1 INTRODUCTION TO PSYCHOPHARMACOLOGY

LEARNING OBJECTIVES

1.1 Discuss the two fields of psychopharmacology.

1.2 List reasons why it's important to read a psychopharmacology book.

1.3 Explain the challenges of defining the term "drug."

1.4 Identify drugs in terms of their uses and intended purposes.

1.5 Explain the differences among generic, brand, chemical, and street names for drugs.

1.6 Interpret drug effects based on dose.

1.7 Summarize the difference between objective and subjective effects of psychoactive drugs.

1.8 Describe study designs used to assess the pharmacological effects of drugs.

1.9 Appraise the quality of outcomes from scientific studies.

1.10 Assess the ethical conduct of drug studies using animal or human subjects.

1.11 Describe the process of therapeutic drug development.

Psychoactive substances are highly prevalent in society. Many people regularly drink alcohol or smoke tobacco or cannabis. Millions of Americans take prescribed drugs for depression or anxiety. Nearly everyone consumes caffeine. In this book, we'll learn about these and many other psychoactive substances. We'll learn about the how these substances are used, how they act in the brain and body, and their physical and mental effects. In this first chapter, we learn some basic concepts about drugs and the ethical considerations involved in studying them.

PSYCHOPHARMACOLOGY

Psychopharmacology is the study of drugs that affect mood, perception, thinking, or behavior. Drugs that achieve these effects by acting in the nervous system are called **psychoactive drugs**. The term *psychopharmacology* encompasses two large fields: psychology and pharmacology.

Thus, psychopharmacology attempts to relate the actions and effects of drugs to psychological processes.

A psychopharmacologist must have knowledge of the nervous system and how psychoactive drugs alter nervous system functioning. A psychopharmacologist can be a medical practitioner, like a psychiatrist, who specializes in prescribing psychoactive medication, or a scientist who studies psychoactive drugs. This approach defines the structure of this textbook. First, this book provides an overview of cells and structures of the nervous system. Second, it covers the basic principles of pharmacology. After this, we apply our knowledge of the nervous system and pharmacology to understand the actions and effects of psychoactive drugs, beginning with recreational and abused drugs and ending with therapeutic drugs for treating mental disorders.

Psychopharmacology is not the only term used to describe this field (**Table 1.1**). Another term is *behavioral pharmacology*. Many consider behavioral pharmacology as synonymous with psychopharmacology, but others classify *behavioral pharmacology* as part of the subfield of psychology called *behavior analysis*. In this respect, drugs serve as behavioral stimuli, such as conditioned stimuli or reinforcers. *Neuropsychopharmacology* is another term for psychopharmacology. The *neuro* prefix represents the nervous system. Although the terms are similar, the neuropsychopharmacology field has a particular emphasis on the nervous system actions of drugs.

TABLE 1.1 ■ Names Used to Describe Psychopharmacology

Field	Description
Psychopharmacology	The study of how drugs affect mood, perception, thinking, or behavior.
Behavioral pharmacology	The study of how drugs affect behavior. Sometimes, behavioral pharmacologists emphasize principles used in the field of behavior analysis.
Neuropsychopharmacology	The study of how drugs affect the nervous system and how these nervous system changes alter behavior.

WHY READ A BOOK ON PSYCHOPHARMACOLOGY?

Psychopharmacology is an important part of modern psychology and neuroscience. First, psychoactive drug use is highly prevalent. In the United States, for example, consider the following:

- 13.2% of U.S. adults currently use an antidepressant drug (Brody & Gu, 2020)
- 30 million U.S. adults have used a benzodiazepine drug for anxiety within the last year (Maust et al., 2019)
- More than 29 million use a prescribed pain-relieving drug (National Center for Health Statistics, 2018).

When we add recreational drugs to the list, psychoactive drug prevalence in the United States increases further:

- 63% of U.S. adults consume alcohol.
- 46% percent of those 12 and older have tried cannabis at some point in their lives, and 19% are current users (Schaeffer, 2023).
- More than 46 million individuals use tobacco products (Cornelius et al., 2023).
- 93% of U.S. adults consume caffeinated beverages and food, most on a daily basis (Food Insight, 2022).

The World Health Organization (WHO) has also reported high rates of psychoactive drug use internationally (WHO, 2012). To understand typical human behavior in the modern world, the sheer prevalence of drug use requires that we understand how drugs affect the way we think and function.

The second reason for reading this text is that the statistics presented show how many of us are consumers of psychoactive substances; as consumers, we should know about the substances we ingest. Greater knowledge of psychoactive substances improves patient understanding of prescribed medical treatments and health implications of taking recreational substances.

Third, you will come to understand how psychoactive substances provide important tools for understanding human behavior. For example, learning about the actions of antidepressant drugs led to understanding the roles that certain neurotransmitters and brain structures play in mood. Researchers use many experimental psychoactive drugs entirely as pharmacological tools for understanding brain function and behavior. Fourth, you will see how psychopharmacologists help develop psychoactive treatments for mental disorders.

WHAT IS A DRUG?

In a way, you know a drug when you see one. After all, the term *drug* is part of our everyday language. We take drugs for headaches, infections, mood, and virtually any other ailment or disorder. We even take drugs to prevent disorders. But, what exactly is a drug?

To provide a simple definition, a **drug** is an administered substance that alters physiological functioning. The term *administered* indicates that a person takes or is given the substance. The phrase "alters physiological functioning" implies that the substance must produce some change in physiological processes.

This definition has challenges. The term *administered*, for example, excludes substances made naturally in the body. The neurotransmitter dopamine is made in the nervous system and elicits important changes in nervous system functioning. However, hospital physicians may administer dopamine to a patient to elevate heart rate. In this context, dopamine is an administered substance that alters physiological functioning. Yet, the same dopamine is made in the

body—distinguishing the two leads us to call dopamine a drug when a practitioner administers it and a neurotransmitter when the brain produces it.

Along the same lines, many of us take vitamins to ward off disease and improve health. We administer vitamins to ourselves. Why not call *vitamins* drugs? We simply describe them as vitamins (**Figure 1.1**). Nor do we describe herbal remedies as drugs despite their physiological effects.

FIGURE 1.1 ■ Examples of Substances Used

(a) Antidepressants (b) Vitamins (c) Vaping (d) Sniffing glue

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The term *substance* in the definition of drug also lacks a precise description. The antidepressant in Panel A for Figure 1.1 has the appearance of a drug, but the substances in the other three panels seem less like drugs. Each substance, however, exhibits physiological changes in the body.

The emphasis on physiological functions also has limitations. Certainly, drugs produce changes in the body—but is food a drug? After all, food also produces physiological changes in the body. In fact, many foods affect mood as well.

Do drugs have a certain appearance? Drugs come in a variety of different forms, including pills, liquids, and powders. We might consider nicotine a drug, although nicotine molecules reside within tar particles inhaled when smoking tobacco or in an e-liquid when vaped. Some may sniff certain types of glue, the vapors of which contain chemicals such as toluene. In this case, drugs also come in vapor form.

Thus, although *drug* is a common term, we must not restrict our perception of a drug to a specific form or usage in psychopharmacology. Doing so risks excluding nonconforming substances that may have powerful effects for altering behavior. As presented in Chapter 5, for example, thinking of food as a drug provides a useful means of understanding food addiction.

STOP & CHECK

Stop & Check questions provide a quick way to self-assess your comprehension of the material. These questions pertain to main points and are provided throughout the chapters of this book.

1. In general, how prevalent is psychoactive drug use?
2. What is the definition of a drug?

1. Both therapeutic and recreational drugs are highly prevalent in society. Alcohol, caffeine, and nicotine are highly prevalent, as are medications for anxiety, depression, and pain. **2.** A drug is an administered substance that alters physiological functioning. A more precise term is lacking, but it's helpful to think critically about the limitations of what we consider a drug to be to appreciate the forms a psychoactive substance may take and ways a substance might affect us.

PSYCHOACTIVE DRUGS ARE DESCRIBED BY MANNER OF USE

Psychoactive drugs broadly fall into two categories: those intended for instrumental use and those intended for recreational use. The major distinction between these categories is a person's intent or motivation for using the substance. **Instrumental drug use** consists of using a drug to address a specific purpose. For example, someone may take an antidepressant drug, such as Prozac, for the purpose of reducing depression. Further, most adults consume caffeinated beverages like coffee to help them wake up in the morning, another socially acceptable purpose. In psychopharmacology, instrumental use often occurs with **psychotropic drugs**—drugs used for treating disorders—for treating mental disorders such as depression, anxiety, and schizophrenia.

Recreational drug use refers to using a drug entirely to experience its effects. For example, recreational use of alcohol may consist of drinking alcohol purely to experience its intoxicating effects. Many drugs can be misused for recreational purposes. The term **drug misuse** applies to drugs that are intended for instrumental purposes but are instead used recreationally. For example, cough syrups that contain codeine or dextromethorphan are misused recreationally to

achieve mind-altering effects such as euphoria or hallucinations. A benzodiazepine drug, such as Xanax, is prescribed for anxiety (an instrumental use) but may be misused if taken to enjoy feeling the drug's effects (a recreational use).

Recreational use may lead to a substance use disorder. With a *substance use disorder*, a user experiences many problems in their life surrounding use of the substance, such as loss of control, a need or urge for using the substance, disruptions to normal everyday life, and difficulty reducing use of the substance. In Chapter 5 we expand upon the clinical characteristics of substance use disorder and consider many scientific models of drug addiction.

GENERIC, BRAND, CHEMICAL, AND STREET NAMES FOR DRUGS

Individual drugs have different names. For example, people commonly take Tylenol to treat headaches. The name *Tylenol* is widely known, but the drug is also known by a different name: acetaminophen. We refer to Tylenol as its *brand name* and acetaminophen as its *generic name*.

Nearly all therapeutic drugs have a generic name and at least one brand name. A pharmaceutical company that develops and markets a drug provides both brand and generic names, each for different purposes. A drug's **brand name** (or **trade name**) is a trademarked name a company provides for a drug. Sometimes, a trade name is designed to be memorable or emotion provoking. For example, common sleep aids include Ambien and Lunesta. The name *Lunesta* resembles the word *luna*, meaning "moon," a symbol for night. Plus, the word *Lunesta* is a soft-sounding name, giving a relaxing connotation to the drug. Companies have leeway in the creative process for brand names, so long as a name does not specifically imply a treatment effect, sound too similar to another drug's name (due to safety concerns arising from confusing different drugs during the prescription process), or utilize a medical term. Approval of the name comes from the U.S. Food and Drug Administration and the European Medicines Agency.

A drug's **generic name** is a nonproprietary name that indicates the classification for a drug and distinguishes a drug from others in the same class. The suffix of a generic drug name conveys that drugs are of the same type. For example, note the generic names of the following antipsychotic drugs: chlorpromazine, clozapine, and olanzapine. All three of these drugs end in *a* followed by a consonant and then the suffix *–ine.* We can guess that drugs with *–apine* or *–azine* in their names act as antipsychotic drugs. The other parts of the name are unique to the particular drug. Generally, the other part of the generic name—the prefix—has two syllables, cannot have a marketing connotation to it (e.g., implying how effective the drug is), uses letters from the Roman alphabet (i.e., no H, J, K, W, or Y), and cannot use a medical term. Within these rules, those proposing a name for the drug aim for something easy to pronounce (Silver, 2023). The first two antipsychotic drugs mentioned earlier, chlorpromazine and clozapine, have chloride molecules in their structures, which may have inspired the prefix portion of their names. The proposed generic names must receive approved from both a U.S. regulatory group and the WHO. Despite a number of guidelines and conventions, generic names do not follow hard rules and cannot be relied upon entirely to inform us about a drug's classification, and they lack sufficient information to describe features of its chemical structure. But as shown in

these examples, generic names can provide ways to show how drugs organizationally compare to others.

Scientific reports normally refer to a drug's generic name. In these cases, the generic name is sometimes followed by the drug's brand name in parentheses. Moreover, brand names, as proper nouns, are capitalized. For example, a report might read "Physicians prescribe zolpidem (*Ambien*) for insomnia." The generic name is zolpidem, and its brand name is Ambien.

Drugs also have chemical names. A drug's **chemical name** details a drug's chemical structure. For example, the chemical name for zolpidem is "N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide." It's beyond the scope of this textbook to cover what the many components of this name mean—general chemistry and organic chemistry textbooks can tell you that. For our purposes, we can appreciate that the chemical name tells anyone with sufficient chemistry education what zolpidem's chemical structure looks like. The rules used for writing a drug's chemical name come from the International Union of Pure and Applied Chemistry (IUPAC), an international, independent organization of chemists focused on advancing the chemical sciences.

Recreational drugs typically have **street names** (or **slang names**), unofficial alternative names for recreational substances. Such substances tend to have many street names. They can serve as benign-sounding aliases, such as the name *ADAM* as a reference to the drug MDMA (an abbreviation of 3,4-methylenedioxymethamphetamine). Street names may also reflect the drug's effects, such as referring to MDMA as *ecstasy*. The unofficial nature of street names coupled with their illicit use also leads inaccuracies. One name may refer to many other substances, and even if a name is used consistently, such as ecstasy for MDMA, the actual substance used may have something else. For example, in analyses of ecstasy tablets collected from users, many pills contained the drug MDEA (3,4-methylenedioxyethamphetamine), methamphetamine, dextromethorphan, ketamine, and cocaine (Cole et al., 2002; Morefield et al., 2011). **Table 1.2** lists common recreational substances and some classically known street names.

TABLE 1.2 ■ Examples of Street Names for Selected Drugs

Drug	Street Name
Amphetamines	Addies, bennies
Benzodiazepines	Benzos, downers, tranqs
Cocaine	Coke, crack
Dextromethorphan (used in cough syrup)	Robo, triple C
Methamphetamine	Meth, crystal
MDMA	Ecstasy, molly
LSD	Acid, blotter
Phencyclidine	PCP, angel dust

DRUG EFFECTS CORRESPOND WITH DOSES

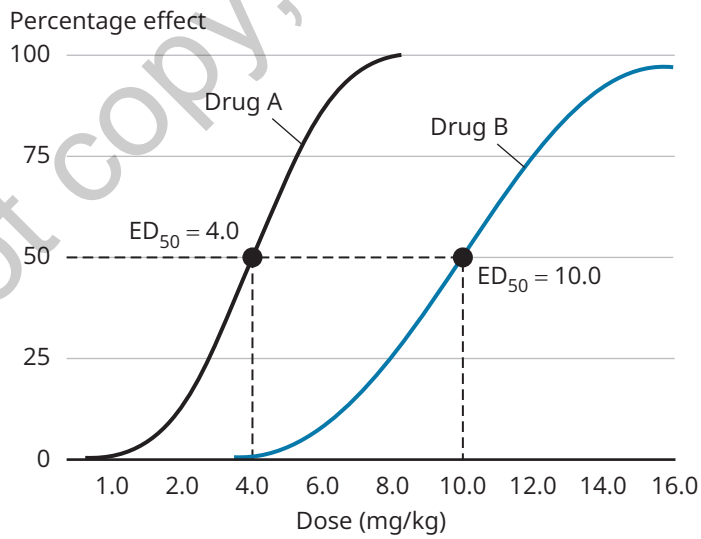
The strength of a drug's effects depend on a drug's dose. **Dose** is a ratio of the amount of drug per an organism's body weight. For example, the dose of a drug given to a laboratory rat might be 1.0 gram of drug per kilogram body weight. This is written as 1.0 g/kg. To put this into context, if a rat weighed 1 kg—an incredibly large rat—then it would receive 1 gram of drug. If, instead, a rat weighed 0.3 kg (a more reasonably sized rat), then it would receive 0.3 grams of drug.

For over-the-counter medications like ibuprofen (Advil), the dosing instructions assume an average adult's body weight. If the instructions describe something like "Take one to two 200 mg tablets," then the "one to two" range refers to differences in body weight between adults. A larger individual might require two tablets, whereas a smaller individual might require only one tablet. A smaller individual might also require a stronger pain-relieving effect and could take two tablets instead. A doctor's office records your weight, in part, to calculate drug dosing. If the doctor prescribes a medication, they determine the dose of a drug to prescribe partly based on your body weight.

Generally, the higher a drug's dose, the greater its effects. Researchers determine the effects of drugs by evaluating a range of different doses. This information is plotted on dose-effect curves. A **dose-effect curve** (or **dose-response curve**) depicts the magnitude of a drug effect by dose. **Figure 1.2** presents two drugs plotted on dose-effect curves.

FIGURE 1.2 ■ Dose-Effect Curves

Both drugs shown here achieve 100% effectiveness but at different doses. Drug A is the most potent because it achieves these effects at lower doses than Drug B. For Drug A, the dose at which 50% of the effect occurs (ED_{50}) is 4.0 mg/kg. The ED_{50} for drug B is 10.0 mg/kg.



For each drug in Figure 1.2, lower doses produce weaker effects, and higher doses produce stronger effects. Both drugs produce a full, 100% effect at a high enough dose. Yet, notice that both drugs achieve full effectiveness at different doses. For Drug A, 100% effectiveness occurs at an 8.0 mg/kg dose, whereas 100% effectiveness for Drug B occurs at a 16.0 mg/kg dose. In fact, the entire dose-effect curve for Drug A is located to the left of Drug B (i.e., the curves do not overlap).

To describe the position of a dose-effect curve, researchers calculate an ED_{50}. An **ED_{50}** is a value that represents the dose at which 50% of an effect is observed.[1] The "ED" stands for "effective dose."

As shown in Figure 1.2, Drug A's ED_{50} is 4.0 mg/kg. This corresponds to a dose that matches with the 50% effect point on the dose-effect curve. Nothing prevents a researcher from determining other ED values if they choose. Perhaps in their particular study, knowing, say, an ED_{75} (i.e., dose at which 75% of the effect was observed) or ED_{15} (i.e., dose at which 15% of the effect was observed), would be important. We tend to calculate ED_{50} values because they represent a middle point on the curve and thus are generally more useful for conveying a drug's effective dose range than other ED values.

ED_{50}s provide a means for comparing the potency of drugs. **Potency** refers to the amount of drug used to produce a certain magnitude of effect. Describing a drug as "highly potent" means that drug effects occur at low doses. The hallucinogen lysergic acid diethylamide, better known as LSD, is considered highly potent because small amounts of LSD—as little as 0.02 mg, so small that users may need to lick LSD powder from the glue side of a postage stamp—produce hallucinations (Greiner et al., 1958). Researchers also use potency to compare different drugs that produce similar effects.

Consider again the drugs in Figure 1.2. Drug A reaches the same magnitude of effects as Drug B, but Drug A does so at lower doses. Thus, Drug A has a higher potency than Drug B. By representing a dose-effect curve, an ED_{50} allows a way to calculate the relative level of potency between different drugs. Drug A has an ED_{50} of 4.0 mg/kg, and Drug B has an ED_{50} of 10.0 mg/kg. The potency difference is calculated from dividing Drug B, the compound with the highest ED_{50}, by Drug A, the compound with the lowest ED_{50}. In this example, we find Drug A to be 2.5 times more potent than Drug B.

When developing a new therapeutic drug, researchers must determine a drug's dose that causes unacceptable adverse effects. We refer to this dose as a *toxic dose* and can produce toxic dose-effect curves using laboratory animals as subjects just as we can produce therapeutic dose-effect curves. Researchers and regulators understand that no drug is free from a host of potential adverse effects, but certain doses of any drug will produce adverse effects too severe to justify giving to a patient even if the same dose produced therapeutic effects.

As noted, toxicity studies also produce dose-effect curves. The ED_{50} for toxic dose-effect curves is referred to as a TD_{50} (TD stands for *toxic dose*). We interpret a TD_{50} as the dose at which 50% of the subjects had the particular toxic effect in question. Researchers also determine lethal doses of drugs, based on animal studies, as a point of information regulators may need to have prior to approving drugs for humans or for veterinary medicine.

In these cases, an LD_{50} (LD stands for *lethal* dose) would be obtained. **Table 1.3** provides a list of selected compounds and their LD_{50} values. Every compound is toxic and even lethal at high enough doses—even the compound dihydrogen monoxide (also known as water). If you're interested in finding an LD_{50} value for compound, conduct an internet search for the compound's *safety data sheet* (also called a *material safety data sheet*, or *MSDS*). Safety data sheets provide key information about a compound's physical properties, exposure risks, safe disposal methods, toxicological information (including LD_{50} values from animals), and other information.

TABLE 1.3 ■ LD_{50} Values for Selected Compounds

Compound	LD_{50} dose*
Aspirin	200 mg/kg
Caffeine	192 mg/kg
Ethanol (beverage alcohol)	7,060 mg/kg
Ibuprofen	636 mg/kg
Water	90,000 mg/kg

Data obtained from Safety Data Sheets.

*Note that these amounts were determined in rats and are expressed per kilogram (for reference, adult males in the United States weigh approximately 80 kg—you would multiple the mgs by 80 kg to determine the LD_{50} amount for average adult male; an additional ratio may be necessary for converting animal dose to humans).

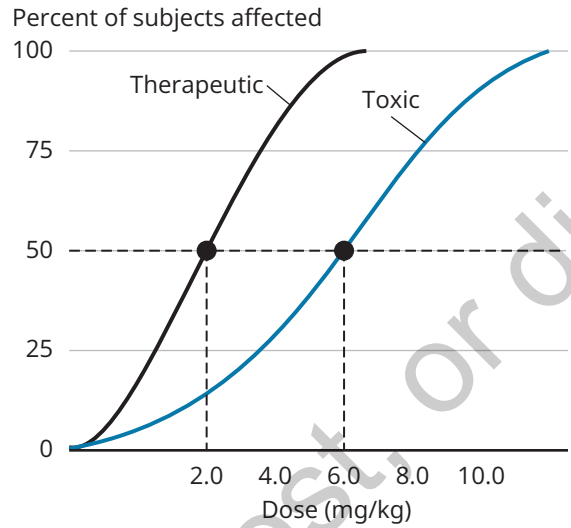
TD_{50} values allow for the determination of a therapeutic index. A **therapeutic index** conveys the distance between toxic and therapeutic doses as a ratio of a drug's toxic dose-effect curve value relative to a therapeutic dose-effect curve value. One way to calculate a therapeutic index is to divide a TD_{50} by an ED_{50}. A therapeutic index answers this question: How different is a dose that causes toxic effects in half of the subjects from a dose of the same drug that produces therapeutic effects in half of the subjects?

Although ED_{50} and TD_{50} values provide a means to calculate therapeutic indexes, these values are not ideal for identifying safe drugs. **Figure 1.3** shows a drug's therapeutic dose-effect curve and toxic dose-effect curve. The TD_{50} dose (6.0 mg/kg) is three times greater than the ED_{50} dose (2.0 mg/kg). Is that good? Notice that approximately 15% of all subjects experience toxic drug effects at the ED_{50} dose. If you look further, a fully effective therapeutic dose caused toxic effects in half of the subjects. This is clearly not a safe drug!

To avoid any overlapping therapeutic and toxic dose-effect curves, drug developers adopt a far more conservative calculation for a therapeutic index, referred to as the Certain Safety Factor. We calculate the **Certain Safety Factor** by dividing a dose that caused toxicity in only 1% of the subjects—referred to as a TD_1—by a dose that achieved a 99% therapeutic

FIGURE 1.3 ■ Therapeutic and Toxic Dose-Effect Curves

Is this drug safe to use? This drug does produce therapeutic effects at doses lower than those that produce lethal effects. In fact, the TD_{50} (TD_{50} = 6.0 mg/kg) is three times greater than the ED_{50} (ED_{50} = 2.0 mg/kg). Yet, notice that at the ED_{50} (2.0 mg/kg), approximately 15% of the subjects experienced toxic drug effects. At a dose at which full therapeutic effects were shown (6.0 mg/kg), approximately 50% of the subjects experienced toxic drug effects. Thus, although the therapeutically effective doses are lower than the toxic doses, many subjects will experience severe adverse effects—clearly this is not a safe drug to use.



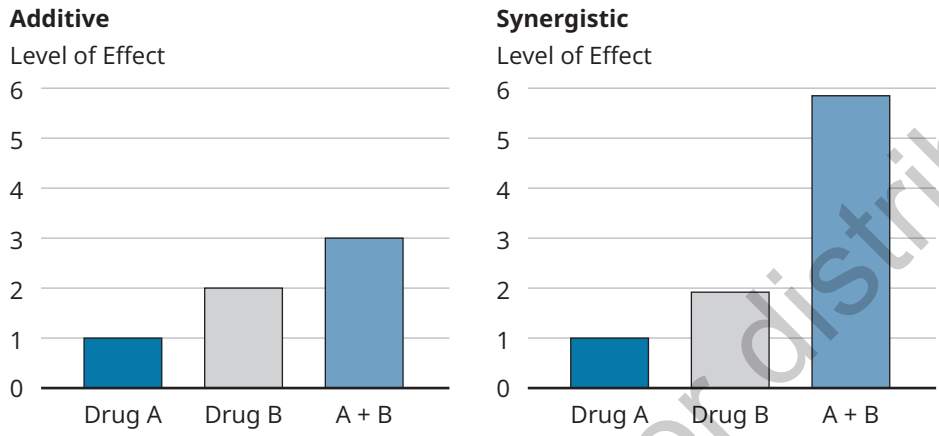
effect—an ED_{99}. Large therapeutic indexes derived from this safer calculation describe separate therapeutic and toxic dose-effect curves.

The U.S. Food and Drug Administration (FDA) and similar regulatory bodies in other countries require safe therapeutic indexes for drugs they approve. For example, the FDA would be unlikely to approve a drug with a Certain Safety Factor less than 10 (FDA, 2005a). However, this is not to say that every drug on the market has a large therapeutic index. For example, the mood stabilizer lithium has toxic doses near therapeutic doses, and for some individuals, taking only twice the recommended dosage might lead to severe adverse effects.

Drugs taken together may have addictive or interaction effects. If two drugs produce the same effect, the two given together might produce a greater effect. One type of drug interaction effect is an *additive effect* (Figure 1.4). For **additive drug effects**, the magnitude of the combined drug effect is the sum of each drug's effect alone. For example, if Drug A alone produced an increase in systolic blood pressure of 5 mmHg, and Drug B produced an increase in systolic blood pressure of 10 mmHg, then combined, an additive effect would be a 15 mmHg increase. Another type of drug interaction is *synergism*. **Synergistic drug effects** consist of a magnitude of effect beyond the sum of each drug's effect. From the previous example, drug synergism might be demonstrated if combining both drugs led to a 20 mmHg increase—well beyond the sum of each drug's effects.

FIGURE 1.4 ■ Additive and Synergistic Drug Effects

The figures illustrate additive (left) and synergistic (right) effects for two fictional drugs, Drug A and Drug B. On the left, we find the combination of both drugs reaching a level of effect (a 3 on the y-axis) that is a sum of Drug A (a 1) and Drug B (a 2).



STOP & CHECK

1. What determines whether a drug is a therapeutic or a recreational drug?
2. What are the two different names provided for therapeutic drugs?
3. What is a dose?
4. What is the safest approach for calculating a therapeutic index?

1. The manner of usage—individuals use therapeutic drugs instrumentally toward treating a disorder or ailment, whereas individuals take recreational drugs entirely to experience the drug's effects. **2.** Therapeutic drugs are provided a generic name, which refers to the organizational fit of a drug with similar acting drugs, and a trade name, which is the company's brand name for the drug. **3.** A dose is a ratio of the amount of drug per amount of body weight. Most of the instructions provided with over-the-counter drug packages advise taking pills based on an average adult weight. **4.** A Certain Safety Factor provides the safest approach for calculating a therapeutic index by dividing a toxic dose for 1% of subjects, referred to as a TD_1, by a 99% effective dose, referred to as an ED_{99}. When this calculation produces large therapeutic indexes, the toxic doses are much higher than therapeutically effective doses.

OBJECTIVE AND SUBJECTIVE EFFECTS OF PSYCHOACTIVE DRUGS

To characterize the spectrum of a drug's pharmacological effects, researchers must measure the drug's objective and subjective effects. **Objective effects** are pharmacological effects that can be directly observed by others. In other words, a researcher can view and measure the drug's effects. For example, psychostimulant drugs can affect blood pressure, which a researcher can easily measure and record (**Figure 1.5**).

FIGURE 1.5 ■ Objective and Subjective Drug Effects

Objective effects (left) are pharmacological effects that can be directly observed by others, whereas subjective effects (right) are pharmacological effects that cannot be directly observed by others; instead, a study participant may describe a drug's effects to a researcher or rate a drug's effects on a questionnaire.

(a) **(b)**

iStock Photo/kali9; iStock Photo/dima_sidelnikov

Subjective effects are pharmacological effects that cannot be directly observed by others. In other words, we cannot view or measure another's drug experience (see Box 1.1). The inability to independently observe subjective effects has certain scientific limitations. In particular, a drug's subjective effects may vary from person to person. To address this, researchers must develop a consensus about a drug's effects among many individuals and assume that this consensus accurately reflects the drug's effects for anyone else who may take the drug.

BOX 1.1: INSTRUMENTS USED FOR STUDYING SUBJECTIVE EFFECTS IN HUMANS

A drug's subjective effects help researchers understand a drug's therapeutic benefits or its potential for recreational use. The measure of subjective effects in humans relies almost entirely on *self-report questionnaires*. A self-report questionnaire for drug effects consists of a study participant noting the features and degrees of effects felt from taking a substance. When a questionnaire has a valid use in clinical characterizations or diagnoses, the questionnaire may also be referred to as an *instrument*. Commonly, self-report questionnaires use *Likert scales*. For a Likert scale, a participant rates the magnitude of attitudes or perceptions about a description of a feeling, viewpoint, or event. Often, Likert scales present an individual with a range of choices, from *strongly disagree* to *strongly agree* or similar terms.

In practice, we find Likert scales employed to assess the degree of feelings a person experiences or specific effects from a psychoactive drug. A well-known instrument for gauging an individual's current mood state is the Profile of Mood States Questionnaire, often referred to by the acronym POMS. A clinician can use the POMS to rate a client's degree of agreement with a feeling or emotion, using terms such as *energetic* or *on edge* (**Box 1.1**, **Table 1.4**). Rating options for these statements range from "not at all" to "extremely" on the POMS (McNair et al., 1971). As an example, a study conducted by Johanson and

Uhlenhuth (1980) used the POMS for study participants they treated with the anti-anxiety medication diazepam (Valium, a type of benzodiazepine covered later in this book). After 1–3 hours following administration, respondents endorsed feelings related to fatigue and confusion and were less likely to endorse feelings related to vigor.

TABLE 1.4 ■ Selected Mood State Terms Used on the Profile of Mood States Questionnaire

Rate the following from 0 "Not at all," 1 "A Little," 2 "Moderately," 3 "Quite a Lot," and 4 "Extremely"			
Tense	Confused	On Edge	Competent
Angry	Proud	Grouchy	Annoyed
Worn out	Sad	Unable to Concentrate	Miserable
Hopeless	Energetic	Nervous	Active

Source: Adapted from McNair, D. M., Lor, M., & Doppleman, L.F. (1971). Educational and industrial testing service. Educational and Industrial Testing Service.

For studies involving recreational substances, researchers often assess how much participants enjoy the effects of a drug. To do this, many studies use a *"liking" scale*, asking participants to rate, from strongly disliking to strongly liking, the effects felt from a substance administered to them by the researchers (in a safe, controlled laboratory setting). These scales may have labels drawn on a horizontal line, allowing a study volunteer to mark the degree of liking for a drug's effects on the line. For this approach, we refer to these instruments as having *visual analog scales*. For example, Soria and colleagues (1996) used visual analogy scales to assess the subjective effects of nicotine in smokers and nonsmokers. Smokers, on average, placed marks around 50 mm for lines that ran from 0 mm to 100 mm to rate nicotine's "good effects." Nonsmokers, in contrast, placed marks around 15 mm.

Researchers also can ask how a drug's effects compare to those produced by other substances. One of these instruments is the Addiction Research Center Inventory (commonly referred to by the acronym ARCI), which consists of questions that coincide with effects produced by classic recreational or abused substances. For example, Soria and colleagues (1996) used the ARCI in their assessments of nicotine in smokers and nonsmokers. Smokers reported that nicotine produced positive effects, somewhat like morphine and Benzedrine, and nonsmokers reported disorienting effects and "weird feelings," somewhat like the drug lysergic acid diethylamide (better known as LSD).

Despite some scientific limitations, a psychoactive drug's subjective effects are often more important for understanding why a drug is used than its objective effects. Subjective effects explain the purpose of recreational and addictive drug use. Subjective effects also explain the therapeutic value of antidepressant, anti-anxiety, and antipsychotic drugs. Only the patient can say whether medications truly help reduce depressed feelings, anxiety, and paranoid thoughts.

STOP & CHECK

1. What is the challenge in studying subjective drug effects?

1. Subjective effects represent an individual's personal and nonpublicly observable effects from a drug, including how a person feels after taking the drug. We must rely entirely on self-reported drug effects. Yet for recreational drugs, subjective effects are the most important to characterize and understand.

STUDY DESIGNS AND THE ASSESSMENT OF PSYCHOACTIVE DRUGS

The logic behind study designs provides the means to assess a drug's behavioral effects. Studies attempt to answer scientific questions about drug effects and the nervous system by using dependent and independent variables. A **dependent variable** is a study variable measured by a researcher. In psychology, dependent variables usually consist of behavioral measures, such as how many words an individual recalls from a list or an evaluation of one's level of depression.

Independent variables are study conditions or treatments that may affect a dependent variable. Independent variables for the previous examples might include teaching individuals a memorization technique or providing depressed individuals an antidepressant drug. In each case, researchers sought to determine whether an independent variable produced changes to a dependent variable.

Experiments

Research studies fall into two categories: experimental and correlational (see **Table 1.5**). In an **experimental study**, investigators alter an independent variable to determine whether changes occur to the dependent variable. For example, many clinical studies use experiments to evaluate drug effects. In a standard experimental study design, individuals sharing a type of disorder are separated into two groups: a control group and a treatment group. The treatment group receives the treatment, and the control group does not. Instead, the control group may be given a **placebo**, or a substance identical in appearance to a drug but physiologically inert. If individuals in the treatment group improve over the course of this study, and those in the control group do not, then researchers attribute improvements to the treatment. Experiments such as these indicate that the independent variable *caused* changes to the dependent variable.

TABLE 1.5 ■ Correlational and Experimental Studies

Study Type	Description
Correlational study	No alteration of study conditions. Changes in study variables are observed, and relationships are inferred.
Experimental study	Researchers alter a study's independent variable and observe changes in a dependent variable. Experiments can identify causal relationships between an independent variable and a dependent variable.

Experiments use random sampling to assign participants to study groups. Through random assignment, researchers seek to achieve groups that have similar characteristics. Many experiments also use blinding procedures to eliminate potential biases by study participants or investigators. In a **single-blind procedure**, researchers do not inform study participants which treatment or placebo they received. To provide informed consent, study investigators provide participants a description of treatments that might be administered, as well as the potential for placebo administration, but they do not identify the assigned treatment to participants during the study.

In a **double-blind procedure**, neither the participants nor the investigators know the treatment assignments during the study. These procedures not only prevent potential biased responses from participants but also prevent potential biased judgments by study investigators. Although researchers consider blinded procedures important for quality experimental studies, not all experiments allow for blinded procedures.

In clinical research, an **open-label study** refers to the assignment of study treatments without using blinded procedures. Open-label studies apply to situations in which disguising study medications may have serious ethical consequences or be impractical. For example, many cancer clinical trials use open-label procedures because withholding a potential effective treatment from cancer patients by using a placebo might have serious health consequences.

Correlational Studies

In a **correlational study**, an investigator determines if the changes in one variable are associated with changes to another variable. Generally, a correlational study identifies one of the variables as an independent variable,[2] but the conditions of this variable are not altered like they are for an experiment. For example, to study the effects of long-term MDMA use on memory, a researcher might recruit participants who used MDMA and then measure each participant's ability to recall words from a list. We could use the duration of MDMA use as the *independent variable*, and each participant's level of memory serves as the *dependent variable*. The investigators did not alter the independent variable but instead studied duration of MDMA use and memory ability as conditions that already existed. Researchers might infer a relationship between MDMA use and memory if long-term MDMA users exhibited poor word recall and if infrequent MDMA users exhibited good word recall. But, it is important that correlational studies do not indicate that a variable *causes* changes to another variable.

VALIDITY AND THE INTERPRETATION OF STUDY FINDINGS

Say you conducted an experiment and found that a newly developed drug reduced symptoms of depression. Great news, but what can you actually infer from these study results? This question addresses the quality of study procedures, the appropriate choice of species tested, the ability to extend these findings to other individuals with the disorder, and many other possible issues. Researchers must address such questions to draw *valid inferences* from a study's findings (Elmes et al., 2006).

College courses on research methodology and design devote considerable time to discussing valid inferences, and they do so in much greater detail than is considered here. For our interests, let's consider some basic types of validity and think about how the issue of validity can affect studies in psychopharmacology. The types of validity we discuss are internal validity, external validity, face validity, construct validity, and predictive validity (**Table 1.6**).

TABLE 1.6 ■ Types of Validity

Validity	Description
Internal validity	Adequacy of controlling variables that may influence a dependent variable
External validity	Ability to extend findings beyond study conditions
Face validity	Test appearing to measure what a researcher considers it to measure
Construct validity	How well a study's findings relate to the underlying theory of a study's objectives
Predictive validity	Ability of model to predict treatment effects

Internal validity refers to the control of variables with potential to influence a dependent variable. Ideal experiments arrange conditions so that only changes to the independent variable will cause changes to the dependent variable. Without appropriately arranging conditions, other variables, referred to as *confound variables*, can cause changes to the dependent variable.

For example, a study designed to test new drugs for depression may involve patients checking in with a clinic physician every morning. After several weeks, the study results indicate a reduction in depression. Might this study have confound variables?

The daily clinic visits are a potential confound variable. The act of talking to a physician daily about depressive symptoms in a clinical setting may have been sufficient to reduce depressive symptoms in this study. Without considering potential confound variables such as these, study investigators risk wrongly concluding that an experimental drug produces therapeutic effects.

To avoid potential confound variables, researchers blind participants to the study medications, and they may also assign a placebo to a participant group. Placebo groups control for many confound variables. If placebo-treated patients also exhibited reduced depression, then we conclude that variables other than the study medication caused reductions in depression.

External validity refers to how well study findings generalize beyond the study conditions. Study samples serve as a key factor in external validity. Studies with strong external validity likely have samples comprised of individuals demographically well represented, such as participants drawn across different genders, races, ages, cultures, and geographic regions. For example, many clinical antidepressant studies examine only adults. Such studies have poor external validity for antidepressant effects in children because they lack evidence of an antidepressant's effectiveness in children. Sample participant representation concerns persist in large part due to limited access researchers may have to participants who have the correct clinical conditions of interest and also happen to come from a wide variety of demographic backgrounds. In a study

that assessed male and female gender representations in human research, Barlek et al. (2022) found that among registered U.S. clinical trials comprising more than 4.7 million study participants, males made up greater than half (56%). Relatively few of the studies had more female than male participants.

External validity also presents limitations for predicting treatment effects in humans from studies conducted in animals. One example of this occurred with the drug thalidomide in the 1950s. Thalidomide induced sleep and prevented nausea and vomiting. For these reasons, pregnant women received thalidomide to aid with severe morning sickness However, thalidomide proved harmful for human fetal development. By 1962, nearly 10,000 babies had been born with missing fingers, toes, and limbs after exposure to thalidomide during pregnancy.

Why did pharmacologists consider this a safe drug for pregnant women? In humans, thalidomide was metabolically transformed into a **teratogen**, a substance harmful to a fetus.

This metabolic transformation did not occur in mice, the animals studied in thalidomide experiments. Had drug developers tested thalidomide in rabbits, which do convert thalidomide into this teratogen, doctors would not have prescribed thalidomide to pregnant women. Thus, in this case, rabbits, not mice, provide proper external validity for this property of thalidomide (Goldman, 2001). Proper drug screening requires a thorough examination of drugs using many different models and approaches, including a variety of animal species.

Face validity refers to the appearance of a test measuring what a researcher considers it to measure. For example, researchers study drugs for Alzheimer's disease by testing mice with memory deficits. Memory deficits are a prominent symptom of Alzheimer's disease. Thus, testing memory in mice offers face validity for Alzheimer's disease. Sometimes, animal models offer no face validity. In particular, testing antipsychotic drugs for treating schizophrenia, a disorder in which individuals can experience auditory hallucinations among many other symptoms, must often be tested in models lacking face validity. That is, we lack animal models for paranoia and hearing voices.

Construct validity addresses how well a study's findings relate to the underlying theory of a study's objectives. Testing new drugs for Alzheimer's disease in Alzheimer's patients offers high construct validity; that is, the drug is tested in an individual who has the disease to be treated, including all of the genetic causes of Alzheimer's disease and the resulting damage to cells in the brain. Yet, we must first screen experimental drugs in animals to ensure their safety and potential effectiveness before testing novel drugs in humans.

Testing such drugs in normal mice, which lack genetic and biological features of Alzheimer's disease, leads to construct validity concerns because normal mice do not have any of the genetic and biological features of this disease in humans. After all, the objective for such a study would be to find the model most similar to Alzheimer's disease to use it for identifying potential treatments. However, researchers have developed genetically altered mice that have certain protein abnormalities similar to those found in Alzheimer's disease. Testing treatments for Alzheimer's disease in these mice provides greater construct validity than testing these treatments in normal mice.

Predictive validity addresses how well a model predicts treatment effects. To continue the preceding example, an experimental drug might improve memory in certain genetically altered mice and later prove to treat Alzheimer's disease. If this were the case, then these mice offer predictive

validity for screening Alzheimer's disease medications. At times, an experimental procedure might offer high predictive validity but fail to offer face or construct validity. Many animal models for antipsychotic drugs fail to exhibit features of schizophrenia, yet antipsychotic drugs produce unique behaviors in these models that scientists have learned predict certain clinical effects in humans. Drug developers rely on models with high predictive validity when screening experimental drugs.

Experimentally well-designed studies using reliable models likely offer many types of sound experimental validity. Going back to the mice with neurobiological features of Alzheimer's disease, a study that uses both affected and normal mice could be used to evaluate an experimental drug treatment and also a well-established clinically effective drug treatment as a comparison drug. Perhaps neither compound improves memory in the normal mice (after all, these mice have normal memory function), but both improve memory performance in the affected mice. Further, the placebo conditions for both drugs have no effect, and the improvements in memory (again only in the affected mice) go along with increases in the drug doses. The use of different control groups (different types of mice plus the use of a placebo condition) shows some elements of a well-designed study (internal validity), and mice with Alzheimer's-like neurobiological deficits provides construct validity. The affected mice, like Alzheimer's disease patients, show memory deficits (face validity), and the improvement in memory by a well-established treatment for Alzheimer's disease suggests that the model can be used to identify new treatments for this disease (predictive validity). Do we have good external validity? Perhaps to some extent, but animal models inherently have limited external validity for human treatments. If we learned that this study used both male and female mice, and perhaps also used older adult mice, then we might argue that such a study has better external validity compared to one using only male mice and young adult mice. Thus, this example provides multiple types of good experimental validity.

STOP & CHECK

1. How is a correlational study different from an experiment?
2. Why is external validity an important concern for animal experimentation?

1. Correlational studies identify potential associations between variables, whereas experiments identify causal relationships between variables. **2.** Important physiological differences exist across all species, and these differences may not accurately reflect a drug's actions in humans.

ETHICAL CONSIDERATIONS IN RESEARCH

Ethics plays another important role in psychopharmacology research. In particular, experimental treatments may cause serious adverse effects or simply be ineffective. Thus, participants may be exposed to a dangerous medication and, more than this, may experience no improvement

in their symptoms. Ethically, and fortunately also legally, researchers engage in years of testing and development before testing a potential treatment in humans.

To develop drugs for human usage, medical research relies heavily on animal testing. Not only do medical research advances depend on animal models, but governmental regulators, such as the FDA, also require proof of extensive animal research before approving drugs for human testing. Medical advances rely on animal research for two major reasons: a lack of feasible alternatives and the ability to predict drug effects in humans.

A Lack of Feasible Alternatives to Animals

Treatment results from studies conducted only on cells and tissues poorly predict treatment efficacy and safety in humans. Although these biological studies provide important steps in medical development, they fail to model the complexity of living organisms. This complexity currently precludes computer simulations or mathematical models from taking the place of animal research. Thus, animal models provide a necessary step in discovery and drug development.

Humans also do not provide a feasible alternative to animal models. Necessary basic research procedures consist of invasive techniques that would be highly unethical to perform in humans. For example, many medical studies require measuring drug-induced changes in cells and tissue by inserting probes into the brain. In addition to invasiveness, experimental drugs that have not been tested in animals carry a risk of severe and possibly irreversible adverse effects in humans. Animal testing prevents dangerous experimental drugs from being tested in humans.

High Predictive Value for Drug Effects in Humans

Beyond having no feasible alternatives, animal models do well in predicting drug effects in humans despite inherent challenges for external validity (as noted earlier in this chapter). During drug development animal models identify effective drugs from the hundreds or thousands synthesized in a drug development program. The FDA requires that all experimental medications be screened in animal models before testing drugs in humans to ensure that there is a reasonable likelihood of improving a disorder in humans. For this same reason, the FDA requires screening for adverse effects in animal models, given that adverse effects occurring in animals may likely occur in humans as well. At the end of this chapter, the "From Actions to Effects" section describes the role that animals play in therapeutic drug development programs.

One challenge for predictive validity in animal research is an overreliance on male research subjects. In one review of scientific journals in the areas of neuroscience, physiology, and pharmacology (including psychopharmacology), only 15% of journal articles used both male and female animal subjects (Beery & Zucker, 2011). The vast majority of these animal studies used male subjects often to reduce influence of sex hormones, which vary more frequently in females, on physiological or behavioral factors. Otherwise, animal studies using only male or female subjects, but not both, were often considered generalizable to the opposite sex, which precluded assessments directly comparing male and female subjects (Karp & Reavey, 2018). We currently see a strong shift toward reducing sex bias in animal research due to changes in expectations

among scientists who provide peer review of scientific reports (i.e., journal articles) and the requirements of research granting agencies, such as at the National Institutes of Health.

The Regulation of Animal Research

Governmental and private agencies exist to oversee the responsible and humane use of animal subjects for research or teaching purposes. Publishers of journals, where scientists report their studies, play a role by insisting that findings produced from animal research followed appropriate regulations and policies. In short, all legitimate journals publishing scientific studies require high ethical standards for animal care and use in research.

U.S. federal regulations require institutions to have an Institutional Animal Care and Use Committee (IACUC). This requirement not only pertains to academic institutions but also to industry, such as pharmaceutical companies. The FDA will not approve any treatments resulting from animal studies that have not complied with federal regulations and policies (FDA, 2002).

The IACUC oversees an institution's entire animal care and use program, including quality of housing, veterinary practices, and research practices. All animal experiments require IACUC approval before they begin. To gain approval, researchers must submit animal research proposals to the IACUC. The IACUC then reviews these protocols and determines their abidance with federal and internal policies. Moreover, the IACUC makes ethical judgments according to the "3 Rs."

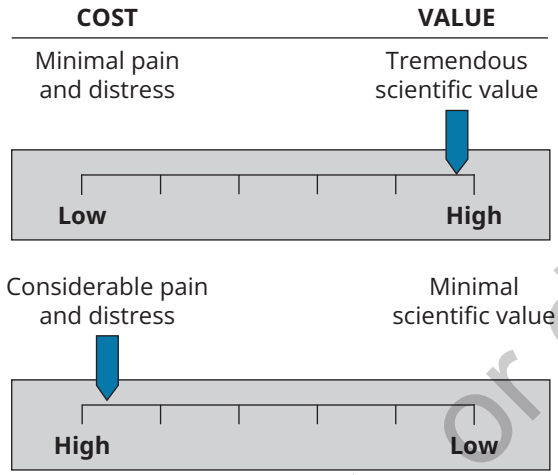
The 3 Rs stand for *replacement, reduction*, and *refinement*, and serve as a basis for determining whether a researcher needs to use animals for a study and, if so, the extent and nature of this research (National Research Council, 2011; Russell & Burch, 1959). For the first R, *replacement*, the IACUC assesses the necessity of using animals for a proposed study by asking, "Can animals be replaced with something else?" Sometimes, equally useful findings may be derived by working only with cells or perhaps with invertebrates (e.g., insects) instead of using animals. An IACUC will reject animal research proposals when such feasible alternatives exist.

The second R, *reduction*, refers to using the minimum number of animals necessary to achieve the study objectives. Generally, IACUCs use statistical methods to ensure that researchers use only the minimum number of animals necessary to detect experimental results. For the third R, *refinement*, the IACUC attempts to minimize any pain and distress experienced by the study animals. These attempts may include changing experimental procedures, requiring analgesic drugs to reduce pain, or using different testing equipment.

IACUCs also weigh the proposed study's ethical costs. **Ethical cost** assessments weigh the value of potential research discoveries against the potential pain and distress experienced by research subjects (**Figure 1.6**). For example, IACUC members easily justify painless experiments in animals that aim to develop treatments for lethal illnesses. Essentially, these studies provide tremendous gains with minimal ethical cost. However, IACUC members cannot justify studies with limited potential for discovery that use highly painful procedures (Carbone, 2000).

FIGURE 1.6 ■ Ethical Costs for Animal Research

During IACUC review, researchers weigh the potential pain or distress experienced by an animal against a study's potential value. In the top panel, the scientific value outweighs the minimal pain or distress experienced by animals, whereas the bottom panel shows that the scientific value fails to outweigh considerable pain and distress expected for the animals.



Researchers Consider Many Ethical Issues When Conducting Human Research

Like animal studies, ethics committees review research practices in humans to ensure federal regulatory and policy compliance and to weigh the ethics of proposed human studies. Beyond the obvious species differences, human and animal research differs in the ability to provide informed consent. **Informed consent** consists of a participant's agreement to enroll in a study after having a thorough understanding of a study's procedures, possible gains, and potential risks. In other words, human participants know what they are getting into and can freely decide to enroll in the study. Animals, of course, cannot provide informed consent (Swerdlow, 2000).

However, some human participants also lack the capacity to provide informed consent. For example, young children lack the ability to understand what may happen during a medical study. Or, an adult may be mentally incapable of providing informed consent. In these cases, informed consent is left to a legal guardian.

The informed consent principle is a relatively modern one, and there is a long history of human experimentation conducted either against the will of the participants or with complete dishonesty about what was being studied. The Nuremberg Principles, which arose from the Nuremberg Trials after World War II, consist of some of the first written statements about the ethical conduct of human research. These principles provided the foundation for the Declaration of Helsinki, another set of guidelines for ethical research using humans.

U.S. federal regulations require that U.S. institutions review and approve all human research in accordance with these federal regulations. U.S. institutions must also file annual reports on human research activities. The penalties for violating government regulations and policies may range from fines to freezing an institution's federal research funding.

STOP & CHECK

1. Why are animal models valuable?
2. When evaluating animal research proposals, what considerations are made in an ethical cost assessment?
3. Aside from species differences, what is the major distinction between human and animal research?

1. Although animal models present important experimental validity challenges, animal models remain the only feasible models because they are effective and provide ways to evaluate drugs under carefully controlled conditions. **2.** By considering ethical costs, an IACUC weighs the benefits of a research proposal against the potential pain and suffering experienced by animal subjects. **3.** Humans can provide informed consent whereas animals cannot.

FROM ACTIONS TO EFFECTS: THERAPEUTIC DRUG DEVELOPMENT

Academic, government, and pharmaceutical company research contributes to the development of therapeutic drugs (e.g., Blake et al., 2006). For the most part, academic and government research consists of basic research discoveries about disorders and the development of theoretical directions for designing new treatments. This work may include characterizing a disorder's effects on the nervous system or developing a theory about chemical structures that mimic chemicals in the nervous system. Although some institutions develop new treatments, the vast majority of new treatments arrive from pharmaceutical companies.

Pharmaceutical drug research and development generally occur in several stages (Blake et al., 2006; Dingemanse & Appel-Dingemanse, 2007; Jenkins & Hubbard, 1991) (see **Table 1.7**). First, a company usually decides for which disorder to develop a treatment. This decision includes carefully considering opinions from scientists, outside consultants, and business executives. These individuals seek to develop a feasible treatment that yields a reasonable likelihood of making a significant profit. The likelihood of a profit coincides with a disorder's prevalence and the amount of scientific knowledge available about a disorder.

TABLE 1.7 ■ Stages of Therapeutic Drug Development

Stage	Purpose	Description
1.	Identify disorder to treat	Decisions include feasibility and profitability concerns.
2.	Drug synthesis	Chemists synthesize experimental compounds.
3.	Biological experimentation	High-throughput screening methods provide basic biological information about compounds. Results are sent to chemists and guide synthesis of further compounds.

(*Continued*)

TABLE 1.7 ■ Stages of Therapeutic Drug Development (*Continued*)

Stage	Purpose	Description
4.	Focused screening methods	Focused testing occurs with most promising compounds identified during Stage 3.
5.	Safety pharmacology	Tests identify adverse effects and toxic doses.
6.	Clinical trials	Most effective and safest compounds tested from previous stages are tested in humans. Regulatory approval sought after positive clinical findings.

Drug synthesis occurs during the second drug development stage. During this stage, a company's chemists develop experimental compounds. To do so, they may develop variations of existing therapeutic drugs for a disorder or develop drugs based on established theories.

Third, the drugs produced by the chemists during Stage 2 are tested in biological experiments. For example, researchers may assess how well experimental drugs bind to certain proteins in tissue samples. During this stage, researchers prefer using **high-throughput screening** methods—rapid testing processes involving a large number of experimental drugs (Garrett et al., 2003; Szymański et al., 2012). Generally, high-throughput tests provide quick results and can determine whether the experimental drugs appear to be achieving a desired biological effect.

Chemists receive these test results and use the information to develop more experimental drugs. The most on-target drugs from the previous batch of experimental drugs serve as the best directions for synthesizing the next series of drugs. The chemists then send the newest drugs back to the high-throughput screeners. The back-and-forth continues as each new series of drugs comes closer to achieving a particular biological effect. When a drug meets the researchers' goal for a biological effect, then drug testing moves to the next stage of development.

Stage 4 represents a shift from high-throughput screening methods to highly focused screening methods. Compared to high-throughput screening methods, these screening methods are slower but offer greater precision about a drug's effect. In particular, researchers use models that have face, construct, or predictive validity. Often, these methods include animal models.

After drugs pass through tests in Stage 4, researchers determine a drug's adverse effects. Thus, Stage 5 consists of **safety pharmacology** testing, or screening processes that identify a drug's adverse and toxic effects (Guillon, 2010; Szymański et al., 2012). Adverse effects include mild to serious physiological effects, addiction risks, and changes in mental functioning. As noted in the chapter, we identify adverse effects too severe to warrant exposing patients to toxic effects. Safety pharmacology tests seek to identify a drug's toxic doses.

Many drugs determined successful in earlier stages of screening reveal a low therapeutic index during safety pharmacology testing—that is, the same doses that produce therapeutic effects are near those that produce toxic effects. For drugs to meet clinical testing approval from governmental regulatory agencies such as the FDA, safety pharmacology tests must demonstrate that a drug's toxic doses are much higher than its therapeutic doses.

Stage 6 of drug development involves human drug testing. Most drugs fail to make it to this stage, having been abandoned because of a lack of efficacy or poor safety. A **clinical trial** is a government-approved therapeutic drug experiment in humans. Clinical trials describe the number of treatments and doses provided to groups of study participants as **treatment arms**. For example, a two-arm design refers to two experimental groups. Often, one group of participants receives an experimental drug, and the other group receives a placebo. A **clinical study report** details a clinical study's design and results (International Conference on Harmonization, 1996).

In the United States and other countries, different phases describe the progression of experimental testing throughout the clinical trial process (**Table 1.8**). Clinical trials begin at Phase 1 and progress through Phases 2 and 3 as long as a drug continues to prove safe and effective. The FDA may request a Phase 4 trial after approving a drug for market to further assess the efficacy and safety of the drug (National Institutes of Health, 2012).

TABLE 1.8 ■ Clinical Trial Phases

Clinical Trial Phase	Goals	Dose and Duration of Treatment	Participants Involved
Phase 1	Determine a drug's most likely and frequent adverse effects to occur during treatment	Low dose of the drug given short term	Normally healthy volunteers if feasible
Phase 2	Determination of therapeutic effectiveness; experimental drug may be compared to standard medical treatment; adverse effects continue to be monitored	May be higher dose of drug but still given short term	Participants with disorder to be treated
Phase 3	Further determination of therapeutic effectiveness; experimental drug may be compared to standard medical treatment; adverse effects continue to be monitored	Dose selected based on Phase 2 results but likely given long term	Participants with disorder to be treated but more inclusive for other populations and those with coexisting conditions
Phase 4	Occurs after FDA approves a drug for the market; might address remaining questions or concerns about the drug; goal is to further determine features of a drug's therapeutic effectiveness and adverse effects	Dose selected based on Phase 3 results but likely given long term	Participants with disorder to be treated; might focus on unique effects in different populations or certain other medical conditions; choice of participants may come from results of Phase 3

The primary goal of a Phase 1 clinical trial is to determine a drug's safety in humans. Phase 1 clinical trials employ a low dose of drug and provide it to healthy human volunteers if feasible or to a specific patient population for a short period of time. For example, a new pain-relieving drug might first be given to healthy human volunteers, whereas a new cancer-treating drug might need to be given to cancer patients, but perhaps only to those with a specific type of cancer. Clinical investigations will not continue with the compound if it is found unsafe in Phase 1.

During Phase 2 clinical trials, researchers primarily seek to measure a drug's therapeutic efficacy by recruiting volunteers with the disorder to be treated. Phase 2 clinical trials tend to use larger doses that are administered short term but perhaps longer than Phase 1. These trials often include for comparison an FDA-approved drug that is normally considered to be a standard medical treatment for the disorder. Through using a comparison drug, drug developers determine how well their drug will compete with others on the market. A company may see no benefit to continuing clinical trials for an experimental drug found only as effective as drugs already on the market.

Phase 3 clinical trials provide greater information about the drug's therapeutic effects and potential adverse effects. These trials rely on results from Phase 2 to determine the selection of drug doses (kept the same or adjusted higher or lower) and normally have a longer duration of drug treatment. Moreover, researchers recruit study participants to have a greater diversity of human populations and health backgrounds than those in previous trials. The FDA grants market approval to drugs deemed safe and effective after Phase 3, although the FDA may request further monitoring after the drug goes to market. Further monitoring occurs during Phase 4 clinical trials, which may be designed to address any remaining questions or concerns from earlier phases. Thus, Phase 4 trials may employ higher doses, use longer durations, or focus on some specific human population or coexisting health condition. For example, a drug for treating nicotine use disorder might be further examined in Phase 4 trials in those with this disorder who are also clinically depressed. The approximate cost for bringing a drug through the research and development process and eventually onto the market is $2.6 billion (Mullard, 2014).

STOP & CHECK

1. What most likely happens after the first time drugs are initially screened?
2. Why might an effective and safe drug be removed from clinical trials?

1. Usually, chemists take data from the first screened batch and make further chemical compounds. The interplay between the chemists and the high-throughput screeners continues until the best drugs are made. **2.** Sometimes, drugs are removed from clinical trials because they fail to be more effective than drugs that are already on the market. A company may decide there's no profit to be made in this case.

CHAPTER SUMMARY

Psychopharmacology is the study of how drugs affect mood, perception, thinking, or behavior. The field bridges psychology and pharmacology. Psychoactive drug use is highly prevalent in society. Learning about psychopharmacology provides a greater understanding of behavior and how mental disorders are treated. Defined as substances that alter physiological functioning, drugs are known by generic, brand, chemical, and street names. Drug amounts used are described as doses, and researchers evaluate treatments by their doses for therapeutic effects and also doses for toxic effects. Drugs fall into two categories: therapeutic and recreational. However, many drugs cross both categories, depending on their usage. Researchers study the objective and subjective effects of drugs in studies that address the importance of drawing valid inferences from study results. Drug studies often employ either animal or human subjects in abidance with regulatory and ethical guidelines. The drug development process for inventing new drug treatments begins with the decision to pursue a disorder and then proceeds through stages, including drug synthesis, tests for efficacy and safety, and finally human clinical trials.

KEY TERMS

Additive drug effects
Brand name (trade name)
Certain Safety Factor
Chemical name
Clinical study reports
Clinical trial
Construct validity
Correlational study
Dependent variable
Dose
Dose-effect curve (dose-response cure)
Double-blind procedure
Drug
Drug misuse
ED_{50}
Ethical cost
Experimental study
External validity
Face validity
Generic name
High-throughput screening
Independent variable
Informed consent
Instrumental drug use
Internal validity
Objective effects
Open-label study
Placebo
Potency
Predictive validity
Psychopharmacology
Psychoactive drugs
Psychotropic drug
Recreational drug use
Safety pharmacology
Single-blind procedure
Street name (slang name)
Subjective effects
Synergistic drug effects
Teratogen
The 3 Rs
Therapeutic index
Treatment arms

2 THE NERVOUS SYSTEM

LEARNING OBJECTIVES

- **2.1** Explain the components and functions of cells in the nervous system.
- **2.2** Identify the features and functions of structures and systems in the nervous system.
- **2.3** Discuss the function of cerebral blood flow and cerebrospinal fluid.
- **2.4** Describe the function of genes and their impact on cells.
- **2.5** Explain the process of using CRISPR genetic technology.

The study of psychoactive drugs requires knowledge about how drugs act on the nervous system. This chapter provides a basic overview of the nervous system with an emphasis on cells and structures important for psychoactive drugs.

CELLS IN THE NERVOUS SYSTEM

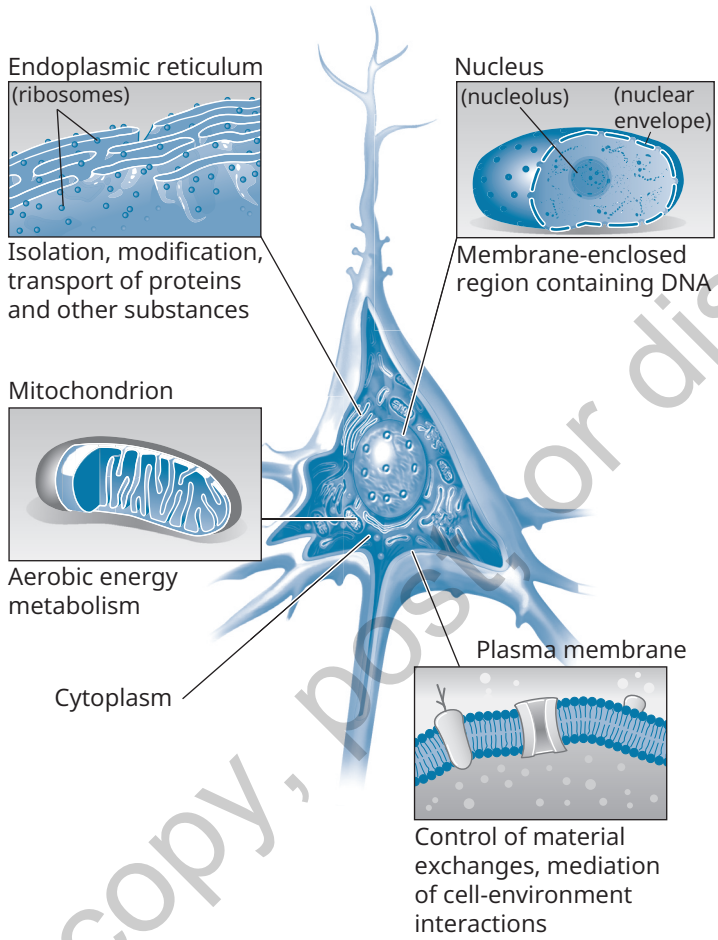
Each structure of the brain contains a dense ensemble of neurons and glial cells. **Neurons** are specialized cells in the nervous system that control behavior, convey sensory information, and signal movement. Neurons communicate by receiving and transmitting information to neurons and glial cells in the nervous system via chemicals called *neurotransmitters* (covered in Chapter 3). **Glial cells** support the function of neurons. General estimates give the brain approximately 86 billion neurons and just as many non-neuronal cells, including glial cells (Herculano-Houzel, 2012).

Neurons

Neurons comprise dense communication networks in the brain. These networks support the function of individual brain structures and facilitate communication among structures. Like other cells in the body, neurons have basic characteristics such as a membrane, nucleus, ribosomes, and an endoplasmic reticulum. These particular components are found within the **soma**, the body of a neuron (**Figure 2.1**).

FIGURE 2.1 ■ Soma of a Neuron

The soma of a neuron contains the basic components of cells.

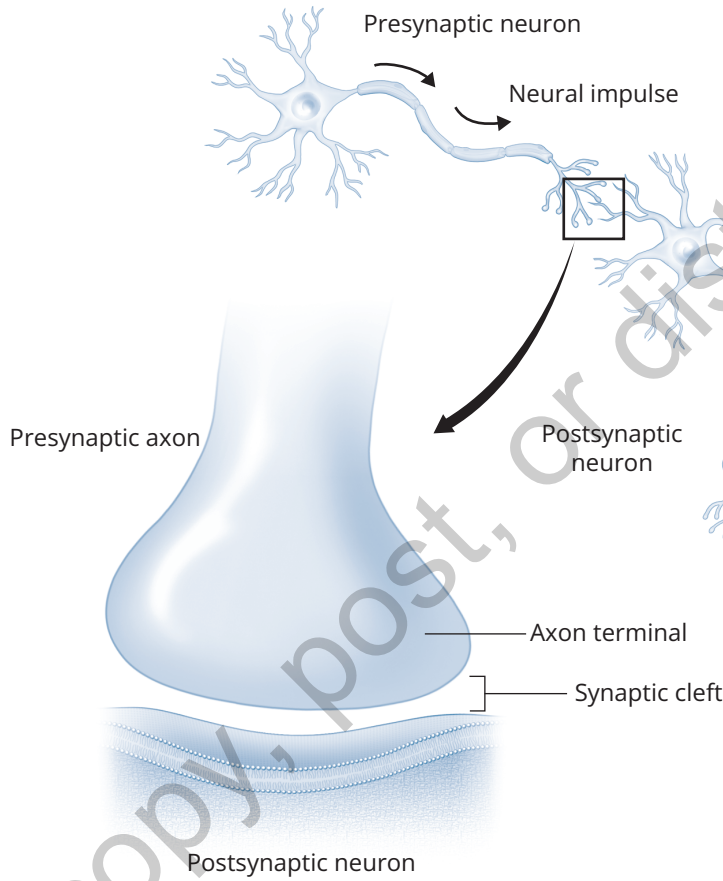


Neurons have four major components: a soma, dendrites, axon, and axon terminal (**Figure 2.2**). Generally, a neuron has many dendrites that branch off from the soma. The **dendrites** of a neuron receive information from other neurons. Small stems called *dendritic spines* grow along the length of dendritic branches. The membranes of dendrites and dendritic spines contain proteins called *receptors* that neurotransmitters can activate. When activated, receptors cause changes in the functioning of the neuron.

Axons release neurotransmitters for signaling with other neurons. Most neurons have only one axon, which branches from the soma, usually opposite from the dendrites. An axon begins at a part of the soma called the *axon hillock* and ends with multiple branches containing axon terminals.[1] These branches are called *axon collaterals*. An axon terminal contains and releases

FIGURE 2.2 ■ Major Components of a Neuron

The four major components of a neuron are the soma, dendrites, an axon, and an axon terminal. Dendrites receive information, and axons send information.



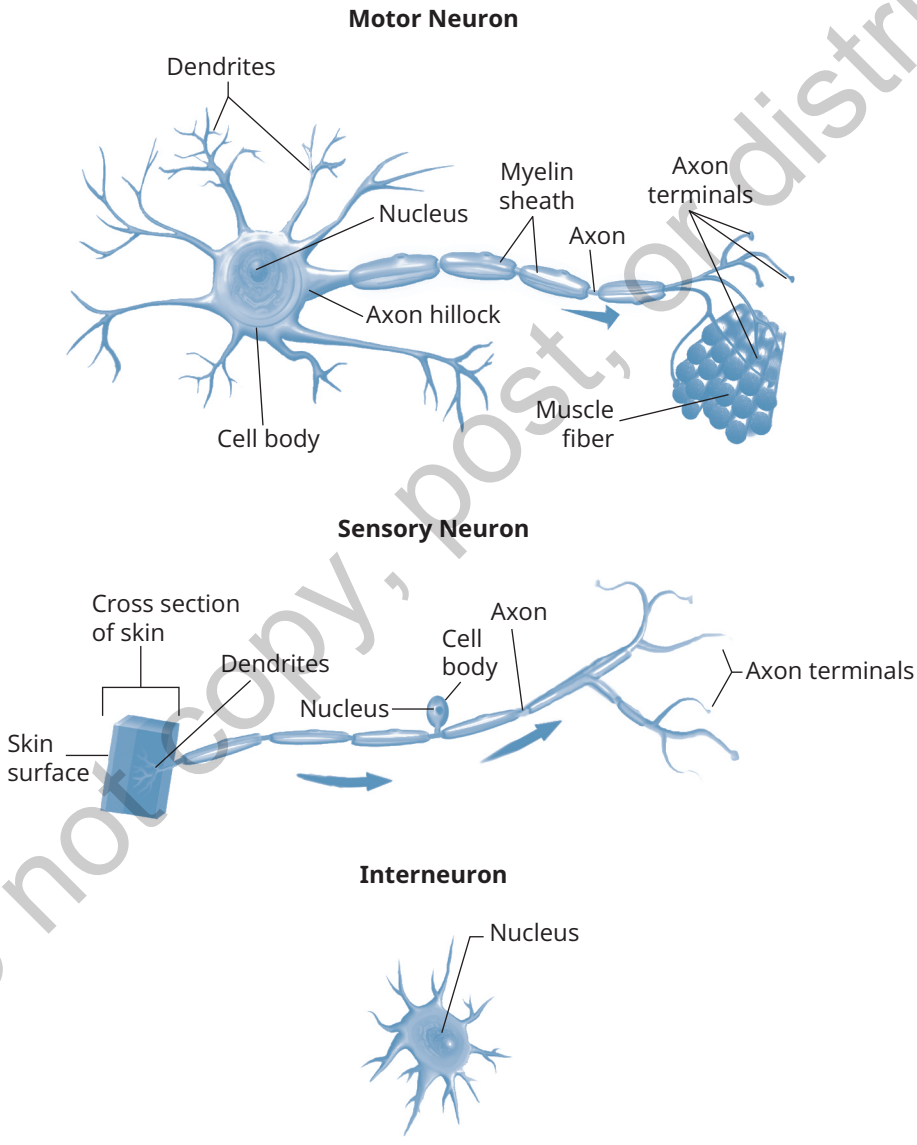
neurotransmitters near a part of a dendrite called a *postsynaptic terminal*. The postsynaptic terminal contains receptors for neurotransmitters. The small space between the axon terminal and postsynaptic terminal is called the *synaptic cleft*. The term **synapse** refers to the components that comprise this connection—the axon terminal, the postsynaptic terminal, and the synaptic cleft.

Neuroscientists use different terms to describe the location of a neuron and the path of its axon (**Figure 2.3**). The term **interneuron** describes a neuron with the soma and axon found within the same structure. An *afferent* neuron has an axon *going to* another structure. **Sensory neurons**, which convey sensory information via axons to the central nervous system, are considered afferent neurons. An *efferent* neuron has an axon *coming from* a structure. **Motor neurons** (or **motoneurons**), which convey motor information via axons from the central nervous system, are considered efferent neurons. Thus, the terms *afferent* and *efferent* can refer to any structure

being studied. For example, the thalamus, a structure that routes sensory information to different parts of the cerebral cortex, has both types of neurons: afferent neurons send axons *to* the thalamus, and efferent neurons send axons *from* the thalamus.

FIGURE 2.3 ■ Motor Neurons, Sensory Neurons, and Interneurons

Motor neurons convey movement information to muscles in the body, and sensory neurons convey sensory information to the central nervous system (CNS). Relative to the central nervous system, motor neurons are efferent neurons (going away from the CNS), and sensory neurons are afferent neurons (going to the CNS). Interneurons have the soma, dendrites, and axon all contained within the same structure.

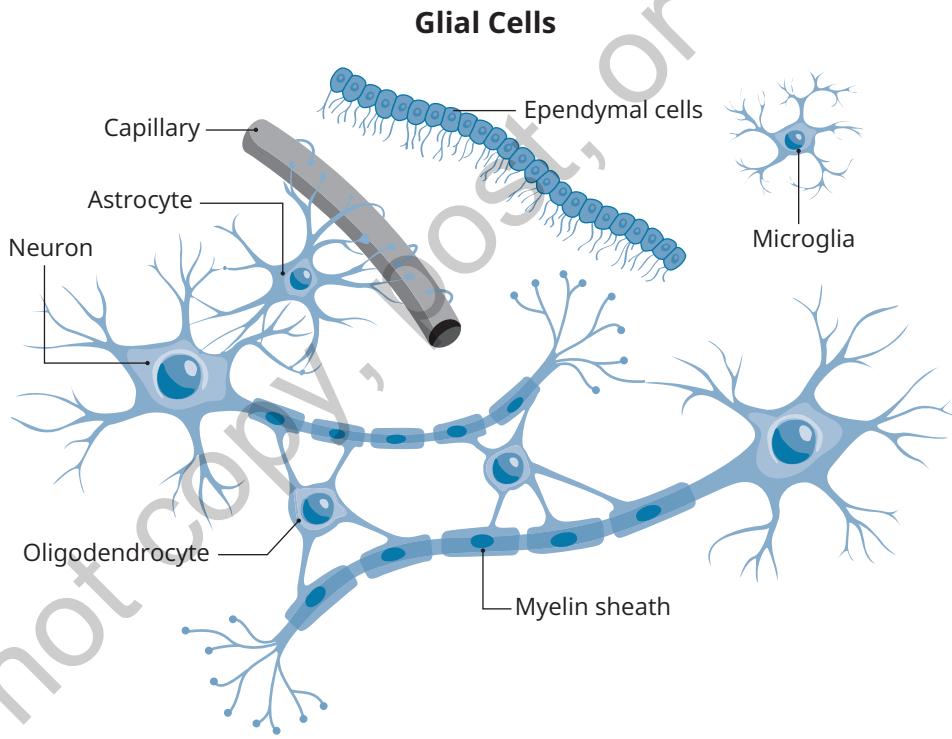


Glial Cells

Glial cells in the central nervous system consist of four different types: (1) oligodendrocytes, (2) astrocytes, (3) microglial cells, and (4) ependymocytes (**Figure 2.4**). **Oligodendrocytes** extend their membranes around axons to form a material called *myelin*. Myelin is found in segments along the length of an axon and serves to facilitate the movement of electrical impulses down an axon (more on this in Chapter 3). *Schwann cells* are like oligodendrocytes, but they are found in the peripheral nervous system, and they extend themselves around an axon to form only a single segment of myelin. Motor dysregulation, paralysis, and other symptoms of multiple sclerosis result from degeneration of myelin sheaths surrounding axons in the nervous system.

FIGURE 2.4 ■ Glial Cells

Glial cells support neuronal functioning. Oligodendrocytes and Schwann cells provide myelin sheathing for axons. Astrocytes form the blood–brain barrier, break down certain neurotransmitters, and respond to injury in the nervous system. Microglial cells remove cellular waste. Ependymocytes circulate cerebrospinal fluid.



Source: Steve McKinley; Vitalii Dumma/iStock

Astrocytes play a role in forming the blood–brain barrier, facilitating neuronal function, and responding to injury. Astrocytes form the blood–brain barrier (discussed in Chapter 4) by forcing endothelial cells to fit tightly together. Astrocytes support neuronal function through acting at synapses during neurotransmission, which we consider in Chapter 3.

Microglial cells remove normal cellular waste and serve as immune cells in the central nervous system. Two types of microglial cells exist: M1 and M2. M1 microglial cells release chemicals that promote inflammation and can damage the blood–brain barrier, whereas M2 microglial cells release chemicals that reduce inflammation and promote the growth and development of cells. Inflammation caused by M1 microglial weakens the blood–brain barrier, allowing in cells that can damage neurons. The potential for inflammation-induced damage to neurons to contribute to mental and neurological disorders provides an important reason to study microglial cells (Nakagawa & Chiba, 2015).

Ependymocytes (also referred to as ependymal cells) line ventricles and the central canal and circulate cerebrospinal fluid. They become filled with cerebrospinal fluid, and their surface contains cilia that facilitate cerebrospinal fluid movement (Jiménez et al., 2001). We refer again to ependymocytes later in this chapter when discussing ventricles in the brain.

STOP & CHECK

1. What are the two types of cells found in the brain?
2. _____receive information from other neurons, and _____send information to other axons.
3. Sensory neurons are also referred to as _____neurons because axons go to the central nervous system.
4. Which type of glial cells provide myelin sheathing for axons?

1. Neurons and glial cells **2.** Dendrites, axons **3.** afferent **4.** Oligodendrocytes produce myelin sheathing around axons in the central nervous system, and Schwann cells produce myelin sheathing around axons outside of the central nervous system.

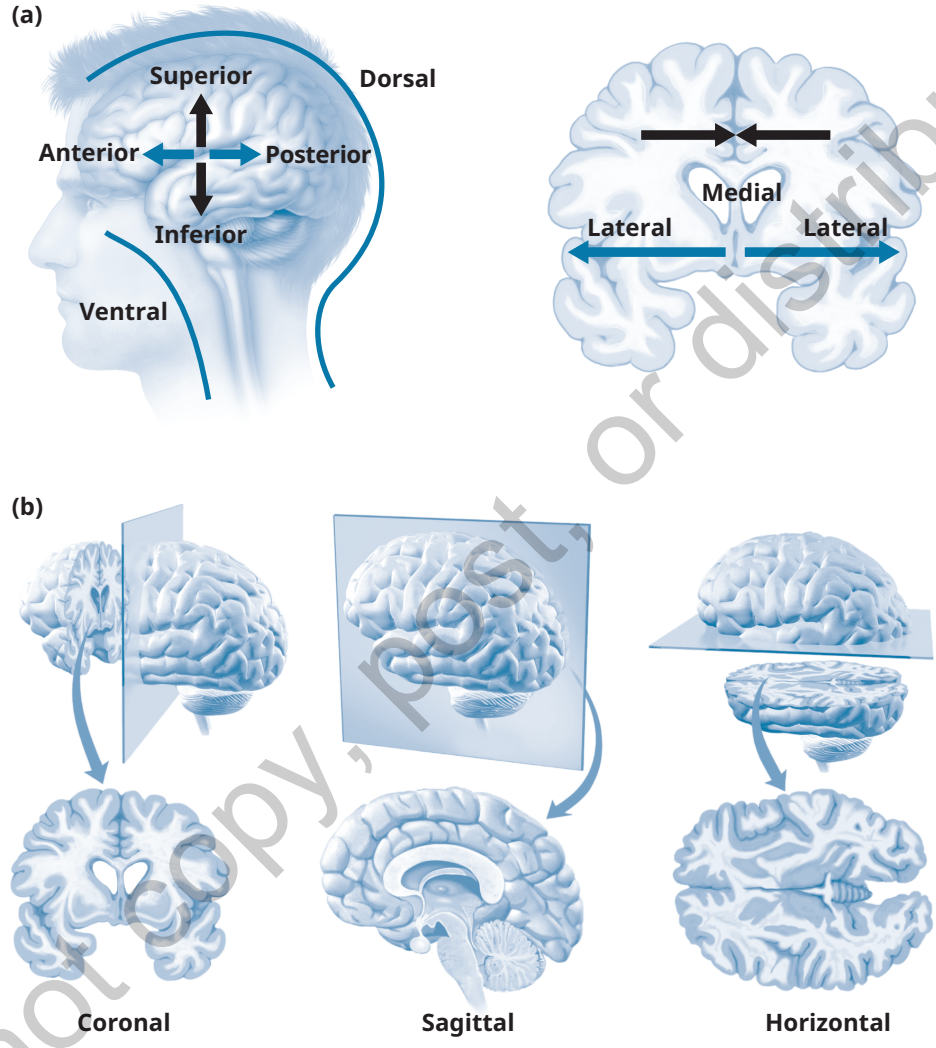
THE NERVOUS SYSTEM

Learning the basic terms used to describe the locations of nervous system structures is an important step for studying the brain. Standard terms describe the location of structures in the nervous system. For example, we refer to the front portion of the brain as *anterior* and the back portion of the brain as *posterior*. The bottom of the brain, the side that faces toward the stomach, is referred to as the *ventral* side, and the top of the brain is referred to as the *dorsal* side. We refer to structures near the sides of the brain as *lateral*; structures near the middle of the brain are described as *medial*. **Figure 2.5** presents these and other terms that describe structures in the brain.

Looking at structures inside the brain may be accomplished through any of three basic types of dissection planes. Slicing the brain from anterior to posterior produces a *coronal* (or *frontal*) section. We produce horizontal sections by slicing the brain from dorsal to ventral, and sagittal sections provide lateral views of the brain. Dissection planes provide different perspectives of a structure.

FIGURE 2.5 ■ The Human Brain

The human brain can be dissected in coronal (i.e., frontal), sagittal, and horizontal sections. We use special terms to describe the location of structures in the brain. See text for further details.

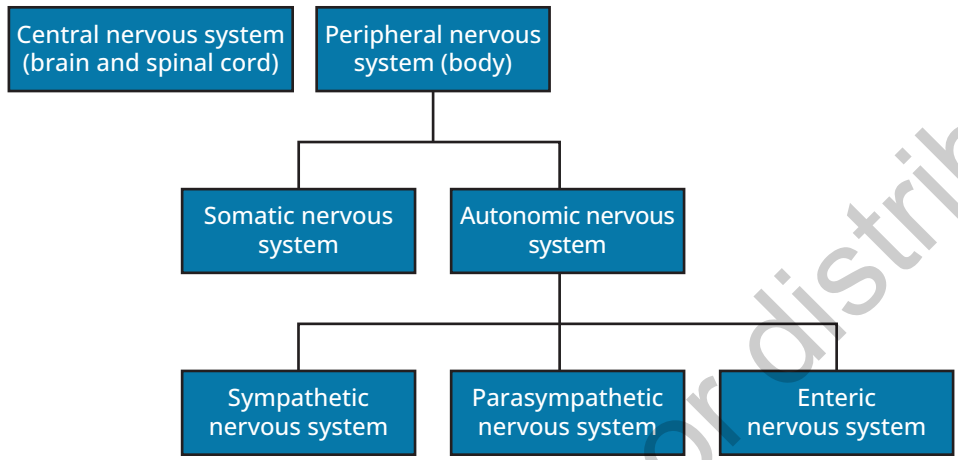


The Peripheral Nervous System

The nervous system consists of two systems: (1) the peripheral nervous system and (2) the central nervous system. Much of what we discuss in this book pertains to the central nervous system, which consists of the brain and spinal cord. Drugs also have many effects on the peripheral nervous system, which contains two subsystems called the *somatic nervous system* and *autonomic nervous system* (**Figure 2.6**).

FIGURE 2.6 ■ The Peripheral Nervous System

The peripheral nervous system contains the somatic nervous system and the autonomic nervous system. The autonomic nervous system consists of the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system.



The Somatic Nervous System: Delivering Motor Signals to Muscles and Sensory Signals to the Spinal Cord

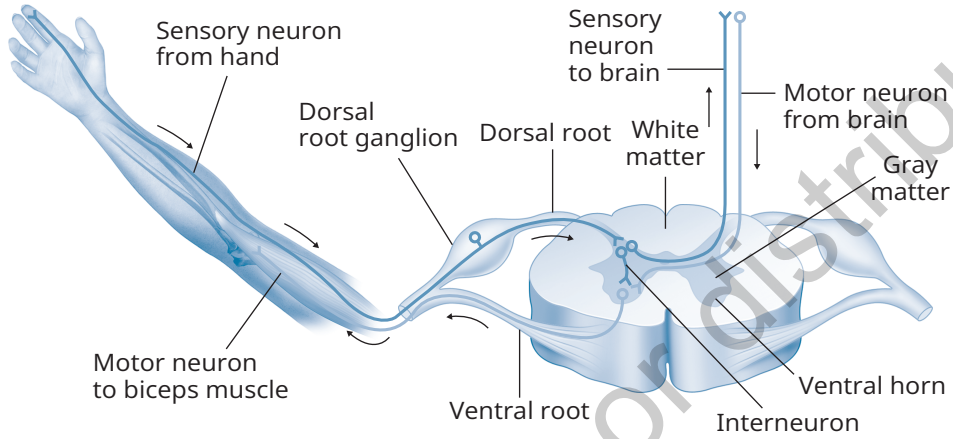
The **somatic nervous system** is responsible for delivering voluntary motor signals from the central nervous system to muscles and for conveying sensory information from the body to the central nervous system. Thus, the somatic nervous system is made up of motor neurons and sensory neurons. Sensory neurons send information to the dorsal part of the spinal cord (through the *dorsal root* to the *dorsal horn*), whereas motor signals are sent to muscles from the ventral part of the spinal cord (from the *ventral horn* to the *ventral root*) (**Figure 2.7**). The point where a motor neuron meets a muscle fiber is called the *neuromuscular junction*. Muscles contract when motor neurons release the neurotransmitter acetylcholine at neuromuscular junctions.

The Autonomic Nervous System: Control of Vital Functions

Whereas the somatic nervous system produces voluntary movement, the **autonomic nervous system** controls involuntary movements for functions such as heartbeat, breathing, swallowing, digestion, and sweating by controlling heart muscle, smooth muscle, and exocrine glands. Exocrine glands secrete substances through a duct, such as sweat, saliva, and tears. The autonomic nervous system consists of three systems: (1) the sympathetic nervous system, (2) the parasympathetic nervous system, and (3) the enteric nervous system (**Figure 2.8**). The **sympathetic nervous system** prepares the body for rigorous activity by increasing heartbeat, inhibiting digestion, and opening airways, among many other involuntary functions. The **parasympathetic nervous system** is dominant during relaxed states and decreases heartbeat, stimulates digestion, and closes airways. The **enteric nervous system** controls digestion via communication within its system and with the central nervous system (Furness, 2007).

FIGURE 2.7 ■ Spinal Cord

Sensory neurons send information to the dorsal part of the spinal cord, whereas motor signals are sent to muscles from the ventral part of the spinal cord. Gray matter appears in the middle portion of the spinal cord, forming an H shape. White matter appears in the outermost portions of the spinal cord.



Both the sympathetic and parasympathetic nervous systems contain ganglia (singular *ganglion*). *Ganglia* are clusters of neuron cell bodies for neurons in the sympathetic and parasympathetic nervous systems. A ganglion fully contains a neuron's soma and dendrite, whereas a neuron's axon extends from the ganglion to smooth muscle tissue or glands. We call this a *postganglionic* neuron because its axon comes after the ganglion and goes toward these structures. A neuron that instead sends an axon from the spinal cord to a ganglion is referred to as a *preganglionic* neuron (**Figure 2.9**).

Preganglionic neurons control sympathetic and parasympathetic nervous system neurons by releasing the neurotransmitter acetylcholine at synapses for postganglionic neurons. Through the process of neurotransmission (discussed in Chapter 3) acetylcholine makes these postganglionic neurons more active. Axons for the activated postganglionic neurons then release neurotransmitters at their axon terminals. This leads target muscles or glands to have decreased (for parasympathetic nervous system neurons) or increased (for sympathetic nervous system neurons) activity. Postganglionic neurons in the parasympathetic nervous system release acetylcholine, whereas most postganglionic neurons in the sympathetic nervous system release norepinephrine as their neurotransmitter and some release epinephrine, dopamine, or acetylcholine.

The enteric nervous system consists of 200-600 million neurons found within the gastrointestinal tract with thousands of ganglia located throughout the system. Whereas this system communicates with the central nervous system, the enteric nervous system handles many of its functions independently—this makes the system unique from the other systems in the peripheral nervous system. As discussed in Chapter 3, the nature of afferent communication to the central nervous system creates a number of intriguing research questions concerning bacteria that live in the gut and the chemical messengers released from these bacteria (Furness, 2007).

FIGURE 2.8 ■ Autonomic Nervous System

The autonomic nervous system is made up of the sympathetic nervous system, parasympathetic nervous system, and enteric nervous system. The sympathetic nervous system enhances the activity of organs in the body, and the parasympathetic nervous system diminishes the activity of these same organs. The enteric nervous system controls digestion, and it carries out independent functions as well as responding to information from the central nervous system.

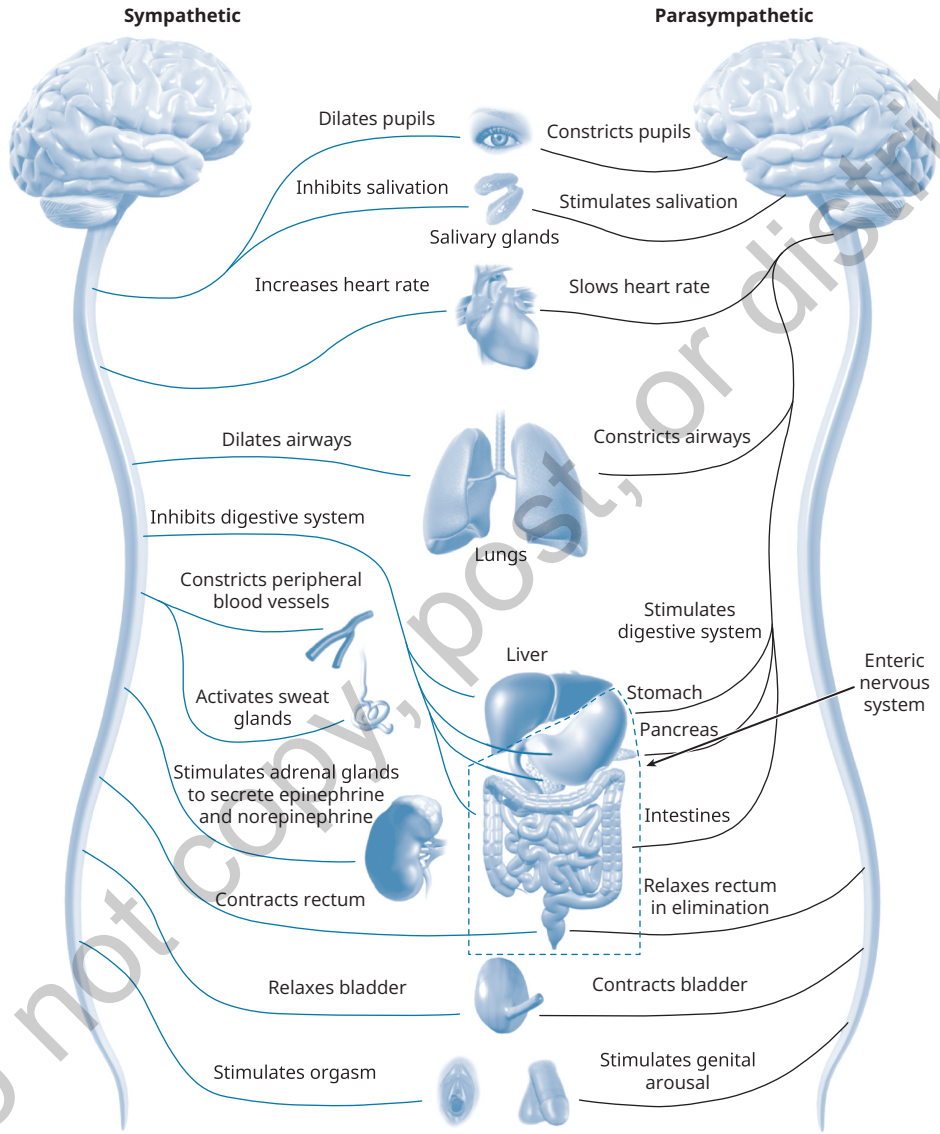
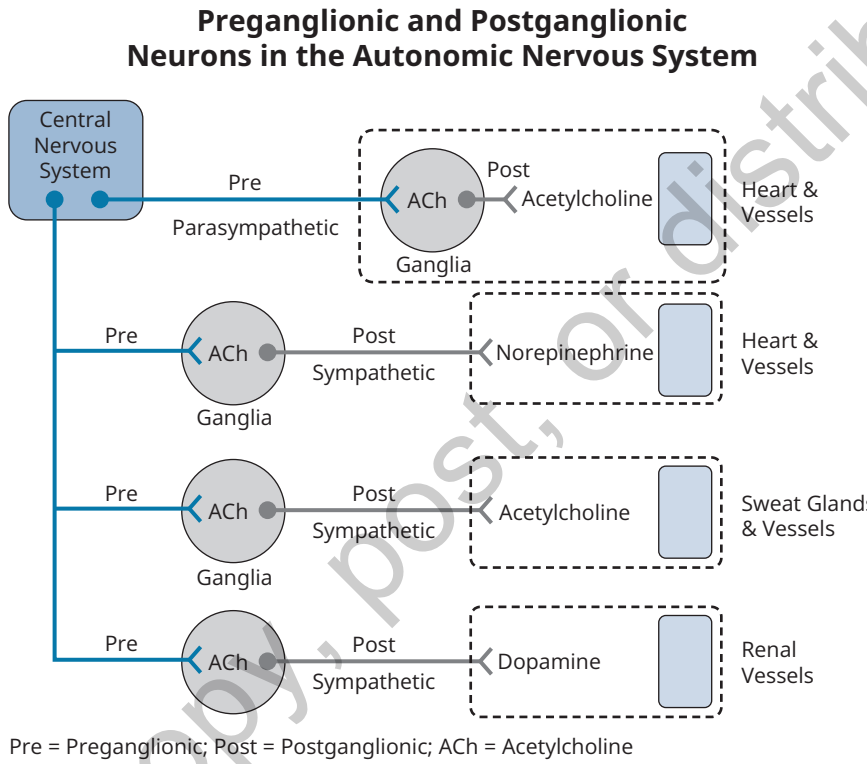


FIGURE 2.9 ■ Preganglionic and Postganglionic Neurons in the Autonomic Nervous System

The autonomic nervous system contains neurons in ganglia. Neuron axons coming from the spinal cord to ganglia (referred to as *preganglionic neurons*) activate, via acetylcholine, neurons in ganglia that in turn have axons that extend from ganglia and act upon smooth muscle or glands (referred to as *postganglionic neurons*). In the parasympathetic nervous system, postganglionic neurons release the neurotransmitter acetylcholine. In the sympathetic nervous system, the neurotransmitter released by postganglionic neurons depends upon the specific pathway (some examples shown in the figure). See text for a further explanation of pre- and postganglionic neurons.



Pre = Preganglionic; Post = Postganglionic; ACh = Acetylcholine

STOP & CHECK

1. Brain sections produced by slicing the brain from anterior to posterior are referred to as _____ sections.
2. The somatic nervous system delivers movement signals to muscles by releasing acetylcholine at _____.
3. The _____system controls vital functions such as breathing and heartbeat.

1. coronal 2. neuromuscular junctions 3. autonomic

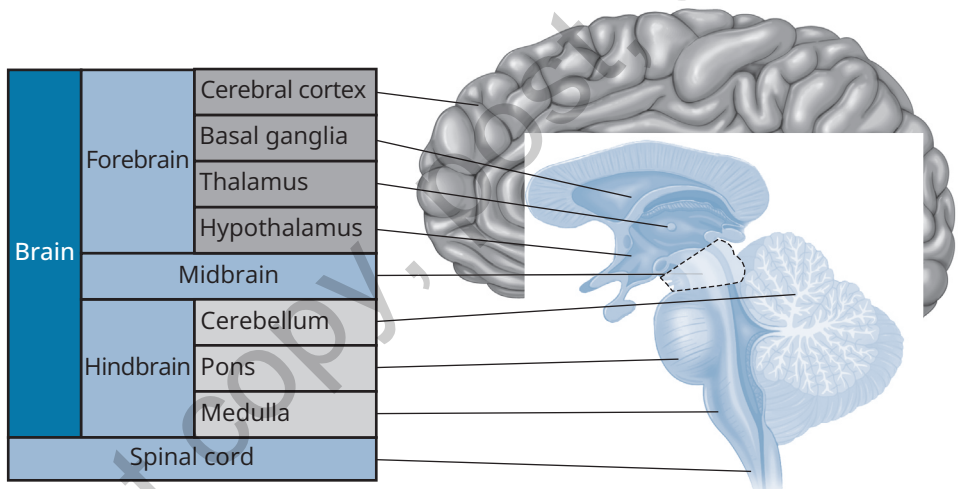
THE CENTRAL NERVOUS SYSTEM

The brain and spinal cord make up the central nervous system. The surface of the brain—the **cerebral cortex**—has hills called *gyri* (singular *gyrus*) and valleys called *sulci* (singular *sulcus*). The base of the brain, where the spinal cord meets, is called the *brain stem*. Above the brain stem sits a structure called the *cerebellum*. The brain is divided into two hemispheres, left and right. Structures found in one hemisphere have a matching structure in the other hemisphere.

The brain has three different divisions called the *hindbrain, midbrain*, and *forebrain* (**Figure 2.10**). The hindbrain consists mostly of the brain stem, and it begins where the spinal cord meets the brain stem at a structure called the *medulla*. The midbrain comprises a region between the hindbrain and forebrain; it includes the *inferior colliculus*, which plays a role in auditory processing, and the *superior colliculus*, which directs eye movement. The forebrain includes the rest of the brain and contains the cerebral cortex and structures beneath the cerebral cortex, such as the *corpus callosum, basal ganglia, thalamus*, and *hypothalamus*.

FIGURE 2.10 ■ Regions of the Brain

The brain is divided into three different divisions or regions called the hindbrain, midbrain, and forebrain.

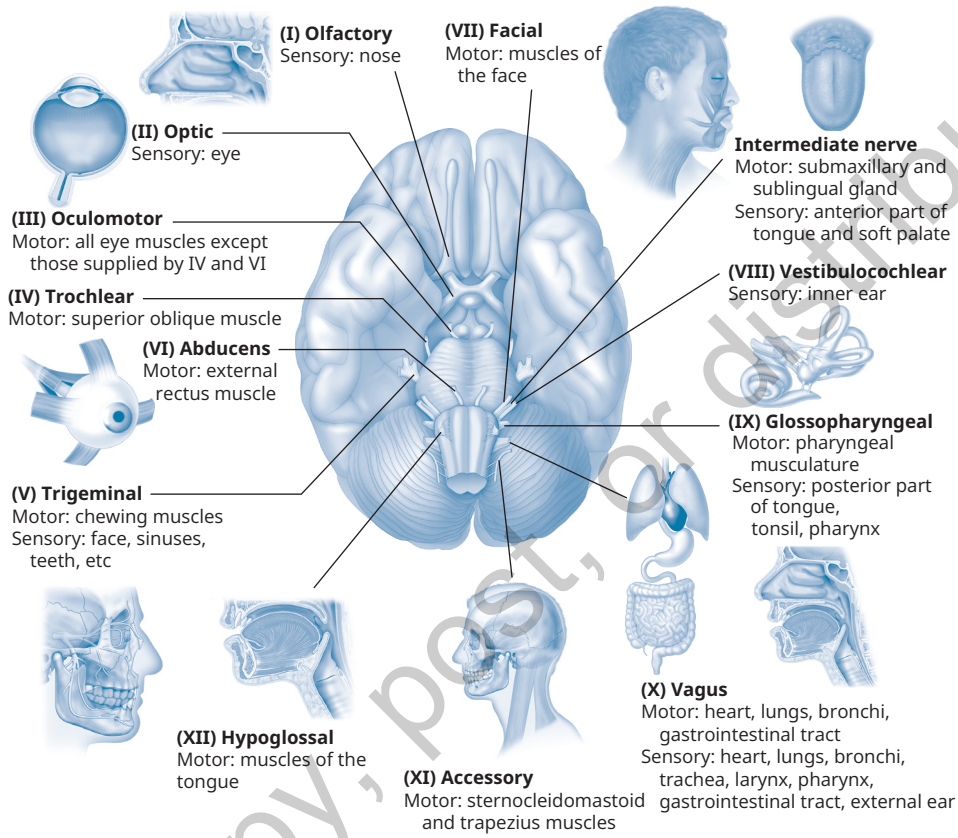


The Medulla and Hypothalamus: Controlling Unlearned Behaviors

We previously discussed the autonomic system, which maintains vital functions in the body. The autonomic nervous system is controlled by the medulla. As already described, the **medulla** rests where the spinal cord meets the hindbrain. In fact, from the surface, the medulla looks like a thicker section of spinal cord. Through controlling the autonomic nervous system, the medulla controls basic autonomic functions such as breathing, heart rate, and vomiting. Many of the cranial nerves also come from the medulla. These nerves are devoted to movement and sensations of the head (**Figure 2.11**). There are 12 cranial nerves, each noted by its number and name.

FIGURE 2.11 ■ Cranial Nerves

The ventral side of the brain reveals all 12 of the cranial nerves.



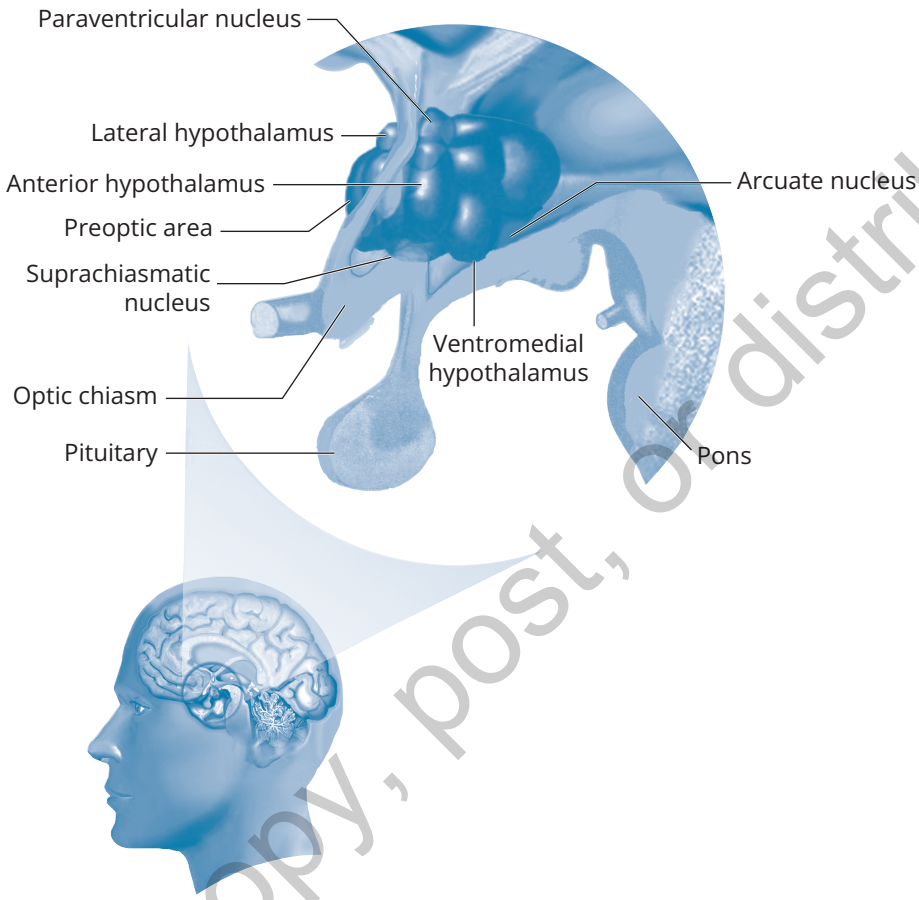
Source: Encyclopaedia Britannica, Contributor, Universal Images Group, Getty.

Damaging the medulla can be life-threatening, and suppressing its functioning can be as dangerous. Narcotics and central nervous system depressants suppress medullary functions, which can be fatal at high-enough doses. Moreover, mixing two or more central nervous system depressants at otherwise safe amounts can produce combined suppressant effects on the medulla's functions.

The **hypothalamus**, a structure found in the forebrain, maintains important physiological conditions (**Figure 2.12**). The hypothalamus maintains many physiological processes by motivating an organism's behavior. When the body requires food, for example, the hypothalamus elicits feelings of hunger. Similarly, the hypothalamus elicits thirst when we become dehydrated. Other processes the hypothalamus regulates include body temperature, sleep, and motivation for sexual activity.

FIGURE 2.12 ■ The Hypothalamus

The hypothalamus plays an important role in homeostasis, partly by eliciting motivation for physiological activities such as eating and drinking.



The hypothalamus controls the *pituitary gland*, which sits on the ventral surface of the brain. The hypothalamus does this via neurons that send axons to the pituitary gland and also by releasing hormones into a blood vessel system that runs a short distance to this gland. The pituitary gland releases many hormones into the bloodstream, affecting organ functions in the body. These effects include water absorption into the kidneys, growth, thyroid function, and reproductive functions. The hypothalamus also controls the *pineal gland*, located posterior to the hypothalamus in the forebrain but above the superior colliculus in the midbrain. The pineal gland releases *melatonin*, a sleep-promoting hormone that you might also know as a common over-the-counter sleep aid. Melatonin released from the pineal gland facilitates a regular pattern of sleepiness and wakefulness by increasing release closer to bedtime and decreasing release closer to wake-up time. Similarly, taking a melatonin pill induces a state of sleepiness and can be especially helpful when sleeping patterns may change abruptly, such as traveling across time zones or working overnight shifts.

STOP & CHECK

1. The central nervous system contains the brain and _____.
2. What is the primary structure in the brain for controlling autonomic functions?
3. How does the hypothalamus alter hormone levels in the body?
4. What hormone regulates a normal sleep cycle?

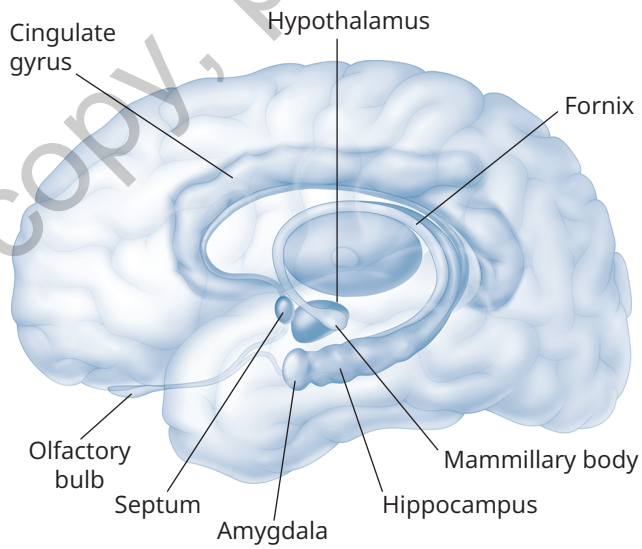
1. spinal cord 2. The medulla 3. The hypothalamus controls the pituitary gland, which releases many hormones throughout the body. 4. Melatonin

The Limbic System and the Nucleus Accumbens: Important Roles in Emotions

The **limbic system** consists of a series of structures that together form a ring around the thalamus and hypothalamus. These limbic system structures include the *cingulate gyrus, hippocampus, amygdala*, and *olfactory bulb* (**Figure 2.13**). Many structures within the limbic system control emotional behavior. The amygdala, for example, facilitates fear and aggression. Many drugs that reduce anxiety decrease the activity of neurons in the amygdala.

FIGURE 2.13 ■ The Limbic System

Structures in the limbic system play roles in emotion, among other functions. The hippocampus, for example, plays an important role in long-term memory.



Source: Carolina Hrejsa, Body Scientific Intl.

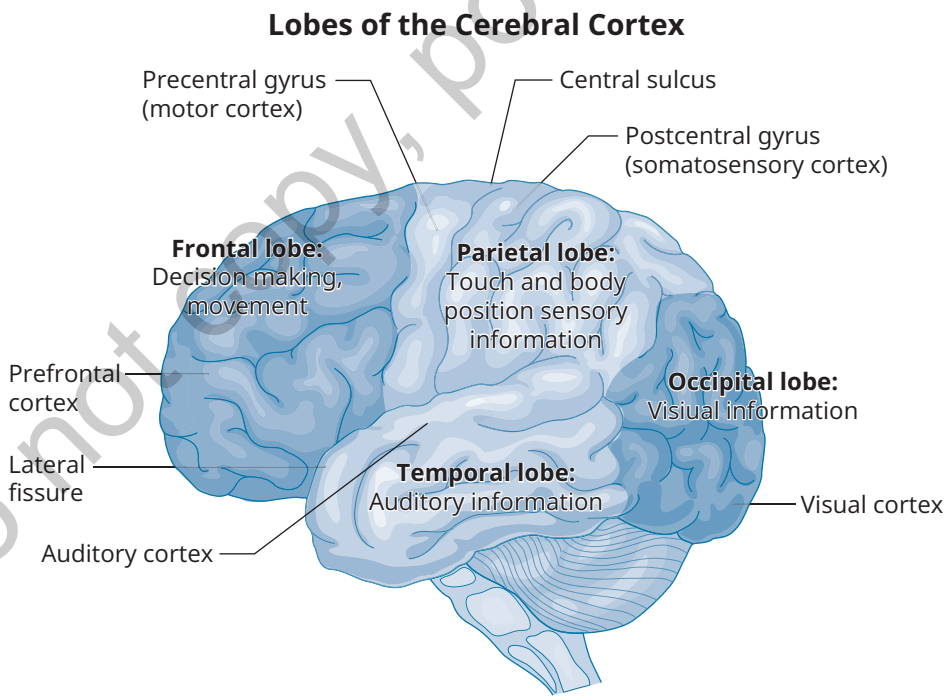
The **nucleus accumbens** rests adjacent and anterior to the amygdala and facilitates rewarding effects. For this reason, we refer to the nucleus accumbens as the brain's *reward center*. The nucleus accumbens belongs to a network of other structures referred to as the *reward circuit*. Chapter 5 presents more information on the brain's reward circuitry and the role this circuitry plays in the rewarding effects of abused substances.

The Cerebral Cortex: Processing Sensory Information, Controlling Cognitive Functions, and Production of Movement

We find the cerebral cortex divided into four areas called *lobes* (**Figure 2.14**). The **occipital lobe** is the most posterior portion of the cerebral cortex and processes visual information. The **temporal lobe** is anterior to the occipital lobe and below the parietal lobe. The temporal lobe processes auditory information and supports language comprehension and production. This area of the cerebral cortex also processes certain aspects of vision, including shape and color analysis. The **parietal lobe** is anterior to the occipital lobe and above the temporal lobe and includes the *somatosensory cortex*, the structure responsible for processing touch information from the body. The parietal lobe also analyzes visual information that contains movement.

FIGURE 2.14 ■ Lobes of the Cerebral Cortex

The cerebral cortex is divided by lobes. Each lobe is responsible for a variety of functions, including the processing of different types of sensory information. The prefrontal cortex, within the frontal lobe, serves as an integration center for all types of sensory information.



The **frontal lobe**, which is at the anterior of the brain, supports decision-making and movement. The frontal lobe contains the motor cortex. The most anterior part of the frontal lobe is called the **prefrontal cortex** and is an integration area for all types of sensory input and where the signal to produce movement occurs. Prefrontal cortical function also supports short-term memory and attention.

The **thalamus** routes sensory information from the body to the appropriate lobes. For example, visual information is sent from the eyes through the thalamus and to the occipital lobe, whereas auditory information is sent from the ears through the thalamus and to the temporal lobe. Olfactory information, however, is sent directly to the prefrontal cortex. After processing, all sensory information integrates in the prefrontal cortex.

STOP & CHECK

1. What are the primary functions of the amygdala and nucleus accumbens?
2. Which lobe analyzes sound, including language?
3. What role does the thalamus play in processing sensory information?

1. The amygdala elicits feelings of fear, anxiety, and aggression, whereas the nucleus accumbens elicits rewarding effects. **2.** Temporal lobe **3.** The thalamus routes sensory information to the appropriate lobes of the cerebral cortex.

The Frontal Lobe and Basal Ganglia: Controlling Voluntary Movement

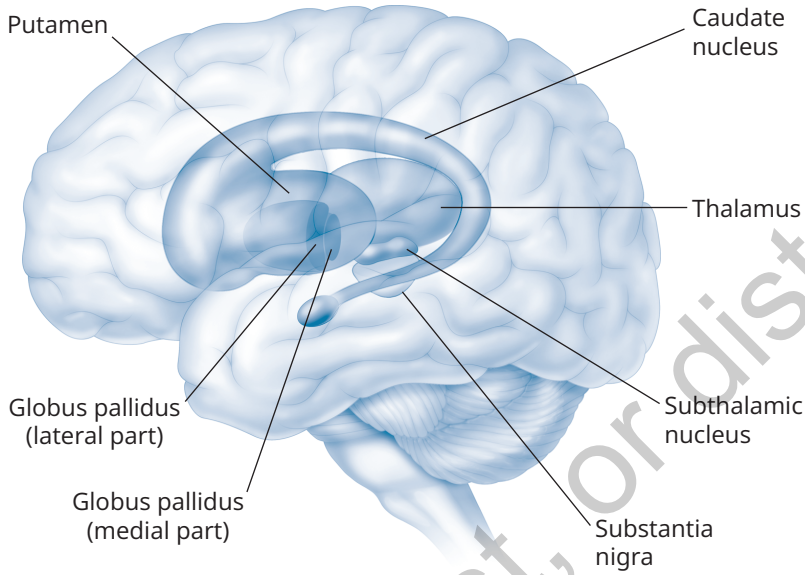
After the prefrontal cortex signals a movement to occur, the **motor cortex** sends movement signals to the body via neurons (in this case, referred to as *tracts*) that cross from one hemisphere to the opposite side of the body to the limbs, hands, and feet. Tracts sent to the middle parts of the body, for posture and balance, have far fewer neurons crossing to the opposite side of the body.

The **basal ganglia** act to stabilize voluntary movements (**Figure 2.15**). The basal ganglia, also called the *striatum*, have three major substructures: the *caudate nucleus*, the *putamen*, and the *globus pallidus*. The term *ganglia* used for this structure comes from early anatomical studies that considered these to be distinct structures, but modern physiologists consider the basal ganglia as a single structure (Lanciego et al., 2012). The *substantia nigra* aids in regulating activity in the basal ganglia. The primary symptoms of Parkinson's disease, a disorder characterized by muscle rigidity, tremor, and resistance to voluntary movement, occurs from the destruction of substantia nigra neurons that go to the basal ganglia. Many of the first drugs to treat schizophrenia, called *antipsychotic drugs*, disrupt these neurons, leading to Parkinson-like symptoms called *extrapyramidal side effects*.

Some other components of the overall motor system must be noted. The *pons*, a structure located above the medulla in the hindbrain, elicits startle reflexes. The **cerebellum** facilitates balance and the timing of movements.

FIGURE 2.15 ■ Basal Ganglia

The basal ganglia, which include the globus pallidus, putamen, and caudate nucleus, regulate movement signals sent from the motor cortex.



Learning and Memory Processes in the Brain

Psychologists characterize short- and long-term memories in different ways. Most consider short-term memory as working memory. *Working memory* consists of short-term verbal or nonverbal memories employed when carrying out a task. In essence, we are "working" with memory. *Long-term memory* (or *reference memory*), consists of stored verbal and nonverbal information. Long-term memories include information that we can declare, such as the capital of the United States, or information we can demonstrate, such as how to swing a golf club.

The prefrontal cortex facilitates working memory function. Recall that information from all sensory modalities integrates in the prefrontal cortex. The prefrontal cortex uses this information to control behavior when engaging in a task.

Long-term memory formation and retrieval requires the **hippocampus**. The hippocampus then sends information to the prefrontal cortex, possibly for use during working memory function. Damage to the hippocampus in Alzheimer's disease may account for impairments in long-term memory. Long-term motor memories, also referred to as *procedural memories*, may depend on the basal ganglia. Procedural memories include things such as riding a bicycle or tying a shoelace.

Other parts of the brain indirectly aid memory formation by keeping the brain active. Many of these parts are found in the **reticular activating system**, which includes the *reticular formation, tegmentum, thalamus*, and *hypothalamus*. The activity within these structures ultimately supports arousal in the cerebral cortex. Another structure important for cortical arousal is the basal forebrain area. Drugs that increase cortical arousal include psychostimulant drugs; drugs that depress cortical arousal include benzodiazepines, barbiturates, and alcohol.

STOP & CHECK

1. Which part of the cerebral cortex sends movement signals to the body?
2. What parts of the brain are damaged in Parkinson's disease?
3. Which structures are linked to working memory and long-term memory, respectively?

1. The motor cortex **2.** Parkinson's disease arises from damage to neurons that begin in the substantia nigra and end in the basal ganglia. **3.** The prefrontal cortex is particularly important for working memory, whereas the hippocampus is important for long-term memory.

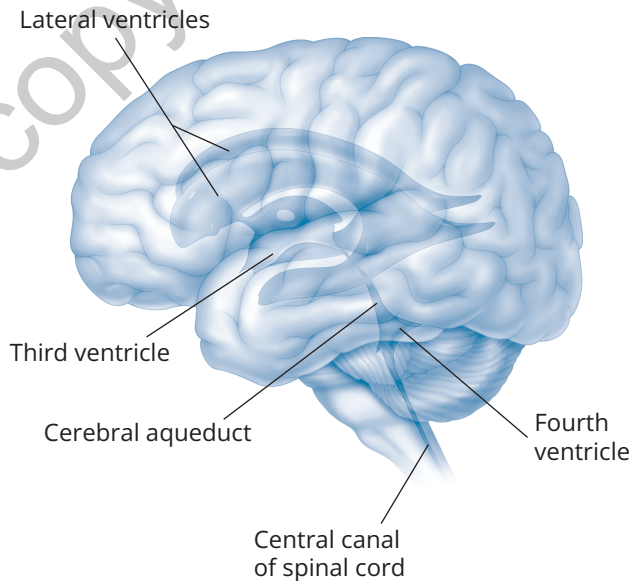
CEREBRAL BLOOD FLOW AND CEREBROSPINAL FLUID

Proper blood flow throughout the brain, called **cerebral blood flow**, is critical for neuron and glial cell function. Highly active brain areas require increased blood flow. When you are working hard on a task such as an exam, your prefrontal cortex is active. Blood flow increases to the prefrontal cortex to sustain this activity. Blood flow changes throughout the brain when blood capillaries dilate and contract. Highly active cells release a chemical called *nitric oxide* that dilates blood capillaries, which in turn delivers more oxygen.

Cerebrospinal fluid is a clear fluid that surrounds cells in the brain. Cerebrospinal fluid provides a medium through which nutrients, a sugar called *glucose*, hormones, and other chemicals access brain cells (**Figure 2.16**). In addition to surrounding cells in the

FIGURE 2.16 ■ Brain Ventricles

The ventricles are filled with cerebrospinal fluid. The third and fourth ventricles are connected by the cerebral aqueduct. Within the spinal cord, cerebral spinal fluid fills the central canal.



brain, cerebrospinal fluid fills many spaces and canals in the brain. The central canal of the spinal cord is filled with cerebrospinal fluid, and there is a smaller canal-like structure in the brain called the *cerebral aqueduct*. The cerebral aqueduct is surrounded by a small layer of tissue called **periaqueductal gray**. The brain also contains cerebrospinal fluid-filled cavities called **ventricles**. A network of blood vessels and cells called the *choroid plexus* lines ventricles and produces cerebrospinal fluid. Cerebrospinal fluid moves through ventricles and connecting channels through the aid of ependymocytes, which were presented earlier in this chapter.

Cerebrospinal fluid is also found in the *meninges* that surround the brain. Cerebrospinal fluid forms in a layer of the meninges called the *subarachnoid space*. By filling this space, cerebrospinal fluid forms a protective cushion around the brain, protecting it from injury. Cerebrospinal fluid serves as the medium through which drug molecules travel upon crossing into the brain from the blood–brain barrier.

STOP & CHECK

1. How might thinking be affected if the brain had poor cerebral blood flow?
2. The meninges protect the brain from injury because they contain a clear fluid called _____.

1. Because cells in the brain require oxygen to meet increased energy demands, thinking would certainly be compromised from poor flow. **2.** cerebrospinal fluid

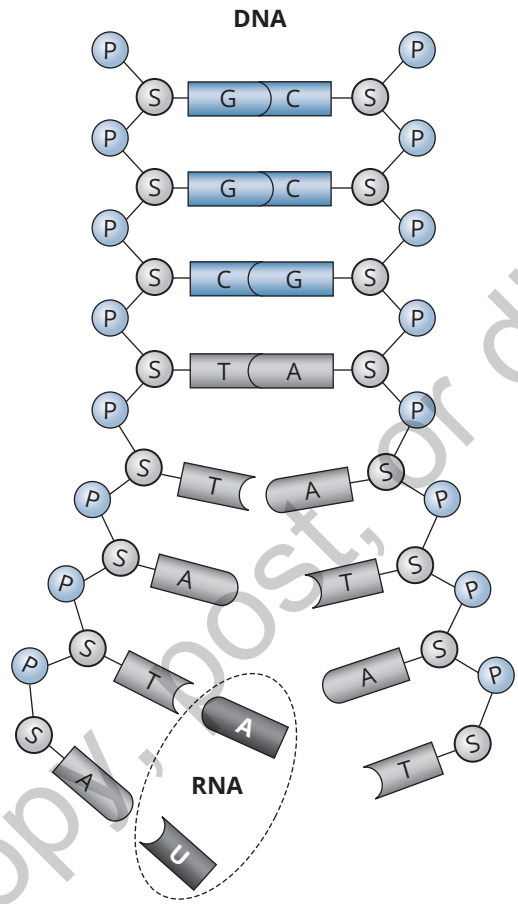
GENES AND THE PHYSIOLOGICAL PROCESSES OF CELLS

The blueprints for a cell and its functions reside within the cell's nucleus. The nucleus of every cell for humans contains 46 chromosomes. A child inherits 23 chromosomes from each parent. Two of the 46 chromosomes consist of X and Y chromosomes, which determine an individual's sex. If both of these sex chromosomes are Xs, an individual is genetically female. However, if one of these sex chromosomes is a Y, the individual is genetically male. All of the other chromosomes are called *autosomal chromosomes*.

Each chromosome contains a strand of *deoxyribonucleic acid* (DNA), which contains the specific coding instructions for the basic functions of cells called **genes**. Genes are encoded with the traits we have (**Figure 2.17**). Within this role, genes contain information to synthesize new proteins. Researchers can alter genetic information in animals to study the nervous system (**Box 2.1**).

FIGURE 2.17 ■ DNA and RNA

When a gene is activated, a specific DNA segment is unraveled and transcribed onto ribonucleic acid (RNA), which may then leave the nucleus and carry the transcribed information to ribosomes that synthesize proteins as instructed.



BOX 2.1: GENETICALLY MODIFIED ORGANISMS

Genetic technologies allow researchers to characterize the role genes play in behavior and physiological functions. These advances led to the creation of genetically modified invertebrate and vertebrate organisms. For vertebrates, most genetic modification research uses mice, although the development of CRISPR technology (discussed in this chapter's "From Actions to Effects" section) makes the use of genetic modification in other species more feasible.

The genetic modification process starts by injecting genetic material into a pregnant mouse. After the mouse has a litter, researchers test the *genotype*, or genetic makeup, of each mouse pup to identify those with the targeted genetic change. Genetically modified mice fall largely into two categories: transgenic animals and knock-out animals. A *transgenic animal* has either altered genes or additional genetic information. For example, researchers alter amyloid precursor protein genes in transgenic mice to cause production of amyloid plaques, a key neurobiological characteristic found in Alzheimer's disease. A *knock-out animal* fails to express traits from a particular gene; in essence, the gene is "knocked out."

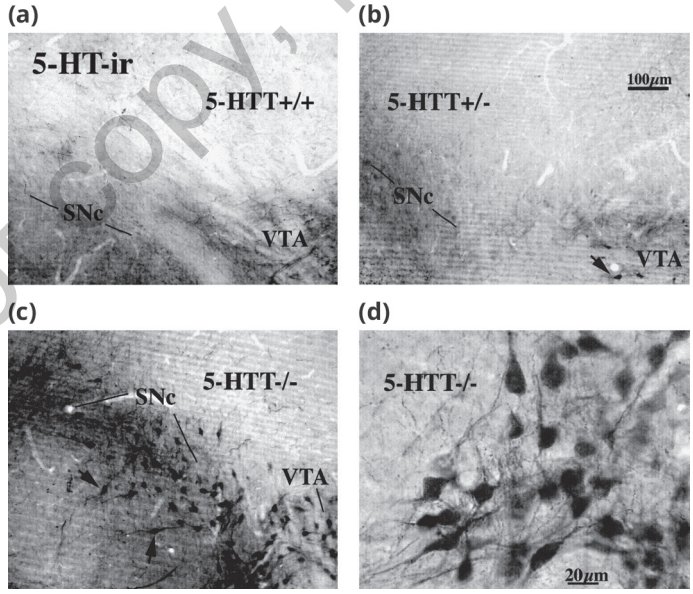
For example, serotonin transporter knock-out mice—again, mice completely lacking serotonin transporter proteins (covered in Chapter 3)—exhibit greater levels of the neurotransmitter serotonin in the synaptic cleft and show anxious behavior (Holmes et al., 2003). A *phenotype* describes the physiological or behavioral changes caused by a genetic alteration. In this example, enhanced serotonin levels and increased anxiety describe the physiological and behavioral phenotypes for a serotonin transporter knock-out mouse.

Although transgenic and knock-out data provide important links between genetics and physiological and behavioral activity, scientists keep in mind that genetic alterations may cause unexpected changes during neurodevelopment. In fact, a study by Zhou et al. (2002) demonstrated a unique and unexpected consequence of knocking out the serotonin transporter.

In this study, researchers compared serotonin levels in serotonin transporter knock-out mice and confirmed that greater serotonin levels occurred at serotonin synapses, as

FIGURE 2.18 ■ Serotonin Transporters on Dopamine Neurons

Few neurons reveal the neurotransmitter serotonin in the dopamine-rich ventral tegmental area and substantia nigra in wildtype mice (top panel, a). However, in serotonin transporter knock-out mice (bottom panel, c & d), many dopamine neurons contain serotonin. These findings suggest that removal of serotonin transporters led to the nervous system adapting to the loss of serotonin by using dopamine neurons for synthesizing serotonin instead. VTA = ventral tegmental area; 5-HT = serotonin; 5-HTT = serotonin transporter; ir = immunoreactive; the labeling technique used to identify serotonin; SNc = substantia nigra. From Zhou et al. (2002).



Source: Dr. Feng Zhou, Brain Research, Elsevier.

described previously. However, these researchers also discovered serotonin neurotransmitters inside of neurons that produce the neurotransmitter dopamine. Exploring further, the team found that dopamine transporters had adapted to allow entry of serotonin into dopamine neurons (Zhou et al., 2002). Thus, instead of having mice with an altered serotonin system, they unintentionally produced mice that also had an altered dopamine system (**Box 2.1**, **Figure 2.18**).

Although genes contain codes to express certain traits such as eye color or production of a particular enzyme, the coding sequence for genes may not be precisely the same from individual to individual. We term these differences *polymorphisms*. A **polymorphism** is a difference in the encoding of a gene compared to the most common sequence in a population. Polymorphisms are common, and determining what type of polymorphism an individual has can aid greatly in understanding a person's response to drug effects. For example, some polymorphisms lead to greater production of certain types of enzymes in the liver. For these individuals, the extra enzymes may break down a drug before it produces any substantial effects.

Activating genes leads to the copying of genetic information, a process referred to as *gene transcription*. A **transcription factor** consists of a substance that increases or decreases gene transcription. During gene transcription, the coding sequence of a gene copies onto ribonucleic acid (RNA). The type of RNA used to trigger protein synthesis is called *messenger RNA* because it leaves the nucleus and binds to ribosomes in the cell. Ribosomes produce the type of protein specified in the message. Gene transcription is one of many areas studied in the field of **epigenetics**, the study of mechanisms of gene expression not involving alterations to DNA sequences. Future drug therapies may target epigenetic mechanisms for treating neurological or mental disorders (Arango, 2015).

STOP & CHECK

1. How many chromosomes does a human cell contain?
2. A _____ is a protein that activates a gene.
3. Genetic code is copied onto _____, which delivers the code to ribosomes outside the nucleus.

1. 46 2. transcription factor 3. messenger RNA

FROM ACTIONS TO EFFECTS: ADVANCES IN THERAPEUTIC USE OF CRISPR GENETIC TECHNOLOGY

Patients suffering from diseases derived from genetic mutations may benefit from emerging genetic technologies to correct or counteract the effects from these mutations. Such efforts require precision genetic alterations, and for this reason, therapeutic genetic strategies

increasingly involve the use of CRISPR technology. CRISPR (pronounced "crisper") is an acronym for *clustered regularly interspaced short palindromic repeats*, referring to sections of DNA that fit this characterization. That is, patterns of DNA are repeated in multiple copies. *Palindromic* refers to a sequence of nucleic acids in one strand of DNA bound to nucleic acids in a matching but opposite order on the second strand of DNA. Spacer DNA refers to noncoding segments of DNA (i.e., DNA that doesn't lead to the production of proteins). Thus, interspaced refers to noncoding DNA that separates the repeated patterns of DNA.

Generally, references to CRISPR technology include the use of a protein that can sever bounds in a DNA sequence associated with a particular CRISPR segment. The current leading strategy for therapeutic genetic editing is *Cas9* (CRISPR-associated protein 9). The Cas9 enzyme includes a DNA sequence that will selectively bind to a short sequence of RNA that is copying the genetic code from a specific pattern of DNA linked to a specific CRISPR sequence. This selective targeting is a step up from previous strategies that held the likelihood of affecting genes unrelated to the therapeutic goals of the genetic manipulation. Thus, lacking specificity in genetic editing can cause more harm than good.

At the present time, CRISPR-Cas9 treatments have received fast-track status for review by the U.S. Food and Drug Administration. Recently, the results from a patient with sickle cell disease enrolled in CRISPR-Cas9 clinical trial were aired on CBS's *60 Minutes* (LaPook, 2019). Sickle cell disease caused the patient to experience severe sharp pain throughout her body due to a miscoding of the gene for the hemoglobin protein that caused what should be doughnut-shaped red blood cells to be cells shaped instead like a sickle. The researchers extracted stem cells from the patient's bone marrow and then introduced corrected gene sequences using CRISPR-Cas9. The stem cells were reintroduced into bone marrow and then developed into normal stem cells.

Researchers also use CRISPR-Cas9 approaches to genetically modify animals for the purpose of mimicking human diseases or disorders. In one such study, Horie and colleagues (2018) used CRISPR-Cas9 to prevent the synthesis of the hormone oxytocin in prairie voles. Oxytocin facilitates sociability, among other functions, and prairie voles are well characterized as social animals that are monogamous with mates and raise their pups together. Thus, the researchers sought to determine how the elimination of oxytocin production might affect social attachment among these animals. The researchers measured anxiety, parenting behaviors, sociability toward a familiar vole versus a novel vole, and repetitive behavior. Without oxytocin, voles appeared normal in regard to anxiety and parenting behavior. However, the affected voles did not show a preference between a familiar vole and a novel vole. Moreover, the voles engaged in repetitive behavior. At the conclusion of their report, the authors suggested that the prevention of oxytocin production in the animals led to behaviors—lack of recognition of a familiar vole and repetitive behavior—that appeared in some ways like autism spectrum disorder in humans.

Overall, CRISPR technology holds promise for novel genetic therapies in humans. Further, CRISPR offers innovative approaches for behavioral neuroscience research.

STOP & CHECK

1. What is the advantage of using CRISPR for genetic therapy in humans?
2. For preclinical research, how does the ability to use genetic manipulation in other species, aside from mice (see Box 2.1), aid in neuroscience research?

1. Genetic manipulation can lead to a host of unintended gene mutations, and thus serious adverse effects, unless high precision can be used for the genetic procedures. CRISPR-Cas9 may meet this "high precision" requirement and, for this reason, is the most promising genetic therapy tool to date. **2.** Although enormous discoveries about the brain and medical advances have come from mice, this species is not always the best to use for the objectives of the study. In the study about prairie voles presented in this section, researchers desired to closely study prosocial behaviors using genetic manipulation. The voles, they found, exhibited a number of social behaviors found in humans, and therefore, the voles (instead of mice) would provide information that would be more useful to translating their findings to humans.

CHAPTER SUMMARY

The cells in the central nervous system consist of glial cells and neurons. Neurons consist of dendrites, a soma, an axon, and an axon terminal. Signals from other neurons are received through dendrites, and the message is sent to other neurons from the axon terminal. Glial cells play an important role in supporting the function of neurons.

The nervous system consists of the peripheral nervous system and the central nervous system. The peripheral nervous system consists of the somatic nervous system—for sensory and motor signals—and the autonomic nervous system—for vital functions. The autonomic nervous system consists of the sympathetic, parasympathetic, and enteric nervous systems.

The central nervous system consists of the brain and spinal cord. We divide the brain into subdivisions called the *hindbrain, midbrain*, and *forebrain*. The forebrain division is the largest and encompasses the four cortical lobes in the brain called the *occipital lobe* (for vision), the *parietal lobe* (mainly for processing touch information), the *temporal lobe* (for audition and language), and the *frontal lobe* (for cognition and movement). The limbic system consists of the amygdala, hippocampus, cingulate gyrus, thalamus, and hypothalamus. An adjacent structure, the nucleus accumbens, mediates rewarding effects. Together these structures play an important role in emotion. With the exception of olfactory information, which goes directly to the prefrontal cortex, sensory information is received from the head and body and routed through the thalamus to the appropriate lobe for processing. The prefrontal cortex is the most anterior portion of the frontal lobe and the integration center for all sensory information. Motor signals are

sent down to the body beginning in the primary motor cortex. The basal ganglia help regulate voluntary movements.

The cells in the brain receive important sugars and nutrients from the cerebrospinal fluid surrounding these cells and oxygen from blood vessels. Cerebrospinal fluid exists throughout the central nervous system through the central canal in the spinal cord and through a network of ventricles and the cerebral aqueduct in the brain. Cerebral blood flow increases in active parts of the brain.

The basic functions and development of cells are directed by genes, which are segments of DNA. Molecules that activate genes are called *transcription factors*. Gene activation causes a copy of the gene to be imprinted on RNA. RNA directs the production of protein synthesis through ribosomes found outside of the cell's nucleus.

KEY TERMS

Astrocyte
Autonomic nervous system
Axons
Basal ganglia
Cerebellum
Cerebral blood flow
Cerebral cortex
Cerebrospinal fluid
Dendrites
Enteric nervous system
Ependymocytes
Epigenetics
Frontal lobe
Gene
Glial cells (glia cells)
Hippocampus
Hypothalamus
Interneuron
Limbic system
Medulla
Microglial cell
Motor cortex
Motor neuron (motoneuron)
Neurons
Nucleus accumbens
Occipital lobe
Oligodendrocyte
Parasympathetic nervous system
Parietal lobe
Periaqueductal gray
Polymorphism
Prefrontal cortex
Reticular activating system
Soma
Sensory neuron
Somatic nervous system
Sympathetic nervous system
Synapse
Temporal lobe
Thalamus
Transcription factor
Ventricles