CHAPTER

2

Behavioral Analysis of Drug Effects

The term *behavioral pharmacology* was first used in the 1950s by Peter Dews of Harvard Medical School to refer to the investigation of drug effects using operant analysis of behavior (more on operant analysis later in this chapter). Before this time, the term *psychopharmacology* was common. This term was coined in the 1920s by David Macht of Johns Hopkins University and is still widely used outside of North America. It increasingly refers to research involving the study of drugs in the treatment of mental illness or psychological disorders. Nowadays, behavioral pharmacology more commonly refers to the study of the effects of drugs on behavior using any of the experimental techniques of modern behaviorally oriented psychology and, increasingly, behavioral neuroscience.

It is important to note that there may be several aims of research in behavioral pharmacology. As Travis Thompson and Charles Schuster (1964), the authors of the first text in the field, put it, "The behavioral pharmacologist is not only interested in observing behavioral changes produced by drugs, but analyzing the mechanisms of the drug's effect." We shall see many examples of this later in the text.

HISTORY OF BEHAVIORAL PHARMACOLOGY

It is clear that people have used mind-altering drugs for millennia, and scholars, including Aristotle and early Greek and Egyptian physicians, have shown a great interest in the effects of those drugs on behavior. Until the beginning of the twentieth century, investigations of these substances involved only verbal descriptions of the effects of the drug on the subjective experience, more often with literary rather than scientific intent. Such descriptions as De Quincey's *Confessions of an English Opium Eater* and Gautier's *Le Club des Hachichins* were fascinating illustrations of the drug experience, but were of limited value to science.

Scientific study of the effects of these substances first had to await the nineteenth-century development of modern chemical techniques that permitted the isolation of drugs from natural substances and the synthesis of substances that do not occur naturally. It also had to await the same sort of maturation of the study of behavior in the twentieth century. This development was inspired by the American scholar and philosopher John B. Watson who pointed out that, to be a science, psychology should study only behavior rather than thoughts and other subjective experiences that could not be observed. What psychology needed was a precise, systematic, and replicable means of describing, recording, and analyzing behavior. By the middle of the twentieth century, the technological, conceptual, and theoretical groundwork to study behavior of both humans and nonhumans had been developed by scientists such as Pavlov, Thorndike, and Skinner.

During the 1940s and 1950s, there was growing interest among pharmacologists with regard to how drugs that affected the central nervous system might alter behavior. Consequently, the behavioral research carried out by pharmacologists mostly involved unstructured observations of laboratory animals after they had been given a drug, and activity counts that estimated the degree of running, sleeping, convulsions, or other similar behaviors. If the drug increased locomotor activity (such as running), it was taken to indicate that the drug was a central nervous system *stimulant*; if activity decreased, the drug was a *depressant*. Similarly, psychologists had explored the effect of drugs on various behaviors in apparatuses such as the Skinner box, runways, and mazes.

Even though both psychologists and pharmacologists were doing behavioral research with drugs, up until the 1950s there was no separate discipline of behavioral pharmacology, per se. The impetus to develop such a field came in the early 1950s and arose largely from three events. The first was the tremendous therapeutic and commercial success of chlorpromazine and other antipsychotic drugs (see Chapter 12), and the resulting need to design tests for laboratory animals that were useful in screening drugs for potential therapeutic effects in humans. Second was the compelling demonstration by Peter Dews of the usefulness of Skinner's operant techniques to study drug effects. The third event was the application of physiology to the understanding of behavior, largely inspired by Joseph Brady, who you will learn more about later in this chapter.

Chlorpromazine and the Psychotherapeutic Revolution

Chlorpromazine was marketed in 1952 by the French pharmaceutical company Rhône-Poulenc as an antipsychotic drug. Until that time, there had been no effective treatment for psychoses, apart from institutionalization. After the development of chlorpromazine and other antipsychotic drugs, it became possible to close many psychiatric hospitals, and the development and marketing of antipsychotic drugs became immensely profitable. The success of chlorpromazine demonstrated the tremendous economic potential of behaviorally active drugs and sparked an intensive search by pharmaceutical and university laboratories for new drugs and new medical applications of older drugs.

The development of chlorpromazine hinged upon behavioral techniques that had been used to confirm its antipsychotic properties and that of other phenothiazine drugs as well. One such behavioral test, developed by David Macht, examined the effect of antipsychotic drugs on the ability of rats to avoid and escape electric shock by climbing up a pole (the *escape–avoidance test* is described later). There was a clear need for a better understanding of how drugs altered behavior; this could be accomplished only by a synthesis of pharmacology and the behavioral techniques developed by psychologists. Such a merger would not only be useful to pharmaceutical companies wanting to develop and test new compounds, but as a separate field of investigation that could lead to a better understanding of the interaction of drugs with behavioral processes.

Operant Analysis of Drug Effects

Peter Dews was trained as a physician, but was doing pharmacological and physiological research at Harvard Medical School when he became interested in the study of the effects of drugs on behavior. In his attempts at research, he was unsatisfied with the technology available to him for measuring the behavioral effects of drugs. But after an encounter with B. F. Skinner at Harvard University, he began studying the effects of drugs on pigeons' pecking for grain reinforcement in a Skinner box.

Dews soon demonstrated how useful operant methodology could be when he published a series of papers that are now considered to be the seminal works of the field that was to become behavioral pharmacology. Figure 2-1 is taken from a paper Dews published in 1955. It shows the effect of different doses of pentobarbital (a *sedative*) on the rate of key pecking of pigeons responding for food on two different schedules of reinforcement (schedules of reinforcement are described in more detail later in this chapter). The administration of pentobarbital produced varying results depending on the reinforcement schedule in effect. At doses of 1.0 to 2.0 mg/kg, the drug increased key pecking rates in pigeons responding on a fixed ratio 50 schedule, but decreased rates on a fixed interval 15-minute schedule.

Dews showed that the same dose of pentobarbital altered the behavior of the pigeon in a different manner depending on the schedule of reinforcement in effect at the time the drug was given. This showed convincingly that the drug's effects depend on the type of behavior that is occurring rather than simply depressing or

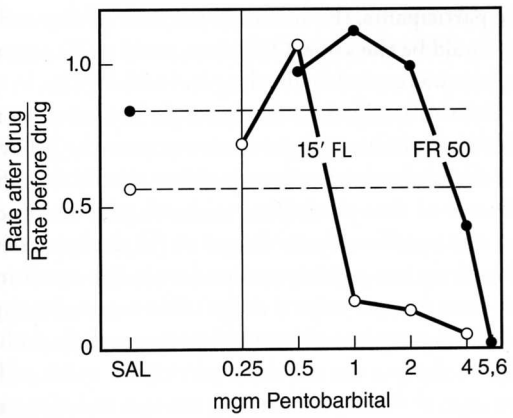

FIGURE 2-1 The log dose–effect curves for pentobarbital on the relative key pecking rate of pigeons responding on FI 15-minute (open circles) and FR 50 schedules (closed circles). The dotted lines indicate response levels after a control injection of saline. (From Dews, 1955.)

stimulating all behavior. This paper and several more like it were published in pharmacology journals. Operant techniques finally captured the attention of pharmacologists and became widely used for studying the effects of drugs on behavior.

Using Physiology to Understand Behavior

In the mid- and late-1950s, Joseph V. Brady established the first university-associated laboratory using behavioral technology to study drug–behavior interactions at Walter Reed Army Medical Center and later at the University of Maryland and Johns Hopkins School of Medicine. Like Dews, Brady, a pioneer in the field of *physiological psychology*, now commonly called *behavioral neuroscience*, was one of the first to use operant technology to study the effects of drugs. Unlike Skinner, he and his students believed that neuroscience could be useful in understanding the effects of drugs on behavior and that behavioral pharmacology research was a useful tool in understanding the nervous system. In addition to numerous publications, Brady stimulated the development of behavioral pharmacology by training many young researchers and urging the pharmaceutical industry and the federal government of the United States to support this new field. Among others, Brady mentored Charles Schuster, a pioneer in the study of drugs as reinforcing stimuli (see Chapter 5), drugs as discriminative stimuli, and conditioned drug effects in addiction. Schuster also served as director of the National Institute on Drug Abuse (NIDA) in the United States from 1986 to 1992 (Schuster, 2004).

Founding of the Behavioral Pharmacology Society

In 1956, a conference was held on "The Techniques for the Study of the Behavioral Effects of Drugs," sponsored by the New York Academy of Sciences. It was chaired by Dews and Skinner and included Brady and many others from both pharmacology and psychology who were doing behavioral research with drugs. Also in 1956, Skinner made a formal call for the development of a new science of behavioral pharmacology. The new science got its formal start when the Behavioral Pharmacology Society was founded. In the mid-1950s, a group interested in pharmacology started having informal evening dinner meetings during the annual meeting of the Eastern Psychological Association. The Society evolved from this group in 1957.

Behavioral Pharmacology in Europe

Early interest in the behavioral analysis of drug effects was not confined to North America. In Britain, interest in the field was stimulated by a pioneering symposium held in London in 1963, sponsored by the Ciba Foundation. It was attended by many prominent European researchers of the time, as well as those from North America including Len Cook and Peter Dews. The proceedings were edited by Hannah Steinberg and published in 1964. Since that time, researchers including D. E. Blackman, David Sanger, Susan Iverson, Trevor Robbins, and Ian Stolerman and their students have had an extensive impact on the field. The continued expansion of behavioral pharmacology in Europe was marked by the founding of *The European Behavioral Pharmacology Society* in 1986.

RESEARCH DESIGN

All scientific experimentation can be thought of as a search for a relationship between events. In behavioral pharmacology, the researcher is usually trying to discover

the relationship between the presence (or dose) of a drug in an organism and changes that occur in the behavior of that organism. In most true experiments, one of these events is created or manipulated by the experimenter, and the other event is measured. The manipulated event is called the *independent variable*, and the observed or measured event is called the *dependent variable*. The independent variable in behavioral pharmacology is usually the amount of drug put into the organism; that is what the researcher manipulates. The dependent variable is usually some change in the behavior of that organism, and this is what the researcher measures. Later in this chapter we will discuss some of the more commonly used measures of behavior, or dependent variables.

Experimental Research Design

EXPERIMENTAL CONTROL. It is not enough to give a drug and observe its effect. For an experiment to be meaningful, the experimenter must be able to compare what happened when the drug was given with what would have happened if the drug had not been given.

A controlled experiment is one in which it is possible to say with some degree of certainty what would have happened if the drug had not been given. This permits comparisons between drug and nondrug states. For example, a researcher could give each person in a group of participants a pill containing tetrahydrocannabinol (THC), an active ingredient in marijuana, and observe that everyone tended to laugh a great deal afterward. These observations would not be worth much unless the researcher could also demonstrate that the increased laughter was a result of the drug and not of the participants' expectations, their nervousness about being observed, or some factor other than the presence of the drug in their bodies. With most behavioral experiments, many factors could influence the results, so it is essential to be sure that the drug, and not something else in the procedure, caused the laughter.

The only truly reliable way to do this experiment and eliminate all other possible causes of the laughter would be to have a time machine so that, after the experiment, the researcher could go back and, under exactly the same circumstances, give the same participants pills identical in appearance but not containing any drug. Comparisons could then be made between the amount of laughter with and without the drug because all other factors (the participants, the situation, the time of day, and so on) would be the same. Only then could we be sure the laughter was caused by the drug and nothing else.

Unfortunately, time machines do not exist, so the behavioral pharmacologist must compare the behavior of a drugged participant with either (a) the drug-free behavior of that participant under similar conditions (i.e., use a *within-subjects design*) or (b) the behavior of other drug-free participants under similar conditions (i.e., use a *between-subjects design*). There are advantages and disadvantages to either strategy. For example, within-subjects designs use the same participant as his or her own control thereby eliminating random variations and the influence of genetic differences between participants. They typically use fewer participants, but take longer to run. Between-subjects experiments are typically faster and involve more participants, but must use group averages, and the behavior of individuals is seldom noted.

PLACEBO CONTROLS. It should be obvious that to be completely useful, a control condition must be as similar as possible to the experimental condition, except for one variable: the presence or absence of the drug. In our example in which the effect of THC on laughing was determined, the control procedure could have been improved. As you recall, we had two conditions: in one, the experimental participant was administered a pill containing THC, and, in the other, the participant was not given anything at all. It is quite possible that being given a pill might have caused the participants to become nervous and that could cause nervous laughter.

For this reason, behavioral pharmacologists always use a control condition that involves the administration of something to both groups. In this case, both groups could have been given an identical-looking pill, but the pill given in the control condition would have contained an inactive substance such as sugar. If injections had been involved, the control group would have been given only the vehicle with no drug dissolved in it (see Chapter 1).

PLACEBO EFFECTS. Such careful controls are especially important with human participants because of the placebo effect. As we have seen, a placebo is a totally inert substance that causes no physiological change but is administered as though it were a drug. If people believe they are getting a drug that will have a specific effect, they will frequently show that effect even though the drug does not cause it.

In an interesting experiment by Fillmore and Vogel-Sprott (1992), three groups of participants were given a cup of coffee before being tested on a psychomotor performance task. One group was told that caffeine would speed their performance, one group was told that caffeine would slow their responding, and the third group was not told anything. In actuality, all groups were given a placebo; the coffee was decaffeinated. The groups' performances matched what the participants had expected: Those who were told to expect improvement did better than those who were told nothing, and those who were told to expect impairment did worse than those who were told nothing.

The placebo effect makes careful control an absolute necessity when evaluating the clinical effectiveness of newly developed medicines because patients will frequently show an effect they expect the drug to produce. For example, let us suppose that we are testing a new pain reliever. We go to a hospital and give the drug to a group of patients who are in postoperative pain and tell them that this new drug should relieve their distress. The next day, we find that 68% of the patients report that their pain was relieved. By itself, this is not a useful experiment because we do not know how many patients would have reported the same thing simply because they had been told the drug was a pain reliever. To do this experiment the proper way, it would be necessary to have two groups of patients. Both groups would be told they were getting a pain reliever, but only one group would get the new drug; the other would be given an identical pill containing only inactive filler. The next day, pain ratings would be taken from all the patients, and comparisons could be made.

The balanced placebo design was developed in the mid-1970s by George Marlatt and his colleagues at Washington State University in Seattle (Marlatt & Rohsenow, 1980). It remains the gold standard for research with humans in which the participants' expectations could influence the results in a manner similar to the Fillmore and Vogel-Sprott experiment described previously. In the balanced placebo design, there are four groups. Two are the same as those in a standard placebo design where participants in both groups expect to get a drug, but one gets a drug whereas the other gets a placebo. In the two additional groups, none of the participants expect to get the drug, but participants in one group do, whereas participants in the other group get a placebo.

This design provides a powerful means of separating the drug effect from the expectancy or placebo effect because there is a group that does not expect the drug, but gets it. Any change in this group must be due entirely to the drug. There is also a group that expects the drug but gets a placebo. Any change seen in this group must be due entirely to the expectation effect and not the drug. In Chapter 3, there is an extended discussion of the nature of the placebo effect.

THREE-GROUPS DESIGN. When a new drug is undergoing clinical trials for use in the treatment of a disease (phase 3 in the long process described later in this chapter by which new medicines are approved), the standard design is what is known as a *three-groups design*. One group is given the experimental drug to be tested, a second group is given a placebo, and a third group is given an established drug with known therapeutic effect. By having three groups, the researchers can answer a number of important questions. Comparisons between the experimental drug group and the placebo group show whether the drug caused any improvement; comparisons between the placebo group and the established drug group indicate whether the research measures were sensitive enough to detect an improvement; and comparisons between the experimental and established drug groups tell whether the new drug has any advantage over established treatment (Overall, 1987). There are some circumstances where the placebo group may be left out. If the drug is being used to treat a life-threatening or serious disease, it would not be ethical to give anyone a placebo. In this case, the new drug would be compared only with the established treatment.

EXPERIMENTER BIAS. Further precautions must be taken in experiments investigating drug effects. It has been known for some time that an experimenter can influence the outcome of research without knowing it. For example, if the researcher knows which patients have been given a placebo, the researcher might unconsciously change the manner in which the patients are interviewed or even make systematic mistakes in recording data. To eliminate experimenter bias, it is usually necessary to conduct the experiment so that neither the patients nor the researchers giving the drug and interviewing the patients know who has been given the drug and who has been given the placebo. This procedure is

called a *double-blind procedure,* and it is essential because it eliminates the possibility of placebo effects and experimenter-bias effects. Experimenter bias can also be a factor in research on laboratory animals, especially in tests where the researcher must make judgments or score some aspect of the animal's behavior.

Nonexperimental Research

A good deal of what we know about drugs is a result of research that does not involve experiments. As explained earlier, experiments attempt to find relationships between two events: a manipulated event and a measured event. *Nonexperimental research* looks for a relationship between two measured events. A good example is the discovery of a relationship between smoking during pregnancy and infant mortality. It was shown some time ago that there was a higher rate of infant death among babies born to women who smoked during pregnancy than among babies born to nonsmoking mothers (see Chapter 8). In this research, nothing was manipulated; there was no independent variable. The two events, smoking and infant mortality, were measured and found to be correlated.

One major difficulty with this type of finding is that it can only show that two variables are correlated. It cannot tell us that one event caused the other. We know that children born to smoking mothers are more likely to die, but we cannot conclude that smoking causes the infants' deaths. The relationship might be due to some third factor that causes both events. For example, it may be that women smoke because they have a biochemical imbalance that causes their bodies to need the nicotine in cigarettes. This imbalance might also be responsible for the higher infant mortality rates. The only way we could be sure that the smoking caused the infant mortality would be to do a true experiment by randomly assigning pregnant women to either one of two groups: forcing the women in one group to smoke and preventing women in the other from smoking. If there were a difference in infant mortality between the two groups, we would be in a good position to argue that smoking caused the infant deaths. Of course, such an experiment is out of the question on ethical grounds and could never be done with humans. For this reason, we must be satisfied with correlation rather than causal data on many issues of drug effects in humans.

MEASURING UNCONDITIONED BEHAVIOR OF NONHUMANS

It is often interesting to know the effect of a drug on the unlearned behavior of laboratory animals, that is, the effect of a drug on coordination, movement, anxiety, or the effect of a painful stimulus. Described next are several standard tests that are often used to evaluate the effects of a drug on such behaviors.

Unconditioned Behavior

The simplest measure of behavior in nonhumans is how much of it there is. Such measures are usually referred to as *spontaneous motor activity* (SMA), which may be quantified in a number of ways. Usually, the animal is placed in an *open field* (a large open box), and its movements are measured either electronically or by drawing a grid on the floor of the open field and counting the number of times the animal crosses a line.

Much can also be learned simply by observing the behavior of animals after they have been given drugs. Some classes of drugs cause animals to exhibit *stereotyped behavior*—the continuous repetition of simple, purposeless acts such as rearing or head bobbing. Other drugs may cause sleep or convulsions.

It is also possible to measure other unconditioned behavior using very simple techniques. For example, muscle tone in rats can be measured using an *inclined plane test* where the animal is placed on a board that can be tilted to various degrees. The degree of tilt where the animal is unable to hold on to the surface and slides off is a measure of muscle tone.

A test used to measure anxiety is the *elevated plus maze,* which consists of narrow boards in the shape of a *plus* raised a foot or more off the ground. Two opposite arms of the plus have walls, and the other two do not. Normally, rats spend most of their time on the arms that have walls and only occasionally venture out on the unprotected arms. Drugs that are known to relieve anxiety cause rats to spend more time than they normally would on the unprotected arms.

There are several tests for *analgesia,* or the ability of a drug to block pain. The most common is the *paw lick latency test.* Rats are placed on a metal surface that is heated to about 50 degrees Celsius. This is about the temperature of a hot cup of coffee. When you first pick it up it feels warm, but the longer you hold it the hotter

it becomes until you have to put it down. When rats are first placed on the hot surface, they do not react. But within a few seconds, they raise one of their hind paws to their mouth as though they were licking it. The length of time it takes for this to happen is called the *paw lick latency*. Analgesic drugs like morphine lengthen this latency, which is often used as a measure of a drug's analgesic effect. Even if the rat does not show this response, it is removed after a fixed number of seconds to prevent the heat from burning the skin.

MEASURING CONDITIONED BEHAVIOR OF NONHUMANS

Learned or *conditioned* behavior is frequently classified by whether it is a result of *classical* or *operant* conditioning.

Classical Conditioning

When a dog salivates at the sight and smell of food, the salivation is a reflexive behavior under the control of the stimulus of food. Such a reflex or response is considered to be unconditioned. Thus, the stimulus, that is, the food, is the *unconditioned stimulus* (UCS), and the salivation is the *unconditioned response* (UCR). Pavlov (1927) found that if the sight of food is paired with a neutral stimulus, such as a ringing bell, the bell alone eventually elicits the salivation in the absence of food. Thus, the bell becomes a *conditioned stimulus* (CS), and the salivation to the bell in the absence of food is the *conditioned response* (CR).

In Pavlov's laboratory in St. Petersburg, one of his students observed the effect of caffeine, cocaine, morphine, and alcohol on conditioned reflexes. These studies were some of the very first experiments in behavioral pharmacology, but such studies are rare in behavioral pharmacology today. It was another experiment from Pavlov's laboratory that had a far greater influence on the field. In that experiment, it was demonstrated that a stimulus that preceded the delivery of a drug could be a CS, which could elicit conditioned drug-like effects (CR; see page 47 in Chapter 3 for a description of this experiment). Pavlov did not pursue this line of research, but, later, other scientists did. Chapter 3 describes the many applications of classical (Pavlovian) conditioning for understanding the effects of drugs on the development of tolerance and addiction.

Operant Conditioning

A dog that learns to beg for food at the table is demonstrating operant conditioning. The begging is the operant, and it is maintained by the occasional delivery of food. If begging no longer results in the delivery of food, the begging stops.

The principles of operant conditioning are thought to apply to nearly all behavior of all animals. Operant behavior is usually studied in the laboratory using a *Skinner box*—a small cage attached to an apparatus that will deliver small quantities of food, water, or some other reinforcing stimulus. It also contains a *manipulandum*, something that the animal can manipulate or move (e.g., a bar, lever, or knob). Figure 2-2 shows a Skinner box for a rat. In this box, a food delivery system delivers one small pellet of rat food at a time. The manipulandum is a lever on the wall near the food dish.

To study operant conditioning, it is usual to first deprive the subject of food or water so that it can act as a reward for performing the desired operant (in this case, pressing the lever). Each lever press is detected electronically and causes food to be delivered. In this way, the rat is rewarded, or *reinforced*, each time it makes the desired response. When the rat has learned this response, it makes it frequently and reliably.

Reinforcement

Many different stimuli can act as a reinforcer depending on the state of the animal and its past experience. Skinner defined a reinforcer as any event that increases the frequency of a response that it is contingent upon. Notice that a reinforcer is defined in terms

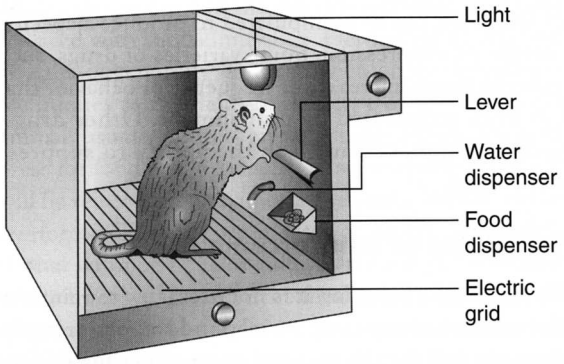

FIGURE 2-2 A typical Skinner box.

of its effect on behavior, not on whether it satisfies a particular need or motivation or causes pleasure. Reinforcers can be either positive or negative. *Positive reinforcers* will increase behavior when they are given or applied following the behavior's occurrence, like food tends to do. *Negative reinforcers* will increase behavior when they are removed or prevented following the behavior's occurrence, as is often seen with electric shock.

Reinforcers can also be primary or secondary. A *primary reinforcer* is a stimulus that acts as a reinforcer without prior experience (i.e., it is rewarding in and of itself). A *secondary reinforcer* is also known as a *conditioned reinforcer* because it acquires its reinforcing properties through classical conditioning when it is paired with a primary reinforcer. As we shall see later in this chapter and in Chapter 5, drug administration can act as a primary reinforcer, and the stimuli associated with its delivery can become secondary or conditioned reinforcers.

Punishment

Responding that is maintained by positive reinforcement may be suppressed if it is also followed by a stimulus such as an electric shock. The effect of punishment on behavior is usually measured by having the animal respond for a positive reinforcer delivered in a manner that produces a steady rate of responding (see schedules of reinforcement next). At various times during a session, a light is turned on and lasts for a minute or two. During this stimulus, each response is followed not only by the positive reinforcer but also by a shock. Responding during the presence of the light will be suppressed. The frequency and intensity of the shock can be manipulated to produce a specific amount of suppression. Some varieties of drugs, such as barbiturates, increase the frequency of behavior that has been suppressed by punishment. Other drugs, such as amphetamine, lack the ability to suppress responding.

Schedules of Reinforcement

To maintain a behavior, it is not necessary to reinforce the animal every time it responds appropriately. Animals will usually respond many times for one reinforcement, and in most operant research, this is the case. Reinforcement may be given after a specific number of responses or on the basis of time. The term *schedule of reinforcement* refers to the pattern that determines when reinforcements are to be given.

Each schedule of reinforcement engenders a characteristic pattern of responding that will be seen no matter what the species or type of reinforcer. These patterns are reliable and predictable, and they are sensitive to the effects of many drugs. Behavioral pharmacologists have found them a useful means of analyzing the behavioral effects of drugs because, as Peter Dews showed, specific schedules are more sensitive to some drugs than others, and similar drugs affect schedule-controlled behavior in a similar manner (refer back to Figure 2-1).

RATIO SCHEDULES OF REINFORCEMENT. When reinforcement is given based on the number of responses an animal makes, the schedule is known as a *ratio schedule*. On a *fixed ratio* (FR) schedule, the animal is required to make a fixed number of responses in order to be reinforced. For example, on an FR 30 schedule, every 30th response produces reinforcement. If only 29 responses are made, the reinforcer is not given. A *variable ratio* (VR) schedule is similar except that the number of required responses varies from reinforcer to reinforcer, so that at any given time the occurrence of a reinforced response cannot be predicted. A VR 30 schedule will produce reinforcement after every 30 responses, on average.

INTERVAL SCHEDULES OF REINFORCEMENT. On an *interval schedule*, an animal's responding is reinforced only if a period of time has elapsed since the previous reinforcer was applied. Responses that the animal makes during (but before completion of) the time interval are recorded, but do not influence the delivery of reinforcement. On a *fixed interval* (FI) schedule, a response is reinforced only after a fixed time has elapsed. A typical example might be an FI 3 schedule; the animal must wait 3 minutes after the delivery of reinforcement for a response to be reinforced again. On a *variable interval* (VI) schedule, the interval during which the animal is required to wait before a behavior is reinforced varies. When a value is specified for a VI, such as VI 2, this indicates that the interval is an average of 2 minutes long.

AVOIDANCE–ESCAPE TASK. Not only will animals learn to press a lever to obtain a positive reinforcer like food, but they will also learn to avoid and escape aversive stimuli such as electric shocks. On a typical avoidance–escape schedule, the animal is presented with a stimulus, such as a buzzer or a light, as a warning that a shock is coming. The warning comes several seconds before the shock. If the animal makes a response during that time, the warning stimulus is turned off and the shock never comes; that is, this is the *avoidance* of shock. If the animal does not respond to the warning stimulus, the shock turns on, and the animal can then *escape* the shock by responding.

As mentioned earlier, the avoidance–escape task has proved to be a valuable tool in identifying drugs that treat psychotic behavior in humans. These drugs interfere with an animal's ability to avoid shock, but do not have any effect on the animal's ability to turn off or escape from the shock when it does come. This finding shows that the drug has not interfered with the motor ability of the animal to respond but has selectively blocked the motivation to avoid the shock.

The avoidance–escape procedure is used in a number of different apparatuses in addition to the Skinner box. It can be used in a *shuttle box*, which is a long narrow box with a grid floor that can be electrified. When the warning signal is sounded, the animal must run across the midline and to the other end of the box to avoid getting the shock. If it does not avoid the shock, it can escape the shock by crossing the midline to the safe end of the box. When the warning stimulus sounds again, the animal must run back to the other side of the box. The *pole climbing task* used by David Macht in the development of chlorpromazine was also an avoidance–escape task.

STIMULUS PROPERTIES OF DRUGS

Drugs as Discriminative Stimuli

A large and productive branch of contemporary behavioral pharmacology deals with drugs as discriminative stimuli. Investigations into the discriminative properties of drugs originated with research in the early neurophysiological theories of Donald Hebb at McGill University.

For years, there had been anecdotal accounts suggesting that events experienced in a drugged state might not have the ability to control behavior when the organism was not in a drugged state, and vice versa. This phenomenon is called *dissociation* or *state-dependent learning*.

While investigating dissociation, Donald Overton, then a graduate student in McGill University's Psychology Department, performed a series of shock escape–avoidance experiments using rats in a *T-maze* (literally, a maze shaped like a "T" in which animals are placed at the bottom of the T and choose to enter the left or right arm at the top of the T). Overton was easily able to demonstrate that rats that learned to avoid the shock in the maze when drugged with pentobarbital were unable to avoid the shock later when given a placebo, and vice versa.

To explore the extent of dissociation, Overton wanted to determine whether information learned on drug days (e.g., turn into the right arm of the T to avoid shock) would interfere with information acquired on saline days (e.g., turn into the left arm of the T to avoid shock), and vice versa. On alternate days, the rats were administered pentobarbital, and one arm of the T-maze led directly to safety. On other days, they were given a saline placebo, and the other arm was safe. Overton discovered that the rats very quickly learned to make the appropriate response depending on whether they were drugged or not. In other words, he showed that the drug administration was acting as a discriminative stimulus, which controlled the direction in which the rat would turn at the choice point of the maze on the first trial of each day. He also found that rats would learn to make the appropriate response at doses much lower than those required to cause complete dissociation.

Since Overton's early experiments, research on the discriminative stimulus properties of drugs has expanded rapidly, and the electrified T-maze has been replaced with the Skinner box. Herbert Barry III, then at Yale, is generally credited with applying operant techniques to the field. In this type of task, a hungry animal, usually a rat, is given a choice of two levers to press for food reinforcement. In some sessions, lever A will be reinforced, and, in other sessions, lever B will be reinforced. The reinforcement is on an FR 20 schedule so that without a cue to guide it, the rat will not know which lever will produce the food until it has made 20 responses on one lever. In this situation, the only cue is the presence of a drug—on days when lever A is reinforced, the rat is injected with a drug, but on days when

lever B is reinforced, it is injected with saline. After a short period of training, the rat will learn to discriminate between the drug and saline so that, on drug days, it will start off responding on lever A, and on saline days, it will start off on lever B. Thus, the first 20 responses on any given day will show whether the rat thinks it has been injected with the drug or with saline.

Using these techniques, it has been demonstrated that most drugs that act on the central nervous system have discriminative stimulus properties, although some classes of drugs, such as the barbiturates, appear to be more easily discriminable than other classes. Such drugs can acquire discriminative control at least as rapidly, and in some cases more rapidly, than more conventional stimuli like noises and lights. It has also been shown that, as well as discriminating between a drug and saline, laboratory animals can discriminate between different doses of the same drug and between different drugs.

The drug discrimination paradigm has been successfully used to investigate many aspects of drug action. For example, you can use this technique to detect how soon the subjective effect of a drug begins after administration, and how long it lasts. Also, by administering drugs that block specific receptor sites (see Chapter 4), it is possible to determine which type of receptor site is targeted by the drug to produce its subjective effects.

A database of all drug state discrimination experiments is available online at www.drugrefs.org (Drug Self-Administration and Discrimination Database, 2011). This database is combined with a similar database for drug self-administration studies.

In addition to determining whether a drug can act as a discriminative stimulus, behavioral pharmacologists can test for generalization between drugs. Such a test is called a *substitution test*. First, an animal is trained to discriminate between saline and a drug. Then, the animal is given a substitute drug. The animal's response will indicate how the new substitute drug makes it feel. If the animal presses the same lever as it learned to do after the training drug, this indicates that the substitute drug made the animal feel the same as the training drug. Otherwise, the animal will press the saline lever. Thus, a rat might learn to press lever A after an administration of cocaine and then be tested with caffeine. If it presses the cocaine lever, this indicates that its subjective state following caffeine administration was similar to that following cocaine. Animals will usually generalize responses across drugs of the same pharmacological class, thus making the substitution test a valuable tool in drug screening and drug development.

REINFORCING PROPERTIES OF DRUGS—ABUSE LIABILITY

As noted previously, Skinner defined a reinforcer as any stimulus that would increase the frequency of a behavior on which it was contingent. As an example, if food follows a lever press and the frequency of that lever press increases, then food is a reinforcer. As you will see in Chapter 5, it is well established that some drugs act as reinforcers. Laboratory animals and people will learn to make some response if it is reliably followed by the administration of these drugs. The reinforcing property of a drug is an indication of its potential for abuse, that is, its *abuse liability*.

It is useful to have a measure of the abuse potential of a drug and a means of determining factors that can alter abuse potential. Several techniques have been developed to measure abuse potential, and they do so by measuring the ability of a drug to act as a reinforcer (Sanchis-Segura & Spanagel, 2006). These techniques were first used with nonhumans and later applied to humans.

Rate of Responding

With traditional reinforcers, we know that the greater the reinforcement, the faster an animal will respond. For example, rats will respond faster for three food pellets than they will for one. We might expect that animals will respond faster for drugs that are more reinforcing, but rate of responding has some problems. One problem is that drugs have different durations of action, and a long-acting drug might well be self-administered at a slower rate than a short-acting drug, merely because the effect of each dose lasts longer. In addition, rate of responding depends on the animal's ability to make a response. Many drugs have effects that interfere with self-administration. For example, monkeys will give themselves infusions of anesthetic doses of pentobarbital that immediately cause them to go to sleep. Such a drug may be highly reinforcing, but it could not be self-administered

at a high rate. Conversely, many drugs, such as cocaine, could stimulate their own self-administration.

Progressive Ratio Schedule of Reinforcement

In a progressive ratio (PR) schedule, the subject is required to work for a drug infusion on an FR schedule that consistently becomes more demanding. For example, the schedule may start at FR 5. After the first drug reinforcement is received, it might change to FR 10, then to FR 20, and so on. At some point, known as the *breaking point* or *break point*, the demand of the schedule will be too high, and the animal will stop responding. Compared to drugs that are not so reinforcing, highly reinforcing drugs will motivate the animal to work harder and will, consequently, produce a higher breaking point and greater potential for abuse. Nevertheless, there is evidence that measures of the reinforcing value of drugs, using the PR schedule, may also be affected by a drug's effect on the ability of an organism to respond (Rowlett, Massey, Kleven, & Woolverton, 1996). Box 10-2 in Chapter 10 provides an excellent example of the use of a PR schedule in rats to model the addictive behavior of humans.

Choice

The choice procedure is fairly simple. With laboratory animals, two levers are presented. In the first session, one lever will cause an infusion of drug A, and the other lever has no consequences. This is followed by a session in which the second lever will cause an infusion of drug B, and the first lever has no consequences. This procedure ensures that the animal has an equal exposure to both drugs A and B. Following this phase of the experiment, both levers will dispense their respective drugs, and the animal has the opportunity to respond on either lever. Presumably, the animal will respond more frequently on the lever that delivers the more reinforcing drug.

Conditioned Place Preference

The *conditioned place preference* (CPP) technique uses a long box that has two distinctive halves separated by a partition. One half of the box may have striped walls and a metal rod floor, whereas the other half may have solid white walls and a mesh floor. Rats are confined to one half of the box after being given an injection of a drug, and they experience the effect of the drug there. On an equal number of occasions, rats are injected with a placebo and confined to the other half of the box. Later, the partition is removed and rats are placed in the center of the box, free to wander between the chambers. The amount of time spent in each half of the box is recorded. Usually, rats will spend more time in the half of the box that has been associated with the reinforcing effects of the drug. The strength of their preference for that end of the box is a good indication of the reinforcing value of the drug (van der Kooy, 1987). A CPP is thought to develop because the location where the drug was experienced has become a conditioned stimulus that evokes the reinforcing effects of the drug. Therefore, the animal is reinforced for approaching that location and spending time there.

MEASURING BEHAVIOR OF HUMANS

Subjective Effects

It is often of interest to determine what effects a drug might have on how people feel; that is, does the drug make them feel happy, sad, or energized? In the early days of drug investigation, determining subjective effect was often done by giving the drug to someone and asking him or her to report his or her experiences, a process called *introspection*. In fact, it was not at all uncommon for investigators to take the drug themselves; because the drug experience is private, it can be observed only by the person who takes it. An essential requirement of scientific data is that they be observable to anyone; therefore verbal self-reports are not particularly helpful as a tool in behavioral pharmacology. This is not to say that unstructured verbal descriptions of drug-elicited internal states are not useful to a researcher. On the contrary, they guide and inspire more systematic study. But the accounts themselves are not adequate scientific data unless they are collected in a systematic or structured fashion.

Rating Scales

Introspection by itself is of no value to the scientist, but it is possible to collect subjective data in a systematic, quantitative manner that is useful. Psychologists have been doing this for many years by creating scales.

They might ask a person to rate how happy they are on a seven-point scale ranging from extremely sad to extremely happy. Sometimes a *visual analog scale* (VAS) is used where the participant makes a mark on a line between the two extreme alternatives to indicate how the variable applies to them. Many scales have been developed over the years and have been tested for their reliability (the stability of results at different time points) and validity (that the scales are measuring what they were designed to measure). Such rating scales have been adopted for use in drug research, and some have been specifically developed to study drug effects.

One scale that has been widely used in drug research is the *Profile of Mood States* (POMS), a paper-and-pencil test that asks participants to indicate on a five-point scale how each of 72 adjectives applies to them at a particular moment. These 72 items yield a score on eight independent subscales: anxiety, depression, anger, vigor, fatigue, confusion, friendliness, and elation. These scales give a reliable and quantifiable measure of a participant's internal state.

Another much more elaborate test is the *Addiction Research Center Inventory* (ARCI). It was developed so that each class of drugs creates a unique profile of mood and physical changes. This makes it possible to classify a new drug and assess its abuse potential by examining its profile and comparing it to the profiles of existing drugs.

Perhaps the simplest scale used to test drug effects is the *liking scale* where the participant indicates how much the drug is *liked*. Other scale items ask the participants to indicate how much they would *want* to use the drug again or whether the drug makes them feel *high* or *sedated*.

Drug State Discrimination

Although human drug state discrimination studies are not as common as those using laboratory animals, the procedure is similar. The big difference is that humans are often given instructions, which speeds up the process. Typically, the person is given a series of separate exposures to a drug and a placebo, either by pill or injection. In each trial, they are told they are getting either condition A or B. Then they are given a series of unidentified exposures to each condition and asked to identify whether it is condition A or B, oftentimes with the promise of a monetary reward for a correct identification. There does not seem to be any significant difference between humans and nonhumans in the ability to discriminate drugs, and the patterns of generalization between drugs are also similar.

Perception

A number of tests and techniques have been developed to measure the acuity of the senses, particularly sight and hearing. Sensitivity changes are reported as changes in thresholds. The term *absolute threshold* refers to the lowest value of a stimulus that can be detected by a sense organ. It is a measure of the absolute sensitivity of the sense organ. *Difference thresholds* are measures of the ability of a sense organ to detect a change in level or locus of stimulation. If a threshold increases, it means that the intensity of the stimulus must be increased in order for it to be detected. In other words, the sense has become less keen. A lowering in threshold means that a sense has become more sensitive.

An example of how threshold is measured is *critical frequency at fusion*. If the speed with which a light flickers is increased, eventually a speed will be reached where the light appears to be steady. This is the critical frequency at fusion, and it is sensitive to many drugs. The ability to detect flicker is a reliable measure of how well the visual system is functioning. To measure the functioning of hearing, an auditory flicker fusion test has also been developed.

Motor Performance

Motor performance is a major concern in assessing the effects of drugs on humans. One of the simplest measures of performance is *simple reaction time* (RT) test where the participant must make a response, like pressing a button as fast as possible, after a noise or a light is turned on. In a *complex reaction time* (CRT) test, there are several possible responses and several different signals associated with each one.

Hand–eye coordination is often measured by a device called a *pursuit rotor*. With this device, the participant is instructed to hold the end of a stylus on a spot contained on a rotating disk. The total time the participant is able to hold the stylus on the moving spot is a measure of hand–eye coordination.

Other commonly used tests of motor ability are finger tapping rate and hand steadiness.

Attention and Vigilance

Attention and vigilance can be affected by many drugs. One widely used test of attention and vigilance is the *Mackworth clock test*. It was developed during the World War II to test the performance of radar operators. In this test, the participant looks at a large circular dial like a radar screen. A clock hand moves around this dial in a step-by-step fashion at regular intervals. Occasionally, the hand will move two steps at once rather than one step. The participant must detect when this happens and push a button. The test may continue for several hours. This test was originally presented on a real panel, but is now administered on a computer, as are most of these tests.

Memory

There are several types of memory that can be affected differently by different drugs. One distinction that is often made is between *short-term memory* (also called *working memory*) and *long-term memory*.

Short term memory can hold a limited amount of information while it is being used for some purpose. We can remember a telephone number for a brief time between looking it up and dialing it. Information can be displaced from this short-term storage easily and is quickly lost unless actively rehearsed. Long-term memory is more or less permanent and can last for years. Memories are transferred from short term to long term by a consolidation process. We are sometimes not able to recall long-term memories without the aid of cues and prompts. Drugs are able to alter both the consolidation and the recall of long-term memories.

One test of short-term memory is the *N-back* test. This test is often used in conjunction with brain imaging. In this test, a series of letters or pictures is shown one at a time on a screen. When a target stimulus, such as an "X", appears on the screen, the participant must recall the stimulus that was shown previously (1-back); two stimuli back (2-back); or three, four, or more stimuli back. In a variation of the procedure, the participant must indicate when the stimulus on the screen is identical to the one that was one, two, three, or more back.

Long-term memory is further classified into two types: *implicit* and *explicit*. Implicit memory is sometimes called *procedural memory*; it is the memory of how to do things. Often, implicit memory is used without conscious awareness. Explicit memory, sometimes called *declarative memory*, is the ability to recall pieces of information—names, facts, dates, etc. There is a special type of explicit memory called *episodic memory* where we remember events that have happened to us. Thus, remembering how to ride a bicycle, even without much conscious effort, is implicit memory, but remembering that it is called a bicycle and recalling the experience of first learning to ride it is explicit memory. Explicit and implicit forms of memory seem to use different brain mechanisms because in some cases of amnesia, explicit memory can be lost, but implicit memory is unaffected. It is also possible for people to lose episodic memory, but not other types of declarative memory. This happens with Alzheimer's disease.

There are many tests of long-term memory, but in the traditional method, the participant is asked to remember a list of words or objects and then, after a period of time, to recall them. The participant may be asked to reproduce the items in the list (*free recall*) or may be shown an array of items and asked to identify the ones that were on the list (*cued recall*). Cued recall is much less demanding than free recall, which is why students typically prefer a multiple-choice exam over an essay exam! Sometimes, drugs can interfere with free recall of memories but have little effect on cued recall, indicating that the memories are there but the drug made them more difficult to retrieve.

Tests of Response Inhibition

It is sometimes noted that drugs can interfere with one's ability to withhold or inhibit actions; this is sometimes called *disinhibition*. Two tests of inhibition or impulse control are the *go–no go task* and the *go–stop task*. Both tests are very much like the simple reaction time test described earlier. In the go–no go task, the participant must respond as quickly as possible to one stimulus, but must not respond to a different stimulus. The percent of no go trials may vary in any session and may be very infrequent. The participant must withhold responding until the nature of the signal, go or stop, is determined. Drugs that interfere with inhibitory control are likely to cause an increase in responding to the no go signal.

The go–stop task is more difficult. There is a go signal, and the participant is instructed to respond to it as quickly as possible, but on some trials, the go signal is rapidly followed by a stop signal. The participant is

instructed to withhold the response if there is a stop signal. The time between the go signal and the stop signal may vary. If the delay is very short, the response to the go signal is easily inhibited, but as the interval is lengthened, it becomes more and more difficult to stop the response. For each participant, the delay at which he or she is able to inhibit the response 50% of the time is determined. Some drugs, like alcohol, lengthen this delay.

Driving

Because driving is such a necessary and common activity, it is important to know the effect many drugs have on the ability of a person to operate an automobile. Determining the effect of a drug on driving ability, however, is not as easy as it might seem. To begin with, driving is a complex activity requiring many skills of perception, motor control, and judgment. There is much more involved than simply moving a car from one place to another. Researchers have tried to assess driving skill using many different strategies. Some simply have participants drive a car through city traffic and have professional driving instructors rate participants' performance on a number of factors. One difficulty with this approach is that the demands of the task will be different for each person tested because traffic conditions are constantly changing. However, the bigger problem is that it is unethical to permit participants to drive in real traffic and endanger their lives and the lives of others if there is any possibility that their skills might be impaired by drugs.

To get around these issues, researchers sometimes have participants operate a vehicle around a closed course where various demands are made on the skill of the driver. This approach is more artificial but safer, and because the task is the same for each participant, comparisons are more easily made between and within participants.

One difficulty with using a real car is that it is sometimes difficult to accurately measure a participant's performance. You can tell if the participant knocks over a pylon, but you will not be able to determine whether the error resulted because the object was not seen, the participant could not estimate the speed of the car, the participant was unfamiliar with the car, or the reaction time was too slow. To answer such questions, many researchers use computerized driving simulators that are capable of measuring a participant's response time, steering ability, and capacity to react to specific crises. With some simulators, it is even possible to measure the participant's eye movements while driving. As you will see in Chapter 6, some laboratories use brain imaging technology to assess participants' processing while in a driving simulator.

DEVELOPMENT AND TESTING OF PSYCHOTHERAPEUTIC DRUGS

From time to time in the news we hear that some laboratory or hospital has made a breakthrough discovery of a new drug that promises to be a great improvement on current treatments for a particular disease. Often these stories end with the warning that it may be years before the new drug will be approved for use. The reason for this delay is that all drugs must undergo rigorous development and testing to demonstrate that they are effective and safe. Only then will they be approved by governmental agencies for sale as a medicine. In the United States, approval is granted by the federal Food and Drug Administration (FDA). Other countries have similar agencies.

Initial Screening and Therapeutic Testing

Scientists do not understand the biochemical basis of mental illness well enough to specifically design drugs with any certainty that they will have a desired effect on psychiatric symptoms and will produce a minimum of side effects. Instead, the laboratories of pharmaceutical companies synthesize many new chemicals they think might be effective. These drugs are then screened using nonhumans to determine whether they have effects similar to those of known therapeutically useful drugs and whether they are safe.

Screening tests, using laboratory animals, can help determine whether a drug might have therapeutic properties. Screening tests can also determine the safety of various drugs by determining the ED_{50} of the drug's behavioral effect and comparing it to the LD_{50} of that drug. When a new drug appears to be reasonably safe and shows interesting behavioral properties in nonhumans, it goes to phase 1 of human testing, which assesses the toxicity and side effects of the drug on healthy human volunteers. These studies are usually carried out using paid volunteers in an inpatient setting.

In phase 2, the drug is tested on patients under very carefully supervised conditions. In addition to recording adverse effects, changes in the medical condition are

noted. If phases 1 and 2 show that the drug has minimal toxic effects and also has a potential therapeutic effect, it then goes to phase 3, expanded clinical trials. These are usually carried out in university-teaching hospitals and other institutions and often use the three-groups design discussed earlier.

If phase 3 investigations are successful, the drug is licensed and marketed. The research, however, does not stop here. Phase 4 involves the accumulation of data on the success of the drug as used in the clinic. Attempts are made to identify adverse effects that were not apparent in the short-term testing during the early stages. In phase 4, improved dosing schedules may be developed, and individuals who are at risk of having adverse reactions to the drug can be identified.

Off-Label Use

When drugs are approved for use by a government agency, it usually specifies the medical condition it was designed to treat and on which it was tested, but the drug may be used by physicians to treat other disorders. This is called *off-label* use. It sometimes happens that the drug works surprisingly well for its off-label prescriptions. An example of this is the drug bupropion. It was developed originally as an antidepressant and given the trade name Wellbutrin. Later, it was coincidently discovered that it reduced smoking in people who took it. Clinical trials were done, and it was found to be an effective aid to smoking cessation. Now, in addition to being marketed as an antidepressant, it is sold as Zyban, a smoking cessation aid.