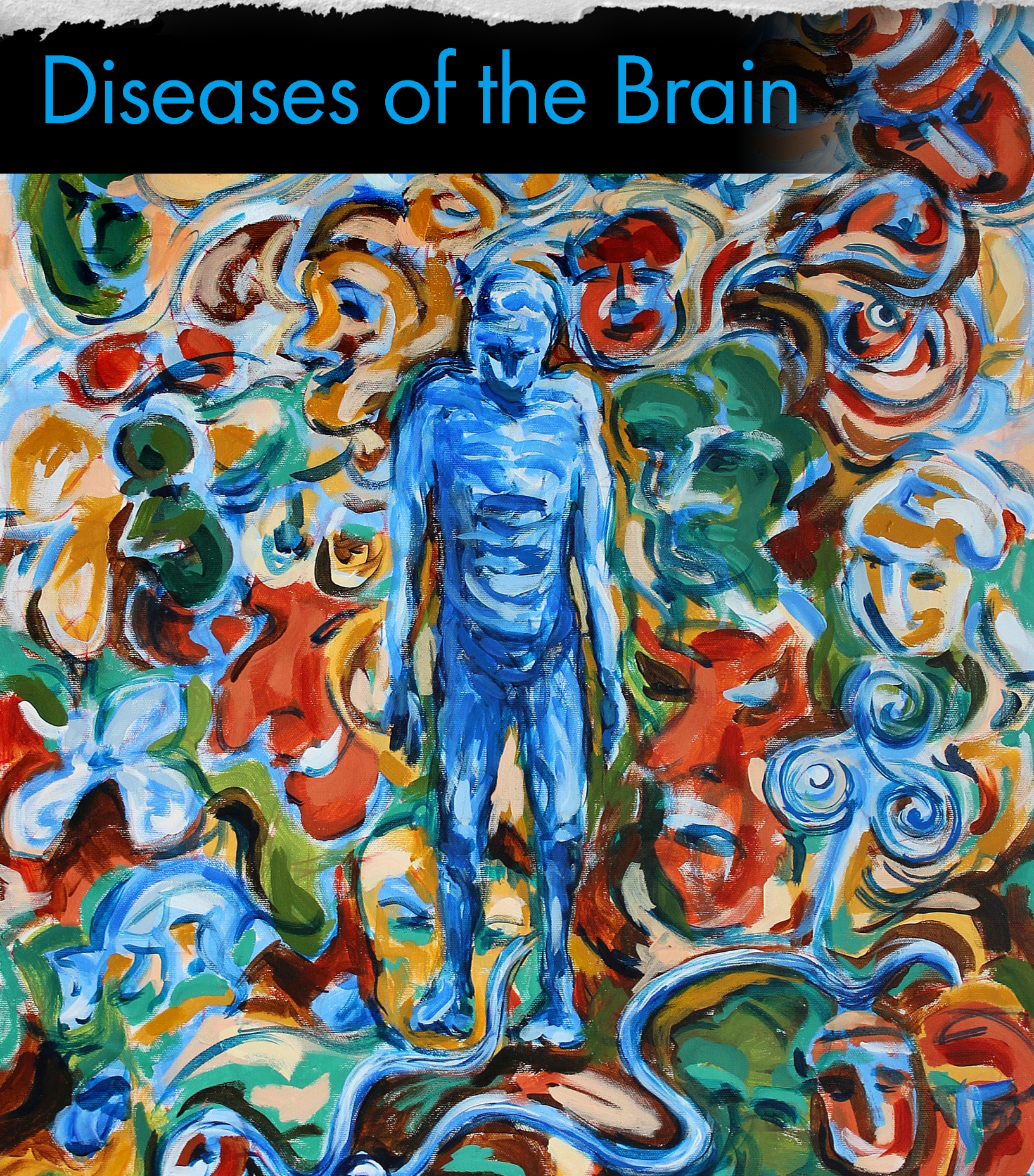
Chapter 16:

Diseases of the Brain



Austin Lim, PhD (DePaul University)
Editor: Monica Javidnia, PhD (Rochester University)

The brain can be thought of as a well-oiled machine made up of hundreds of billions of moving parts, all cooperating in tandem for healthy behavior and function. There is redundancy in the way these parts are organized, allowing for occasional mishaps without any significant loss of function. But when these parts interact in unusual or atypical ways, a person may develop some psychiatric disorder. The conditions described in this section likely involve dysregulations in molecules, cells, or circuits, and are therefore complex.

As far as we know, the likelihood of developing these conditions is not exclusively determined by either genes or influence from the environment. Instead, there is probably some influence from both. That is to say, none of these conditions are 100% **penetrant**; none of them are dictated exclusively by genetics. Having two parents or an identical twin with the condition may indicate an elevated baseline risk over the population at large, but it is not a guarantee that the disease will manifest. Environmental triggers and other exposures may lead to a sudden onset of the condition; on the other hand, certain factors in the environment may be protective against these diseases.

One of the major challenges with understanding these brain diseases is related to the difficulty of making an accurate diagnosis - as almost everything in biology exists on a spectrum, so do these brain disorders. The symptoms of these disorders frequently overlap, adding another layer of complexity. To help establish a diagnosis, the American Psychiatric Association (APA) has put together a series of criteria for psychiatrists to diagnose these complex conditions. The guidelines are compiled in a book called the **Diagnostic and Statistical Manual of Mental Disorders**. They are currently on the fifth revision of the text, referred to as the **DSM-5**. It's an imperfect set of criteria, but it is a start towards understanding these remarkably complicated conditions.

Figure 16.1 Environment and genetics both contribute to these diseases. Studies comparing twins can be helpful in identifying the influence of genetics.

Many of the treatments we currently have for neuropsychiatric disorders aren't always effective. Our ability to treat these conditions depends on our understanding of the disease. The better we understand the causes of these conditions, the wider variety of new therapies we can test. Therapeutic strategies for these conditions are often first tested using cells and non-human animal models, but these have shortcomings. Most of the time, animal models of disease incompletely mimic the symptoms of

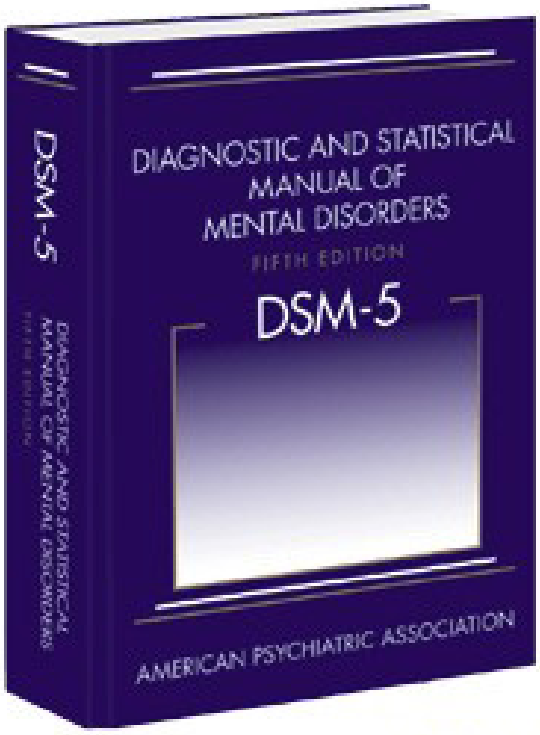


Figure 16.2 The DSM-5 is the manual that is used by psychiatrists to diagnose various psychiatric conditions.

the disease. Animal research concerns itself with three different forms of validity.

1. Face validity. If an animal model of a disease looks similar to the human condition, whether behaviorally or in physical appearance, we say that the model has good face validity. The animal exhibits the same set of symptoms that you would see in a human affected by the same condition, such as a rat model of post-traumatic stress disorder (PTSD) where the rat is exposed to a predator. Future exposure to predator-associated cues causes the rat to exhibit anxiety and avoidance, which are symptoms of human PTSD. In this case, the model has good face validity.

2. Construct validity. Sometimes, an animal model of a disease starts with the same pathological changes in the brain that are observed in human patients. We say that these models have good construct validity. The risk of developing Huntington's disease (Chapter 10) in humans is associated with the number of poly-glutamine repeats in the Huntingtin protein. Developing a genetically modified animal model that has several poly-glutamine repeats is an example of a model with good construct validity. Because humans and non-humans are very different animals, having the same origin of disease does not always produce the disease symptoms.

3. Predictive validity. An animal model has good predictive validity if the animal model can be used to predict whether a therapy would be effective in treating humans with that same condition. For example, if there were a genetic mouse model that showed symptoms of depression, and an experimental antidepressant reverses depression in both the mouse and humans with depression, the model would be said to have good predictive validity.

Unfortunately, we don't have any animal models that reproduce the symptoms of the most complex human conditions - it is almost impossible to create a mouse model of

Figure 16.3 A predator exposure paradigm has strong face validity because it causes a mouse to become anxious, just like a human when they are exposed to a predator.

dissociative identity disorder or dyslexia, and even if we could, scientists would struggle to quantify the behaviors that we use as diagnostic criteria, which are too subtle to be observed or quantified in non-humans. And for the animal models that we do have, they are often imperfect or incomplete, modeling only some of the deficits seen in humans. Furthermore, most human diseases have many symptoms, and only a few can be assessed with behavioral tests. We can only study disorders of the brain that have a clearly and easily quantifiable behavioral component.

16.1 Schizophrenia (SZ)

Schizophrenia is a psychiatric condition affecting just under 1% of people. SZ affects men slightly more often than women and affects people of all races. There is a strong association between low socioeconomic status and the risk of developing schizophrenia, indicating that stresses such as neonatal nutritional deficiency or food insecurity may be risk factors. Other risk factors that contribute to increased SZ risk include prenatal drug exposure, heavy drug use during early adolescence, and childhood adversity.

A diagnosis is generally made while a person is in their late adolescent years through their thirties. During this phase of life, the brain is still undergoing subtle maturation processes, which may account for why a person is more vulnerable in these years. After this age, the risk of developing SZ decreases significantly. Also, the later in life that SZ symptoms appear, the better the health outcomes are.

It is worth noting that people with SZ have the neurotypical range of intelligence, with the occasional outliers: John Nash, the real-life Nobel prize-winning economist depicted in the movie A Beautiful Mind, was first diagnosed with SZ in 1959.

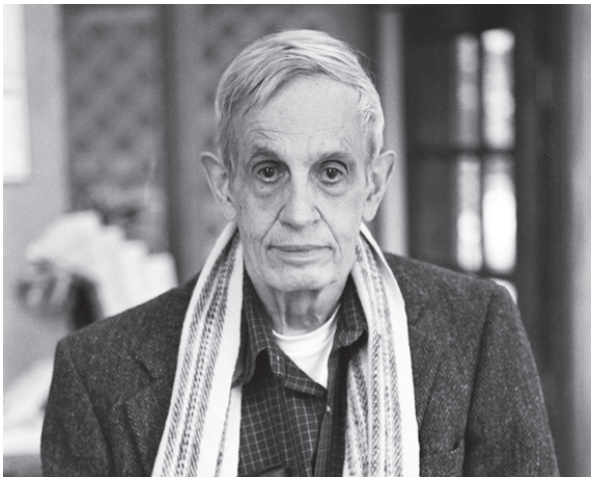


Figure 16.4 Dr. John Forbes Nash was diagnosed with schizophrenia before receiving the Nobel Prize in Economics in 1994.

Symptoms of schizophrenia

The symptoms of SZ can be roughly classified into two categories, positive symptoms and negative symptoms. These phrases are used to describe whether there is an excess of some function (**positive symptoms**) or a deficit of a function (**negative symptoms**). The symptoms do not appear uniformly across patients, so not all patients develop every symptom.

The most well-known positive symptom of schizophrenia is **hallucinations**, perceiving something that is not there (as opposed to illusions, which are misinterpretations of things that are there). Usually, patients experience auditory hallucinations, but they more rarely have visual hallucinations. The voices that these people hear may be consistent or can change over time. Interestingly, the nature of these hallucinations is influenced by society. In cultures with strong ancestor reverence, they may hear the voices of their grandparents, whereas people in religious cultures may hear the voices of deities.

Figure 16.5 Auditory (and sometimes visual) hallucinations are a common positive symptom of SZ.

Relatedly, people with SZ may experience a variety of **delusions**, untrue beliefs that cannot be changed despite overwhelming evidence. The delusions can come and go spontaneously. Delusions exist in many forms. A paranoid delusion is when a person believes that they are being spied on, maybe by the government or by aliens. A persecutory delusion is a persistent thought that the world is out to get them or to do them harm. Delusions of grandeur are when a person has a tremendously high sense of self-esteem, believing that they are royalty or are the reincarnation of God.

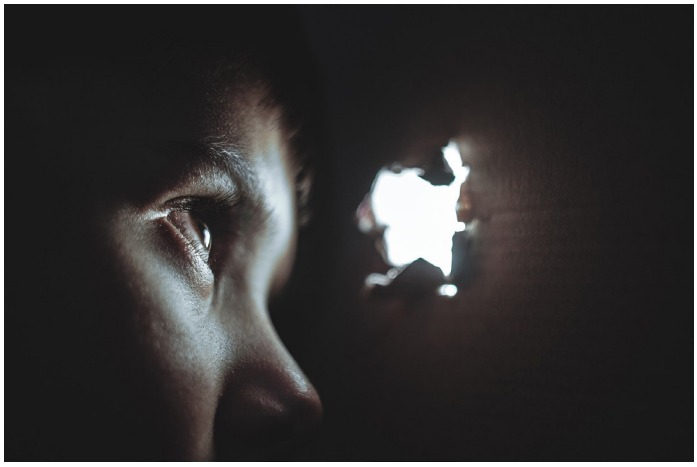


Figure 16.6 Persecutory delusions, a symptom of SZ, is the persistent belief that someone or something is constantly watching you.

Other positive symptoms that can present in SZ are a variety of motor disturbances. Basal ganglia and cerebellar structural deficits are found in SZ, two brain structures involved in motor control (see chapter 10), which may explain why deficits are observed. One motor difficulty is **catatonia**, where a person can hold their body in a highly unusual position for a prolonged period of time. They may also display **stereotypy**, a series of repetitive, purposeless behaviors, such as the persistent rocking of the body or self-caressing

The negative symptoms of SZ may include deficits in expression. One common symptom is a **flat affect**, where a patient does not show or express emotion in situations where you would expect to see them. A related negative symptom is **alogia**, a decrease in the use of language. People with alogia often use vague language that is lacking in content or repetitive.

Negative symptoms also include deficits in motivation or interest. Two closely-related negative symptoms include **anhedonia**, a loss of a sensation of pleasure and the inability to expect upcoming pleasure. Furthermore, patients with SZ may also exhibit **avolition**, a decrease in goal-directed activity, which can cause a person

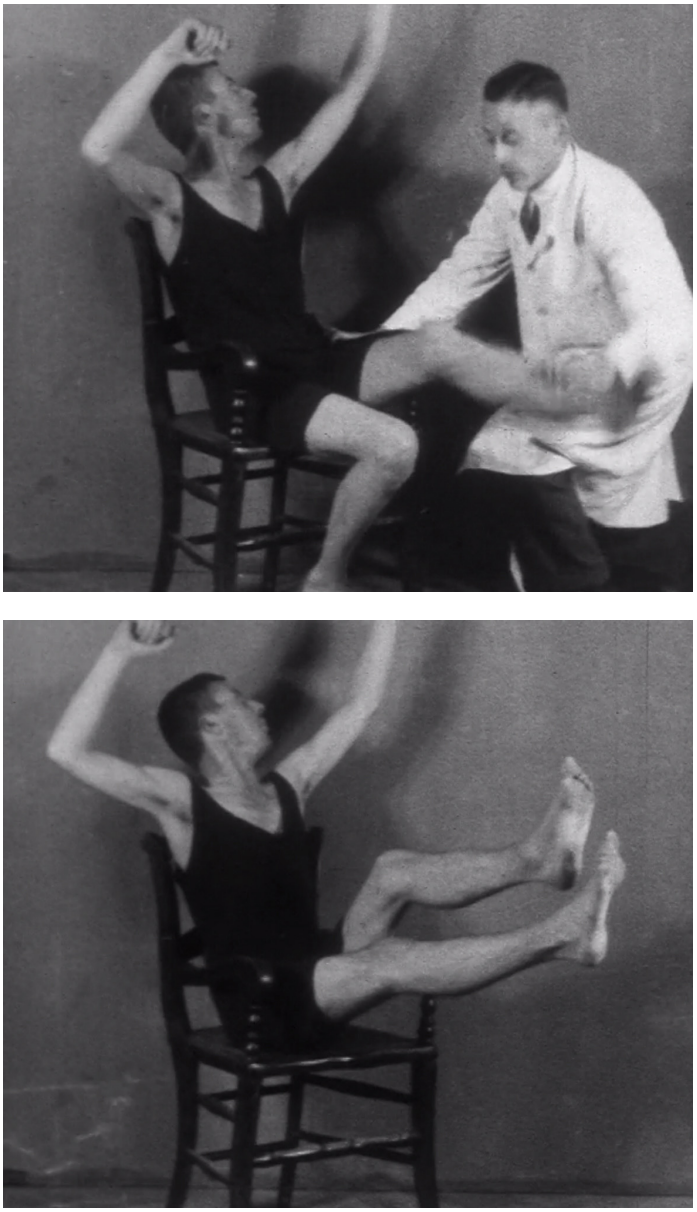


Figure 16.7 After being moved gently into an unusual body position, a person with catatonia may stay in that position for a prolonged time.

to stop seeing their friends and cease displaying interest in social gatherings, leading to worsened interpersonal relationships.

Negative symptoms may also manifest as a deficit of a patient's cognitive abilities, particularly shortcomings in episodic memory (Chapter 13). They may also present with difficulty in performing attention-related behavioral tasks.

Potential causes of schizophrenia

In a healthy person, dopamine is important for motor control and motivation, two behaviors that are changed in patients with SZ. Therefore, scientists have suggested that abnormal dopamine signaling may be an underlying root cause. While the **dopamine hypothesis** is one of the earliest theories of SZ, modern genetics studies have shown that polymorphisms in the dopamine D2 receptor are risk factors.

Atypical cortical neuron network development is also likely to be present in SZ. In the healthy brain, networks of cortical neurons produce cyclic patterns of activity in the 40 Hz range, a pattern called a gamma oscillation. These gamma oscillations result from a combination of excitatory and inhibitory neurons. In SZ, there is a decrease in the density of dendritic spines on the excitatory neurons with a simultaneous decrease in GABA-ergic signaling, which leads to unpredictable gamma oscillations.

Figure 16.8 Many environmental factors contribute to the risk of developing SZ.

Animal models of schizophrenia

One animal model for SZ is based on the hypothesis that excess dopamine leads to the disorder. Introducing high doses of the drug amphetamine, which increases dopaminergic signaling, induces a temporary schizophrenic-like state in non-human animals. The hyperdopaminergic model of SZ produces cognitive deficits with no changes in memory or other negative symptoms. Alternatively, administration of NMDA glutamate receptor antagonists, like ketamine or PCP, is also used as a behavioral model of SZ.

Other non-human models of SZ are neurodevelopmental models. In these models, a pregnant dam is exposed to the compound MAM, which causes the newborns to develop atypically and display behavioral deficits similar to SZ. Inducing an unusually strong immune response in the pregnant mother can also cause atypical development in utero, which causes the animals to experience behavioral deficits after birth.

The biggest limiting factor to developing an animal model is that many symptoms in human SZ, like paranoid delusions or auditory hallucinations, are impossible to detect and quantify in non-humans. The PCP model can cause changes in rodent social behaviors, but it is hard to tell if this model causes any of the positive symptoms that you might see in a patient with SZ. Despite the limitations of these non-human models of SZ, they have been helpful in testing the therapeutic efficacy of anti-schizophrenia drugs.

Treatments of SZ

The dopamine theory of SZ has led to a few novel therapeutic strategies, especially in the context of the dopamine D2 receptor. D2 antagonists decrease hallucinations and delusions in some patients with SZ, and the effectiveness of the antagonist is correlated with the ability of that drug to block the D2 receptor. Clozapine, an atypical antipsychotic that functions as a dopamine receptor antagonist, can decrease SZ symptoms as well.

Unfortunately, pharmacological therapies are not always effective in humans. Around a third of patients discontinue their treatment regimen, and around a fifth of them report adverse side effects such as extrapyramidal motor symptoms, sedation, and weight gain.

A potential new therapy is based on transcranial magnetic stimulation (Chapter 6). Some evidence suggests that targeted activation of the cortex can decrease the severity of auditory hallucinations. There may also be some mild improvements in the negative symptoms.

Approximately 65% of North Americans with SZ are smokers, compared to 25% in the population at large. If they are smoking as self-medication to activate dopamine- or acetylcholine-sensitive networks in the brain, this observation may lead to a new therapeutic strategy. Alternatively, they may smoke to get pleasure, which acts to reverse the anhedonia

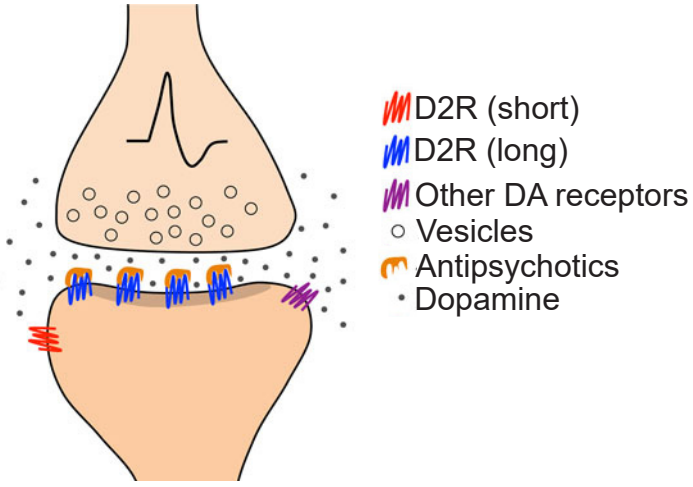


Figure 16.9 Atypical dopamine signaling is believed to contribute to schizophrenia.

16.2 Major depressive disorder (MDD)

Depression is a highly prevalent condition with a lifetime risk of about 18%. Depression gets diagnosed more frequently in women than in men, affecting about 5% of women and 2.5% of men. Even with treatment, there is a high rate of relapse: an estimated 80% of people with depression have more than one episode in their lifetime. The prevalence of depression is similar across both high-income and low-income countries, indicating that biological factors contribute significantly to the disease.

Figure 16.10 Spanish artist Pablo Picasso likely experienced some form of depression, and the paintings made during his "Blue Period," like *The Old Guitarist* (1903), reflect his emotional state.

MDD is also called **unipolar depression** to differentiate it from the depression that represents a phase seen in bipolar disorder (See section 16.3).

Clinical depression is often associated with another medical or psychiatric condition. For example, rates of depression are higher among people with terminal diagnoses, like cancer. In this case, we say that the two are **comorbid**. Additionally, a set of particularly challenging circumstances, like the death of a loved one, could trigger a depressive episode.

MDD represents a severe health risk across all ages. About 18% of adolescents report at least one instance of non-suicidal self-injury, and the lifetime risk for suicide among people with MDD is estimated to be about 10%.

Symptoms of MDD

The fundamental criteria that are used to diagnose people with MDD is a depressed mood/ self-esteem, low energy, and anhedonia, the decrease in sensitivity to pleasure. Because of the decrease in pleasure, they have a lessened desire to engage in activities that once produced happiness, thus leading them to become withdrawn from their friends and family.

Short-term changes in mood are completely normal and not clinical. The main diagnostic criteria for MDD is the severity and duration of the symptoms. When the depression begins to affect other aspects of life, including feelings of worthlessness, changes in sleep or appetite, difficulty concentrating, or suicidal ideation that persist daily for two weeks or longer, then a person may be diagnosed as clinically depressed.

To diagnose MDD, a trained psychiatrist or psychologist would use a combination of interview with a self-report questionnaire such as the **Hamilton Rating Scale for Depression (HAM-D scale)** or the **Beck Depression Index**. Items that appear on these sorts of tests include:

"Feels like life is not worth living"
"Experience frequent weeping"
"I blame myself all the time for my faults"

To date, there is no biomarker for depression.

Treatments for MDD

There is currently no completely effective treatment for MDD that reliably works for everyone. The currently accepted strategies can be divided into behavioral treatments and chemical treatments.

Cognitive behavioral therapy (CBT) is a therapist-guided form of talk therapy that may help a person manage their depression. In CBT, a patient's behavior, including their coping mechanisms, erroneous thoughts, and emotional responses, is analyzed through careful clinical examination and patient self-reflection. Then, the patient is taught mechanisms to counteract those maladaptive behaviors and replace them with adaptive behaviors. For example, a person undergoing CBT for MDD might learn to identify the moments when they dwell on something negative in their lives, and then learn to tell themselves "that thought does not function to make my day better. Let's start the day by getting out of bed and see what happens next." It should be known that CBT is not exclusively for the treatment of MDD; CBT can also be effective for anxiety, OCD, PTSD, insomnia, substance use disorders, behavioral addictions, and many others.

Clinical connection: Seasonal affective disorder (SAD)

Seasonal affective disorder (SAD) is one type of depression that has a dependence on daytime sunlight, increasing in prevalence in the winter and decreasing in the summer. The prevalence of SAD is heavily correlated with distance from the equator: people living closer to the poles experience longer nights in the winter, which increases SAD risk. In the US, for example, SAD affects about 1% of people in Sarasota, Florida, but about 9% of people in Anchorage, Alaska.

Light exposure therapy, while controversial, may show benefits for people with SAD, particularly intense broad-spectrum light or blue wavelength light. People with SAD may have something unusual about their intrinsically photosensitive retinal ganglion cells.

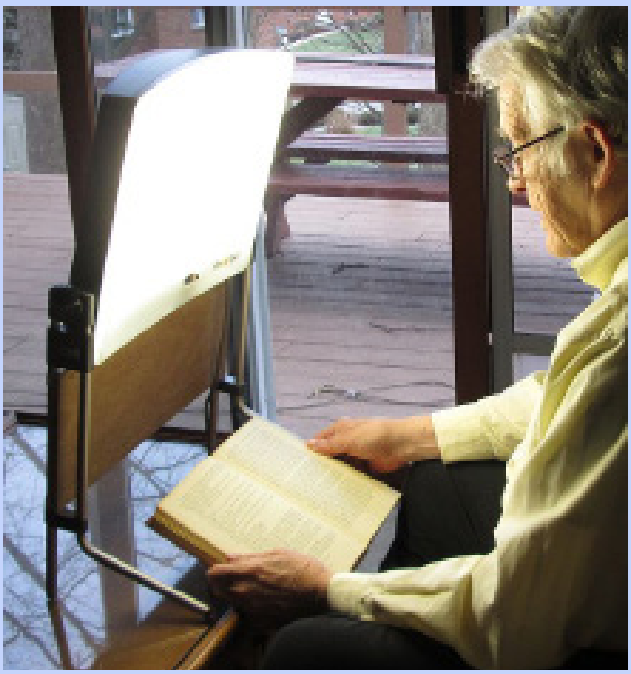


Figure 16.11 Light exposure therapy may be effective at treating some cases of seasonal affective disorder.

A wide variety of drugs are used for the treatment of depression. The **first-generation antidepressants** were developed in the 1950s and 1960s. These drugs acted to increase the action of the monoamine neurotransmitters: primarily dopamine, norepinephrine, and serotonin. Our body uses an enzyme called **monoamine oxidase (MAO)** which degrades these chemicals into inactive components that do not signal at receptors. These first generation antidepressants block the action of MAO; biochemically, we call them **monoamine oxidase inhibitors (MAOIs).** In the presence of an MAOI, the neurotransmitter signal remains in the synapse longer, similar to how an acetylcholinesterase inhibitor increases ACh signaling (Chapter 10).

Most of the MAOIs, while sometimes effective, have fallen out of fashion clinically because of the adverse side effects associated with their biochemical activity (however, they are still commonly used in treatment of Parkinson's disease). Some of them interact dangerously with foods rich in tyramine (particularly fermented foods, such as aged cheeses or beer, as well as beans and processed meats), an amino acid that is degraded by MAO. Excess tyramine can activate the sympathetic nervous system, and body levels of tyramine can rise to dangerous levels in the presence of an MAOI, leading to adverse cardiovascular events like stroke.

Many of the common MAOIs, like phenelzine and isocarboxazid, can be damaging to the liver. Some MAOIs also produce unwanted side effects, such as psychosis or nausea.

A different class of antidepressant drugs called the **tricyclic antidepressants (TCAs)**, named for the shape of their chemical structure, was also developed around this time. They generally act as monoamine reuptake inhibitors, resulting in elevated neurotransmitter signaling.

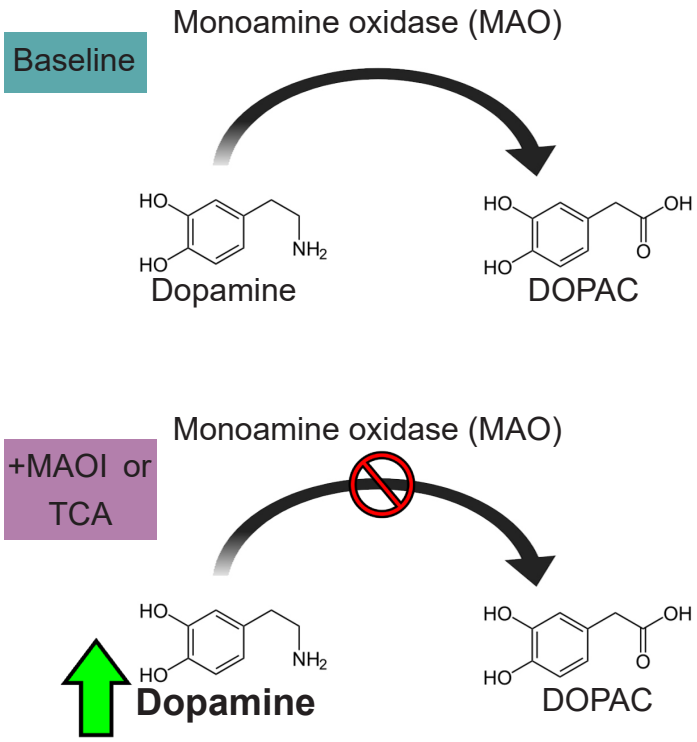


Figure 16.12 MAOIs and TCAs both increase neuronal signaling by decreasing the metabolic degradation of neurotransmitters, such as dopamine.

Unfortunately, these tricyclics may produce many severe side effects, such as seizures, tachycardia, and heart attacks, so prescriptions must be monitored closely. The tricyclics are still prescribed today for several other nervous system disorders, ranging from insomnia to neuropathic pain, but due to their potential cardiotoxicity, they are not often the first line of treatment in depression.

Our current, most often prescribed class of compounds for MDD, called the **third-generation antidepressants**, are focused on boosting the signaling activity of serotonin. Instead of preventing degradation, like the MAOIs, these compounds block the reuptake of serotonin out of the synapse. These chemicals are called **selective serotonin reuptake inhibitors (SSRIs),** of which fluoxetine (Prozac) is one of the most well-known examples.

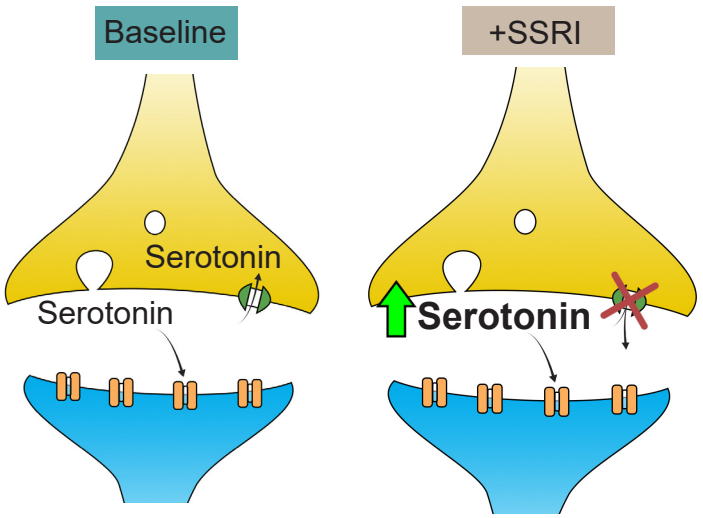


Figure 16.13 Third-generation antidepressants act to increase neurotransmission at the synapse by inhibiting reuptake.

While SSRIs can be effective at reversing the side effects of depression, they are not perfect drugs. One shortcoming is that a person needs to be on the drug for 2-4 weeks before they start to experience a clinically meaningful reversal of depressive symptoms. This finding is highly unusual since the pharmacological, molecular-level effects of SSRIs take place within hours after taking the medication. Similar to SSRIs, SNRIs (serotonin and norepinephrine reuptake inhibitors) can also be used to treat depression.

One of the unsavory side effects of SSRIs is **serotonin syndrome**, a set of somatic changes resulting from excessive serotonergic signaling. In mild cases, a person may have an elevated body temperature, excessive sweating, rapid heart rate, and elevated blood pressure. In more severe cases, a patient may have severe fevers or seizures. Serotonin syndrome can happen in the event of an SSRI overdose, or as a consequence of some interaction between an SSRI and other drugs like MAOIs, MDMA (ecstasy), amphetamines, or cocaine.

Our newest treatment options for depression, recently approved by the FDA in March of 2019, is **ketamine**, a dissociative anesthetic typically used as a veterinary tranquilizer and a recreational club drug. Branded as Spravato, it can be administered rapidly via nasal spray. The strength of esketamine is the speed of its action. After taking a dose, the antidepressant effects of the substance can be observed within hours.

For severe or treatment-resistant depression, **electroconvulsive therapy (ECT)** is a treatment option. Introduced in 1938, the procedure has since been refined over the years (it is currently performed under anesthesia) and is considered to be well-tolerated and highly effective. However, side effects include aches, nausea, and memory loss.

One future therapy that is currently making significant medical advancements in curing depression is the use of psychedelic drugs, particularly **psilocybin** – a substance found in some species of wild mushrooms. As a potent serotonergic agonist, a single dose of psilocybin has been shown to decrease depression scores in various self-report studies with little to no adverse side effects.

Animal behavioral tests of depression

Behavioral neuroscientists have developed a variety of tests to assess the effectiveness of antidepressant drugs in non-humans. They are roughly divided into two categories.

1. Despair-based tests. One symptom of depression is that a person "gives up," a behavior that can be modeled in a variety of rodent tests. One such example is in a **tail suspension test**. The mouse is held by the tail upside down. While it does not cause injury to the animal, they do experience discomfort, and will generally struggle

to either free themselves or to get upright again. The sooner they stop struggling (more time spent immobile), the more despair they experience, or the more depressive they are. Giving a mouse an antidepressant like fluoxetine causes them to fight for a longer duration.

A similar test to assess "giving up" is the **forced swim test**. Here, a rodent is put into a container with some water. While they are naturally buoyant and are not at risk of drowning, they do not like being wet and will try to swim so that they can climb out of the water-filled container. As in the tail suspension test, they are unable to escape their predicament, and will eventually become immobile. Giving them an antidepressant decreases time spent immobile.

Figure 16.14 The tail suspension test (left) and the forced swim test (right) are despair-based tests that assess depression-like behaviors in non-humans.

2. Reward-based tests. These tests seek to measure the severity of anhedonia, one of the main symptoms of depression. For example, a rodent may be presented with a **two-bottle choice task**, where they are put into a cage with two different bottles to drink from: one filled with standard water, and the other filled with a more desirable sugar-water solution. A depressed rat will not drink from the sugar-water bottle as frequently as a healthy rat but give that rat an antidepressant, and they will prefer the sweet water.

An intracranial self-stimulation paradigm can also be tested here in the context of depression (see chapter 11). When an electrical stimulator is placed in a reward area of the brain and the rodent is trained to perform some operant task to receive activation of these areas, we find that depressed mice do not activate these areas of their brain as much as one on antidepressants.

16.3 Bipolar disorder (BD)

A person with bipolar disorder (BD) experiences phases of clinical depression as described above, and at other times they experience **mania**, a state of exhilarating high energy. During this state, they may sleep very little, have difficulty concentrating, and experience pressure of speech: a perceived need to speak very rapidly to get their thoughts out. They might make poor financial or life decisions, such as deciding to abruptly leave their family behind. Historically, BD has been called "manic depression." Notably, actress Carrie Fisher and musician Demi Lovato both struggled with BD.

The estimated prevalence of BD is around 2.5%, but the disease is often misdiagnosed in the clinic as MDD. One reason this happens is that more people are aware of the symptoms of depression, and these symptoms are generally more easily observed. Mania is more difficult to identify, since in mild cases it may be hard to distinguish from a person just "being in a really good mood."

For a diagnosis of BD according to the DSM-V, a mood cycle has to last for a week or more. The word "bipolar" is often misused in pop culture. Frequent changes in mood from happy to sad does not characterize BD. In fact, for a person to be diagnosed with **rapid-cycling bipolar disorder**, they need to experience four mood transitions annually!

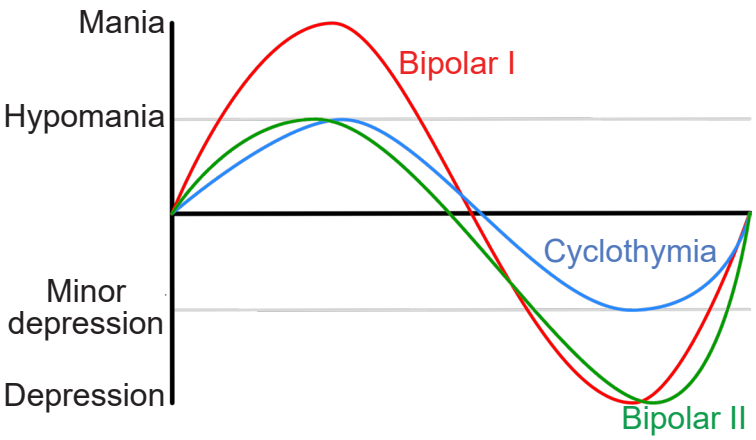


Figure 16.15 Severity of symptoms is used clinically to differentiate between Bipolar I, bipolar II, and cyclothymia.

BD is usually diagnosed in adolescence and early adulthood. As with depression, there are some genetic factors involved, since a family history of BD is a risk factor. Concordance rates for identical monozygotic twins are estimated to be between 35%-80%. But, environmental influences may be the precipitating factor in the onset of BD.

BD is diagnosed into two categories, based roughly on the severity of symptoms. **Bipolar 1 disorder** is the more severe of the two conditions, with a clinical diagnosis made when a patient experiences depressive or manic events that cause significant social or occupational impairment, or hospitalization to prevent serious self-harm. A diagnosis of **bipolar 2 disorder** is less severe, but the behavioral changes are still noticeable by friends and family. A related diagnosis is **cyclothymia**, where a person has alternating mood states that shift from depression to hypomania, a less severe state of mania. Like most other disorders, BD exists on a spectrum, and these labels only exist for simplicity.

Treatments for BD

The main issue with BD therapy is bringing the patient to some "middle" state: an antidepressant may treat the depression phase, but could also swing the patient into mania. Similarly, a mania-controlling drug could initiate depression.

Currently, our most reliable therapy for BD is **lithium** drugs. These compounds are described as mood stabilizers since they act to move the patient's mood to the center, rather than being at either the high end of mood (mania) or the low end (depression). The way lithium acts to reverse the symptoms is still unknown, and it probably acts on multiple pharmacological targets.

The main downside of this therapy is that lithium is very toxic. It has a very narrow therapeutic window: blood levels of lithium lower than 0.6 mEq/L produce no effect, and anything above 1.5 mEq/L causes delirium, tremor, fatigue, and deadly side effects like seizures and coma. It is also harmful to the kidneys after long exposure. Therefore, a person taking lithium drugs regularly undergo **therapeutic drug monitoring (TDM),** a procedure by which the concentration of lithium is assayed. TDM requires frequent visits to a hospital. Usually, patients get multiple blood draws in the first month when they start lithium treatment, decreasing to one test every 2 months, before decreasing to about four times a year.

BD is very challenging to model in non-humans. A genetically modified disruption of the circadian rhythm can induce mania-like symptoms, as can extending the length of daytime light exposure; oppositely, decreasing daily light exposure can induce depressive behaviors. Exposure to amphetamine can increase manic behaviors, while withdrawal from the drug can induce depression. Clearly, neither of these models for BD exhibit strong validity.

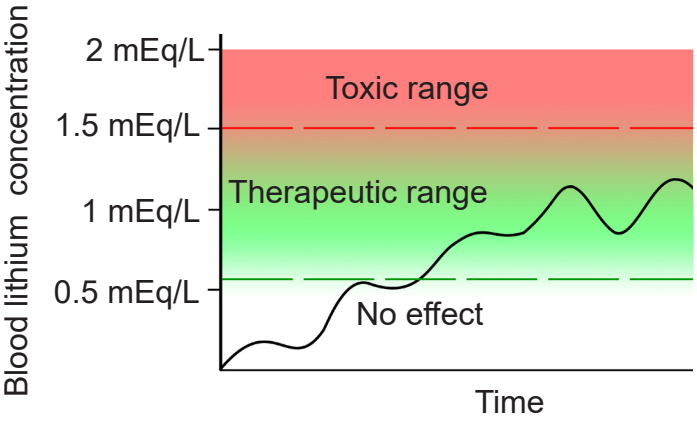


Figure 16.16 Therapeutic drug monitoring is important for people taking lithium for BPD since the medication is ineffective at low doses, but toxic at high doses.

16.4 Anxiety disorder

Anxiety is something that everyone has experienced at many points in their life. An anxious person may experience cardiovascular symptoms such as elevation of blood pressure and heart rate, shortness of breath, profuse sweating, and a state of panic. In many ways, the anxiety response is similar to the fight-or-flight response observed during sympathetic nervous system activity.

However, a clinical diagnosis of anxiety is different from the passing anxiety that we all experience. Anxiety disorders can be very common, and lifetime prevalence estimates suggest 29% of people could develop clinically significant anxiety over their life span.

According to the DSM-V, anxiety disorders have different presentations.

1. Generalized anxiety disorder (GAD). People with GAD experience a constant sensation of being overwhelmed, accompanied by fear and worry. Many times, this worry is not about a single concern, but rather a combination of issues all at once, such as financial issues, relationship issues, uncertainty of the future, and many others. GAD is much more severe and persists longer than the normal worries that affect everyone.

In GAD, worry persists for several months and is uncontrollable. There are also associated cognitive symptoms, such as fatigue, irritability, difficulty with concentration, and changes in sleep patterns.

2. Specific phobias. With specific phobias, a person develops the anxiety-related symptoms (cardiovascular and psychological changes) in response to highly specific stimuli, such as snakes, enclosed spaces, deep ocean, or public speaking. The person with the phobia perceives the stimulus to be a great threat, even though it does not actually pose a genuine threat. Most people with specific phobias will go to great lengths to avoid exposure to their particular phobia trigger. These phobias are often influenced by social and cultural conditions.

Developing a specific phobia has a lifetime prevalence of about 7%, but only a very small number of people with specific phobias ever seek treatment for their phobia. Like other forms of anxiety, there is a range of severity of these phobias.

Figure 16.17 A person with a specific phobia such as agoraphobia, the fear of unfamiliar environments where they have little control over their circumstance, may experience a panic attack in a crowd.

3. Panic disorder. A person with panic disorder experiences frequent **panic attacks**, characterized by sudden increases in heart rate, shortness of breath, dizziness, and sudden numbness or tingling (panic attacks can also be seen in specific phobias, but are not observed in GAD.) In panic disorder, these panic attacks may occur independently of external influences.

Pharmacologically, there are a wide variety of drugs that can be used to treat anxiety,

broadly called anxiolytics. The first-line therapies are usually SSRIs, the same class of compounds that are used in depression treatment. Other anxiolytics, such as the benzodiazepines alprazolam or clonazepam, act as positive allosteric modulators which increases the effect of the GABA system. Benzodiazepines are not always preferred since they may have abuse potential and can be addictive. Opioids and norepinephrine inhibitors can also decrease anxiety.

The exact cause of anxiety is still unknown. One theory suggests that anxiety is a maladaptive evolutionary response to our modern living conditions. The argument is based on the observation that an anxiety response looks a lot like a mild version of the fight-or-flight, sympathetic nervous system response: both elicit cardiovascular and respiratory changes. For 99% of the evolutionary history of *Homo sapiens*, we benefited from the sympathetic nervous system as a reflex to improve the odds of survival in dangerous situations. However, our modern civilized living conditions over the past few centuries have been very tame in comparison to the risks that our earlier ancestors experienced. The relative ease of living has let the main function of the sympathetic nervous system fall into disuse. The theory argues that people experience GAD because a part of them encourages sustained activity in the sympathetic nervous system. Although thought-provoking, this theory can't be tested experimentally and offers no explanation about a biological mechanism that can help to develop a therapy.

Animal behavioral tests for anxiety

As with depression above, there are non-human behavioral tests used to assess anxiety in rodents, such as the **elevated plus maze.** The maze is a raised platform, with four arms in the shape of a plus sign. Two of the arms have walls surrounding the sides, while the other two are open, exposed on all sides. The rodent is free to move between any of the arms as they choose. Standing in one of the open arms, where they can see the floor far below them, is an anxiety-provoking condition. Under normal circumstances, rodents choose to spend more time in the arms that are surrounded by walls. But if you give these animals an anti-anxiety drug, they increase the time spent in the open arms, indicating a decrease in the behavioral expression of anxiety.

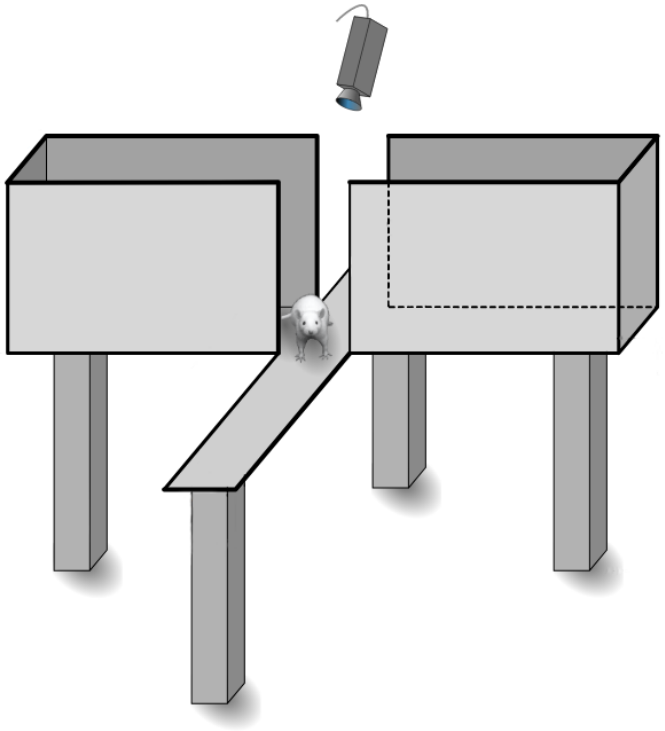


Figure 16.18 An elevated plus maze is one behavioral test for measuring anxiety behaviors in non-human animals.

A related behavioral test is the **open field test**. The test apparatus consists of a large, flat area where the rodent can move around freely, and some method to track the animal - either an aerial view camera or a series of parallel invisible

infrared beams that can locate the animal in the field. In the wild, rodents, as prey animals, prefer to spend more time close to the sides of the testing arena up against the wall, avoiding the wide-open space in the middle where their instinct warns them that they may be snatched up by some predator. However, if you give the rodent an anti-anxiety drug, they will spend more time venturing into the middle of the open field.

Another non-human model of anxiety is the **predator exposure paradigm**. In this paradigm, an ethologically-relevant stimulus is presented to the rodent, such as one of their naturally occurring predators. In this paradigm, rodent anxiety presents itself as a freezing response, an autonomic nervous system activity spike, and a reduction in non-survival behaviors. Although the predator exposure paradigm has good predictive validity, they may struggle with poor face validity, since the anxiety measures also may appear as many of several other conditions, such as PTSD or stress.

The Open Neuroscience Initiative is funded by a grant from the Vincentian Endowment Fund of DePaul University.

Cover https://pixabay.com/photos/lewy-body-dementia-dementia-2965713/
16.1 https://pixabay.com/photos/children-twins-girls-young-652270/
16.2 https://upload.wikimedia.org/wikipedia/commons/4/4b/Dsm-5-released-big-changes-dsm5.jpg
16.3 https://pixabay.com/photos/cat-animal-cute-pet-room-play-3162458/
16.4 https://upload.wikimedia.org/wikipedia/commons/a/a9/John_Forbes_Nash%2C_Jr._by_Peter_Badge.jpg
16.5 https://upload.wikimedia.org/wikipedia/commons/a/a6/Schizophrenia_image.jpg
16.6 https://pixabay.com/photos/hiding-boy-girl-child-young-box-1209131/
16.7 https://wellcomecollection.org/works/wv5n6jjx
16.8 https://upload.wikimedia.org/wikipedia/commons/7/7f/Schizophrenia_risk_factors-PLOS.png
16.9 Amato D, Kruyer A, Samaha A-N and Heinz A (2019) Hypofunctional Dopamine Uptake and Antipsychotic Treatment-Resistant Schizophrenia. Front. Psychiatry 10:314. doi: 10.3389/fpsyt.2019.00314
16.10 Pablo Picasso, The Old Guitarist
16.11 https://commons.wikimedia.org/wiki/File:Light_Therapy_for_SAD.jpg
16.14 https://upload.wikimedia.org/wikipedia/commons/8/89/201407_tail_suspension_test.png
https://upload.wikimedia.org/wikipedia/commons/e/e0/201407_porsolt_forced_swim_test.png
16.15 https://upload.wikimedia.org/wikipedia/commons/f/f0/Bipolar_disorder_subtypes_comparison_between_Bipolar_I%2C_II_disorder_and_Cyclothymia.svg modified by Austin Lim
16.17 https://pixabay.com/photos/crowd-of-people-crowd-football-fans-1488213/
16.18 https://upload.wikimedia.org/wikipedia/commons/a/ab/ElevatedPlusMaze.svg modified by Austin Lim