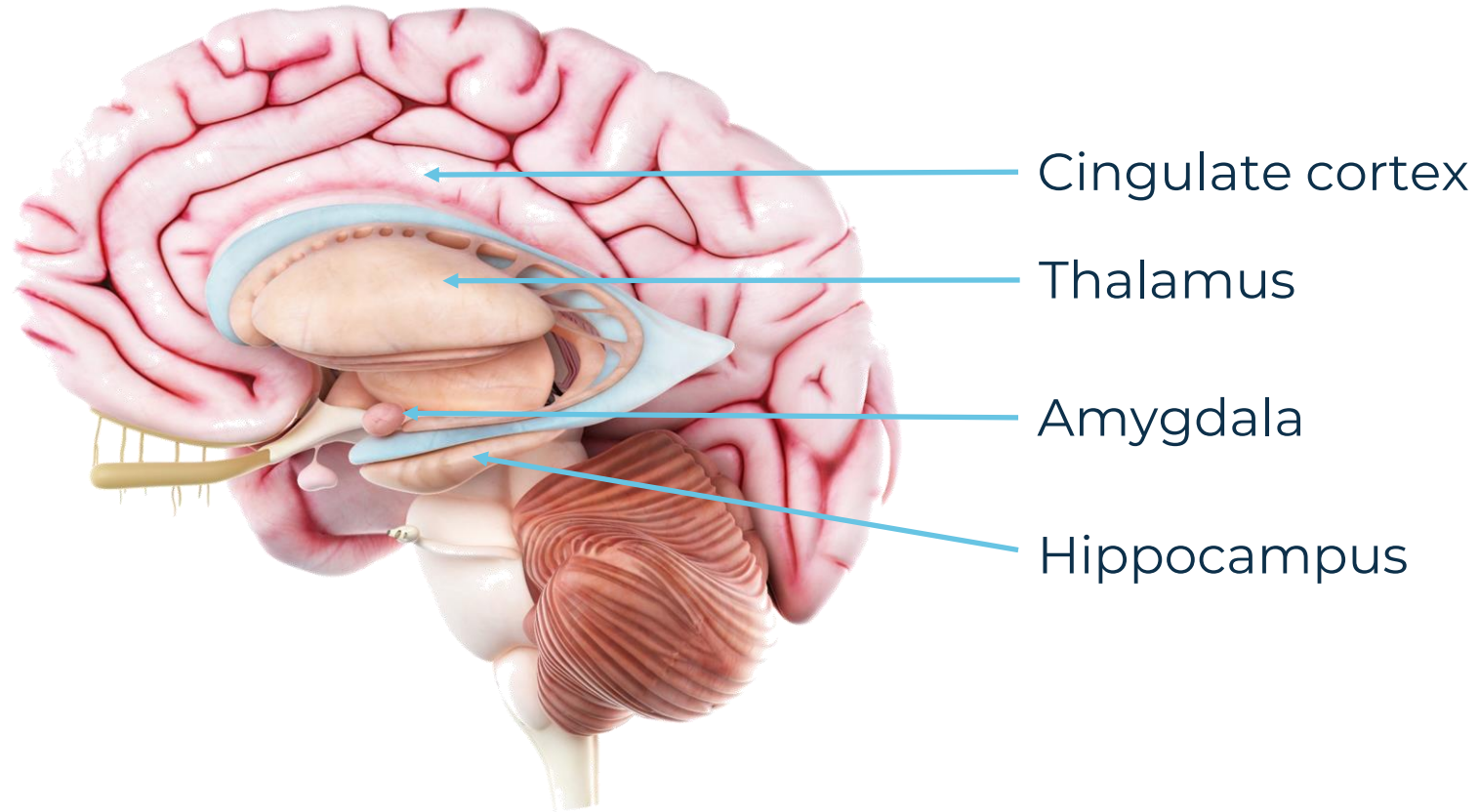


The brain has remarkable plasticity that enables **rapid creation and elimination of synapses**, as well as **alteration of neurocircuits** (arrangements of neurons and their interconnections) in learning and adaptation<sup>3,4</sup>

- Individual synaptic connections are constantly being remodeled as a result of **experience, emotion processing, learning, memory, and stress**<sup>5</sup>

1. Mateos-Aparicio P, Rodriguez-Moreno A. Front Cell Neurosci. 2019;13:66.  
2. Holtmaat A, Svoboda K. Nat Rev Neurosci. 2009;10(9):647-658.  
3. Dean J, Keshavan M. Asian J Psychiatr. 2017;27:101-111.  
4. APA Dictionary of Psychology. Accessed February 20, 2023. <https://dictionary.apa.org/neural-circuit>.  
5. Sanacora G, et al. Neuropharmacology. 2012;62(1):63-77.

# Changes in Brain *Structure* Have Been Identified in Individuals With Depression



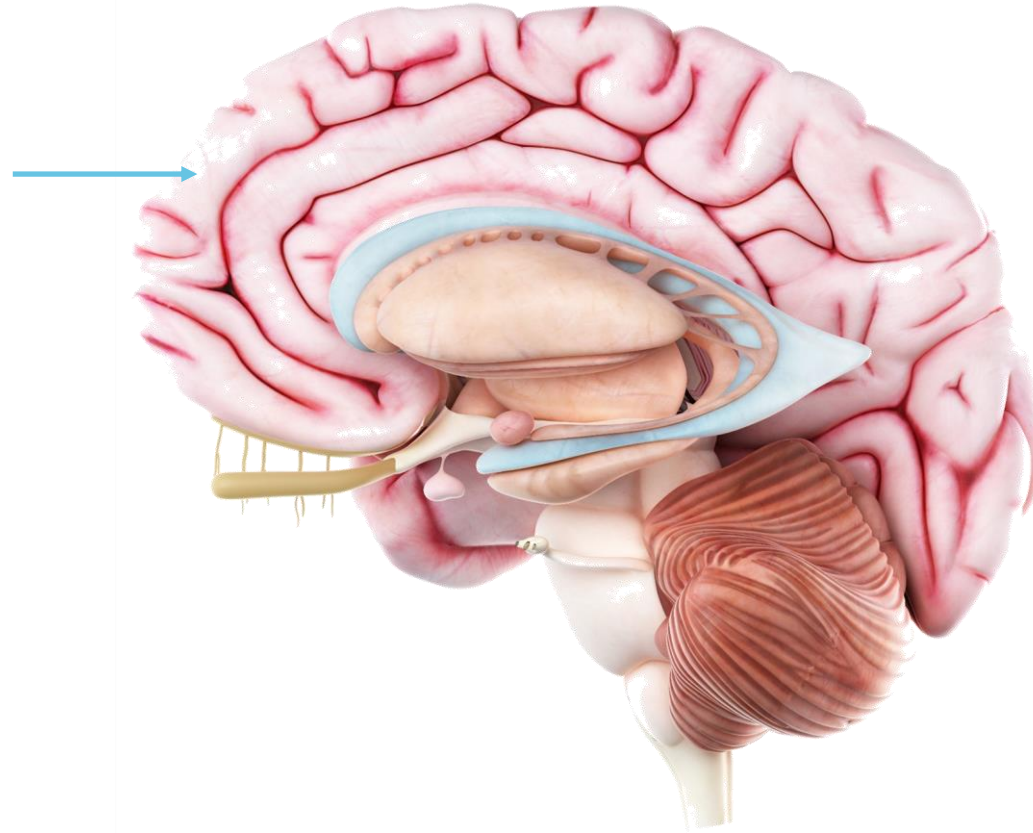
**Volume reduction** has been observed in areas of the **limbic system**, which governs **emotion and memory**

MDD, major depressive disorder.

1. Dai L, et al. *PeerJ*. 2019;7:e8170.

# Changes in Brain *Structure* Have Been Identified in Individuals With Depression (cont'd)

Prefrontal cortex



**Atrophy** of the **prefrontal cortex**, which governs **cognition**, is evident in depression

MDD, major depressive disorder.

1. Dai L, et al. *PeerJ*. 2019;7:e8170.

# Changes in Brain Function Have Also Been Identified in Individuals With Depression

Neuroimaging studies in MDD suggest an interplay between brain regions with

**INCREASED**

and

**REDUCED ACTIVITY**

resulting in **cognitive and emotional changes**

**INCREASED ACTIVITY**



Amygdala

Insula

Thalamus

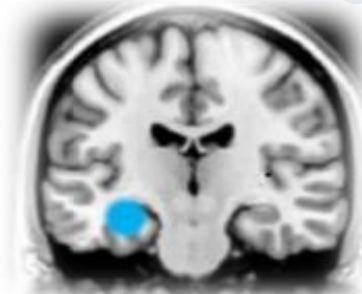
Medial thalamus

vACC

DLPFC

OFC

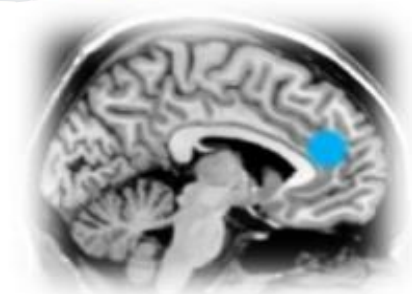
**REDUCED ACTIVITY**



Hippocampus



DLPFC



Dorsal part of the vmPFC

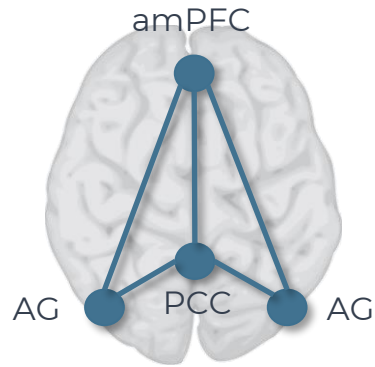
DLPFC, dorsolateral prefrontal cortex; MDD, major depressive disorder; OFC, orbitofrontal cortex; vACC, ventral anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.

1. Arnone D. Prog Neuropsychopharmacol Biol Psychiatry. 2019;91:28-37.

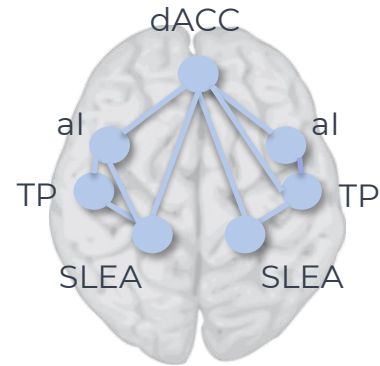


# Neurocircuit Dysfunction May Be Responsible for Distinct Features of Depression

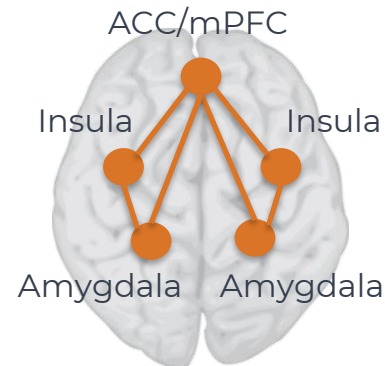
## DEFAULT MODE



## SALIENCE



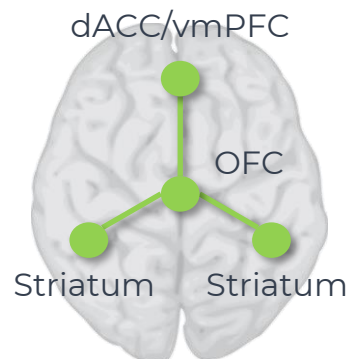
## NEGATIVE AFFECT



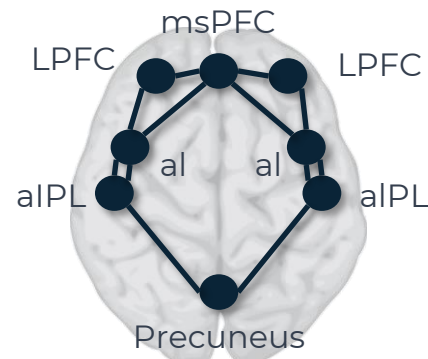
**Specific neurocircuits** may be implicated in **distinct features of depression and anxiety**<sup>1</sup>

Circuit dysfunctions underlying these features may include **hypo- or hyperconnectivity, hypo- or hyperactivity, and structural abnormalities**<sup>1</sup>

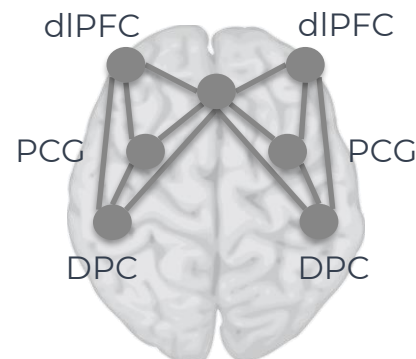
## POSITIVE AFFECT



## ATTENTION



## COGNITIVE CONTROL



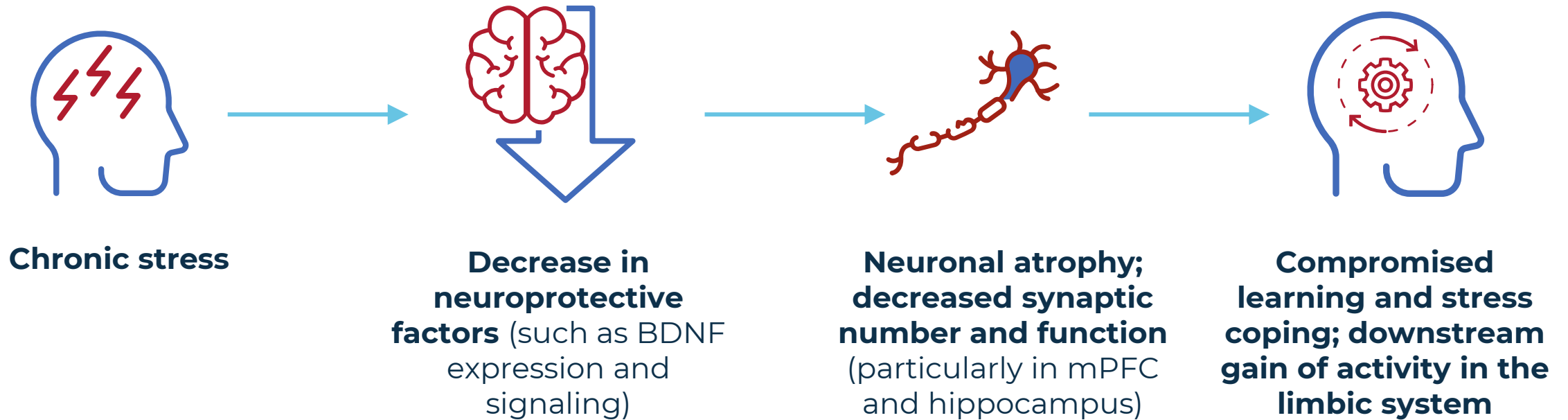
Changes in the **default mode circuit** and **connectivity between cortical and limbic structures** have been noted following treatment for depression<sup>2</sup>

**Learn more about these neurocircuits in the slide notes field**

ACC, anterior cingulate cortex; ACC/mPFC, dorsal medial prefrontal cortex (includes dorsal ACC and vmPFC, including ventral—subgenual and pregenual—and rostral ACC); AG, angular gyrus; al, anterior insula; aIPL, anterior inferior parietal lobule; amPFC, anterior medial prefrontal cortex; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex (includes anterior prefrontal cortex and inferior frontal cortex); DPC, dorsal parietal cortex; LPFC, lateral prefrontal cortex; mPFC, medial prefrontal cortex; msPFC, medial superior prefrontal cortex; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex (includes precuneus); PCG, precentral gyrus; SLEA, sublenticular extended amygdala; TP, temporal pole; vmPFC, ventromedial prefrontal cortex.

1. Williams LM. *Lancet Psychiatry*. 2016;3(5):472-480.
2. Gudayol-Ferré E, et al. *Front Hum Neurosci*. 2015;9:582.

# Neurocircuit Dysfunction Associated With Depression May Be Due to Maladaptive Neuroplasticity



BDNF, brain-derived neurotrophic factor; mPFC, medial prefrontal cortex.

1. Price RB, Duman R. *Mol Psychiatry*. 2020;25(3):530-543.

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[www.PsychU.org](http://www.PsychU.org)



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