7.2: Causes of Depression

There are several possible causes of depression, including faulty mood regulation by the brain, genetic vulnerability, stressful life events, medications, and medical problems. Based on current research, it is believed that several of these forces interact to bring on depression.¹

The Brain

Certain areas of the brain help regulate mood, including the hippocampus, amygdala, and hypothalamus. See Figure 7.1² for an image of these areas of the brain. Researchers believe that nerve cell connections, nerve cell growth, the functioning of nerve circuits, and levels of specific brain chemicals (called neurotransmitters) have a major impact on depression.³

Figure 7.1 Areas of the Brain Regulating Mood

The hippocampus is part of the limbic system in the brain that has a central role in processing long-term memory and
recollection. For example, this part of the brain registers fear when you are confronted by a frightening situation, like an aggressive dog, and the memory of such an experience may make you wary of dogs you come across later in life. The hippocampus is smaller in some depressed people, and research suggests that ongoing exposure to the stress hormone impairs the growth of nerve cells in this part of the brain.\footnote{4}

The amygdala is also part of the limbic system and is a group of structures deep in the brain that are associated with emotions such as anger, pleasure, sorrow, fear, and sexual arousal. The amygdala is activated when a person experiences or recalls emotionally charged memories, such as a frightening situation, and sends signals to the hypothalamus to stimulate the sympathetic fight-or-flight response. Activity in the amygdala is higher when a person is sad or clinically depressed. This increased activity continues even after recovery from depression.\footnote{5}

The hypothalamus is involved in the stress response. The stress response starts with a signal from the hypothalamus. The hypothalamus, pituitary gland, and adrenal glands form the hypothalamic-pituitary-adrenal (HPA) axis, which governs a multitude of hormonal activities in the body and also plays a role in depression. When a physical or emotional threat looms, the hypothalamus secretes corticotropin-releasing hormone (CRH) that rouses the body. CRH follows a pathway to the pituitary gland, where it stimulates the secretion of adrenocorticotropic hormone (ACTH) into the bloodstream. When ACTH reaches the adrenal glands, it prompts the release of cortisol. The boost in cortisol readies the body to fight or flee by causing the heart to beat faster, the blood pressure to rise, and the respiratory rate to increase. CRH also affects the cerebral cortex, part of the amygdala, and the brain stem. It is thought to play a major role in coordinating one’s thoughts and behaviors, emotional reactions, and involuntary responses. Working along a variety of neural pathways, it influences the concentration of neurotransmitters throughout the brain. Disturbances in hormonal systems affect neurotransmitters and vice versa.\footnote{6}

**Neurotransmitters**

There are many types of neurotransmitters that play a role in depression\footnote{7}:

- **Acetylcholine** enhances memory and is involved in learning and recall.\footnote{8}
- **Serotonin** helps regulate sleep, appetite, and mood and inhibits pain. Research supports the idea that some depressed people have reduced serotonin transmission. Low levels of a serotonin by-product have been linked to a higher risk for suicide.\footnote{9}
- **Norepinephrine** constricts blood vessels, raising blood pressure. It may trigger anxiety and be involved in some types of depression. It also seems to help determine motivation and reward.\footnote{10}
- **Dopamine** is essential to movement. It also influences motivation and plays a role in how a person perceives reality. Problems in dopamine transmission have been associated with psychosis, a severe form of distorted thinking characterized by hallucinations or delusions. It’s also involved in the brain’s reward system, so it is thought to play a role in substance abuse.\footnote{11}
- **Glutamate** is a small molecule believed to act as an excitatory neurotransmitter and to play a role in bipolar disorder and schizophrenia. Animal research suggests that lithium stabilizes glutamate reuptake and smooths out the highs of mania and the lows of depression in the long-term.\footnote{12}
- **Gamma-aminobutyric acid (GABA)** is an amino acid that researchers believe acts as an inhibitory
neurotransmitter. It is thought to help subdue anxiety.[13]

See Figure 7.2[14] for an illustration of neurotransmitter communication between neurons at the synapse. Antidepressants immediately boost the concentration of chemical messengers in the brain (neurotransmitters), but people typically don’t begin to feel better for several weeks or longer. Experts have long wondered why people don’t improve as soon as the level of neurotransmitters increases. New theories explain that antidepressants spur the growth and enhanced branching of nerve cells in the hippocampus (a process called neurogenesis), and mood improves over several weeks as nerves grow and form new connections.[15]

Figure 7.2 Neurotransmitters at the Synapse Level

Genes

Every part of our body, including our brain, is controlled by our genes. Humans have almost 22,000 genes in their DNA within 46 chromosomes inside the nucleus of each cell. The sequence of nitrogen-containing bases within a strand of DNA forms the genes that act as a molecular code instructing cells in the assembly of amino acids into proteins. See Figure 7.3[16] for an image of sequences of bases within a DNA strand that forms genes. Genes make proteins that are involved in biological processes. Throughout life, different genes turn on and off and make the right proteins at the right time. However, genes can alter biology in a way that results in a person’s mood becoming unstable. In a person who is genetically vulnerable to depression, any stress (such as a missed deadline at work or a medical illness) can then push this system off balance.[17]
It is well-known that depressive and bipolar disorders run in families. Mood is affected by dozens of genes, and as our genes differ, so does depression. As researchers pinpoint specific genes involved in mood disorders and better understand their functions, it is hoped that treatment for depressive disorders can become more individualized and more successful as patients receive targeted medication for their specific type of depression.\footnote{18}

Genetics provides one perspective on how resilient an individual is in the face of difficult life events. Temperament is determined by a person’s genetic inheritance and the experiences they have had in life. For example, one person may have the temperament of an introvert and tend to withdraw from social situations, whereas another person may have the temperament of an extrovert who seeks out social situations and feels energized by them. Cognitive psychologists believe that one’s view of the world and assumptions about how the world works influence how a person feels. Individuals develop their assumptions about life early and automatically fall back on them when loss, disappointment, or rejection occurs. For example, a person who was continually criticized as a child may have the genetic inheritance and temperament where they become so self-critical they can’t bear the slightest criticism from others, which can slow or block their career progress and make intimate relationships more difficult. Therapy and medications can shift thoughts and attitudes that have developed over time.\footnote{19}

Stressful Life Events

At some point, nearly everyone encounters stressful life events such as the death of a loved one, the loss of a job, the...
diagnosis of a severe illness, or the end of a significant relationship. Many individuals have also experienced traumatic childhood experiences that continue to affect their coping and functioning into adulthood. It is estimated that 61% of adults have experienced early adverse childhood experiences (ACEs) such as abuse, neglect, or growing up in a household with violence, mental illness, substance use, incarceration, or divorce. See Figure 7.4 for an illustration of adverse childhood experiences. Toxic stress from ACEs can change brain development and affect how the body responds to stress. ACEs are linked to chronic health problems, mental illness, and substance misuse in adulthood. 

Figure 7.4 Adverse Childhood Experiences (ACEs)

Stress triggers a chain of chemical reactions and responses in the body. If the stress is short-lived, the body usually returns to normal. But when stress is chronic or the system gets stuck in overdrive, changes in the body and brain can be long-lasting. Every real or perceived threat to one’s body triggers a cascade of stress hormones that produces physiological changes called the stress response. Normally, a feedback loop allows the body to turn off “fight-or-flight” defenses when the threat passes. In some cases, though, the floodgates never close properly, and cortisol levels rise too often or simply stay high. These elevated cortisol levels can contribute to problems such as high blood pressure, immune suppression, asthma, and depression. Studies have also shown that people who have depressive disorders typically have increased levels of CRH. Antidepressants and electroconvulsive therapy are both known to reduce these high CRH levels. As CRH levels return to normal, depressive symptoms recede. Research also suggests that trauma during childhood can negatively affect the functioning of CRH and the HPA axis throughout life.

Read the Adverse Childhood Experiences Prevention Strategy PDF.

Medical Problems

Certain medical problems are linked to up to 10% to 15% of all depressions. For example, hypothyroidism, a condition where the body produces too little thyroid hormone, often leads to exhaustion and depression, whereas hyperthyroidism (excess thyroid hormone) can trigger manic symptoms. Heart disease has also been linked to depression, with up to half of heart attack survivors reporting feeling blue and many having significant depression. Another example of depression linked to a medical condition is postpartum depression that occurs after pregnancy.  

The following medical conditions have also been associated with depression and other mood disorders:

- Degenerative neurological conditions, such as multiple sclerosis, Parkinson’s disease, Alzheimer’s disease, and
Huntington’s disease
• Cerebrovascular accidents (i.e., strokes)
• Some nutritional deficiencies, such as a lack of vitamin B12
• Endocrine disorders with the parathyroid or adrenal glands
• Immune system diseases, such as lupus
• Some viruses, such as mononucleosis, hepatitis, and HIV
• Cancer
• Erectile dysfunction in men

When considering the connection between health problems and depression, an important question to address is which came first, the medical condition or the mood changes. Stress of having certain illnesses can trigger depression, whereas in other cases, depression precedes the medical illness and may even contribute to it. If depression is caused by an underlying medical problem, the mood changes should disappear after the medical condition is treated. For example, after hypothyroidism is treated, lethargy and depression often lift. In many cases, however, the depression is an independent problem, which means that in order to be successful, treatment must address depression directly. [25]

Symptoms of depression can be a side effect of certain drugs, such as steroids or some types of blood pressure medication. A health care provider can help sort out whether a new medication, a change in dosage, or interactions with other drugs or substances might be affecting an individual’s mood. [26]

2. “1511_The_Limbic_Lobe.jpg” by OpenStax College is licensed under CC BY 3.0. Access for free at http://cnx.org/content/col11496/1.6/

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