Biopsychology of Psychiatric Disorders
The Brain Unhinged

18.1 Schizophrenia
18.2 Affective Disorders: Depression and Mania
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This chapter is about the biopsychology of psychiatric disorders (disorders of psychological function sufficiently severe to require treatment). One of the main difficulties in studying or treating psychiatric disorders is that they are difficult to diagnose. The psychiatrist or clinical psychologist must first decide whether a patient’s psychological function is pathological or merely an extreme of normal human variation: For example, does a patient with a poor memory suffer from a pathological condition or is he merely a healthy person with a poor memory? If a patient is judged to be suffering from a psychiatric disorder, then the particular disorder must be diagnosed. Because we cannot identify the specific brain pathology associated with various disorders, their diagnosis usually rests entirely on the patient’s symptoms. The diagnosis is guided by the DSM-IV-TR (the current edition of the Diagnostic and Statistical Manual of the American Psychiatric Association). There are two main difficulties in diagnosing particular psychiatric disorders: (1) patients suffering the same disorder often display different symptoms, and (2) patients suffering from different disorders often display many of the same symptoms. Consequently, experts often disagree on the diagnosis of particular cases, and the guidelines provided by the DSM change with each new edition.

This chapter begins with discussions of four psychiatric disorders: schizophrenia, affective (emotional) disorders, anxiety disorders, and Tourette syndrome. It ends with a description of how new psychotherapeutic drugs are developed and tested.

### 18.1 Schizophrenia

Schizophrenia means “the splitting of psychic functions.” The term was coined in the early years of the 20th century to describe what was assumed at that time to be the primary symptom of the disorder: the breakdown of integration among emotion, thought, and action.

Schizophrenia is the disease that is most commonly associated with the concept of madness. It attacks about 1% of individuals of all races and cultural groups, typically beginning in adolescence or early adulthood. Schizophrenia occurs in many forms, but the case of Lena introduces you to some of its common features.

### The Case of Lena, the Catatonic Schizophrenic

Lena’s mother was hospitalized with schizophrenia when Lena was 2. She died in the hospital under peculiar circumstances, a suspected suicide. As a child, Lena displayed periods of hyperactivity; as an adolescent, she was viewed by others as odd. Although she enjoyed her classes and got good grades, she seldom established relationships with her fellow students. Lena rarely dated. However, she married her husband only a few months after meeting him. He was a quiet man who tried to avoid fuss or stress at all costs and who was attracted to Lena because she was quiet and withdrawn.

Shortly after their marriage, Lena’s husband noticed that Lena was becoming even more withdrawn. She would sit for hours barely moving a muscle. He also found her having lengthy discussions with nonexistent persons. Lena rarely dated. However, she married her husband only a few months after meeting him. He was a quiet man who tried to avoid fuss or stress at all costs and who was attracted to Lena because she was quiet and withdrawn.

Shortly after their marriage, Lena’s husband noticed that Lena was becoming even more withdrawn. She would sit for hours barely moving a muscle. He also found her having lengthy discussions with nonexistent persons.

About 2 years after he first noticed her odd behavior, Lena’s husband found her sitting on the floor in an odd posture staring into space. She was totally unresponsive. When he tried to move her, Lena displayed waxy flexibility—that is, she reacted like a mannequin, not resisting movement but holding her new position until she was moved again. At that point, he took her to the hospital, where her disorder was immediately diagnosed as stuporous catatonic schizophrenia (schizophrenia characterized by long periods of immobility and waxy flexibility).
In the hospital, Lena displayed a speech pattern that is exhibited by many schizophrenics: echolalia (vocalized repetition of some or all of what has just been heard).

**Doctor:** How are you feeling today?

**Lena:** I am feeling today, feeling the feelings today.

**Doctor:** Are you still hearing the voices?

**Lena:** Am I still hearing the voices, voices? (Meyer & Salmon, 1988)

### What Is Schizophrenia?

The major difficulty in studying and treating schizophrenia is accurately defining it (Heinrichs, 2005; Krueger & Markon, 2006). Its symptoms are complex and diverse; they overlap greatly with those of other psychiatric disorders and frequently change during the progression of the disorder. Also, various neurological disorders (e.g., complex partial epilepsy; see Chapter 10) have symptoms that might suggest a diagnosis of schizophrenia. In recognition of the fact that the current definition of schizophrenia likely includes several different brain diseases, some experts prefer to use the plural form to refer to this disorder: the schizophrenias (Wong & Van Tol, 2003).

The following are some symptoms of schizophrenia, although none of them appears in all cases. In an effort to categorize cases of schizophrenia so that they can be studied and treated more effectively, it is common practice to consider **positive symptoms** (symptoms that seem to represent an excess or distortion of normal function) separately from **negative symptoms** (symptoms that seem to represent a reduction or loss of normal function).

**Positive Symptoms**

- **Delusions.** Delusions of being controlled (e.g., “Martians are making me steal”), delusions of persecution (e.g., “My mother is poisoning me”), or delusions of grandeur (e.g., “Tiger Woods admires my backswing”).
- **Hallucinations.** Imaginary voices making critical comments or telling patients what to do.
- **Inappropriate affect.** Failure to react with the appropriate emotion to positive or negative events.
- **Incoherent speech or thought.** Illogical thinking, echolalia, peculiar associations among ideas, belief in supernatural forces.
- **Odd behavior.** Difficulty performing everyday tasks, lack of personal hygiene, talking in rhymes, catatonia (remaining motionless, often in awkward positions for long periods).

**Negative Symptoms**

- **Affective flattening.** Reduction or absence of emotional expression.

- **Alogia.** Reduction or absence of speech.
- **Avolition.** Reduction or absence of motivation.
- **Anhedonia.** Inability to experience pleasure.

The recurrence of any two of these symptoms for 1 month is sufficient for the diagnosis of schizophrenia (Tammenga & Holcomb, 2005; Walker et al., 2004). Only one symptom is necessary if the symptom is a delusion that is particularly bizarre or an hallucination that includes voices.

### Causal Factors in Schizophrenia

In the first half of the 20th century, the cloak of mystery began to be removed from mental illness by a series of studies that established schizophrenia’s genetic basis (see Walker & Tessner, 2008). First, it was discovered that although only 1% of the population develops schizophrenia, the probability of schizophrenia’s occurring in a close biological relative (i.e., a parent, child, or sibling) of a schizophrenic patient is about 10%, even if the relative was adopted shortly after birth by a healthy family (e.g., Kendler & Gruenberg, 1984; Rosenthal et al., 1980). Then, it was discovered that the concordance rates for schizophrenia are higher in identical twins (45%) than in fraternal twins (10%)—see Holzman and Matthyse (1990) and Kallman (1946). Finally, adoption studies have shown that the risk of schizophrenia is increased by the presence of the disorder in biological parents but not by its presence in adoptive parents (Gottesman & Shields, 1982).

The fact that the concordance rate for schizophrenia in identical twins is substantially less than 100% suggests that differences in experience have a significant effect on the development of schizophrenia. The current view is that some people inherit a potential for schizophrenia, which may or may not be activated by experience. Supporting this view is a recent comparison of the offspring of a large sample of identical twins who were themselves discordant for schizophrenia (i.e., one had the disorder and one did not); the incidence of schizophrenia was as great in the offspring of the twin without schizophrenia as in the offspring of the twin with schizophrenia (Gottesman & Bertelsen, 1989).

It is clear that schizophrenia has multiple causes. Several different genes have been linked to the disorder (see Hall et al., 2009; O’Tuathaigh et al., 2007; Walsh et al., 2008). However, the mechanisms by which these genes contribute to schizophrenia have yet to be determined. Also, a variety of early experiential factors have been implicated in the development of schizophrenia—for example, birth complications, early infections, autoimmune reactions, toxins, traumatic injury, and stress. These early experiences are thought to alter the normal course of neurodevelopment, leading to schizophrenia in individuals who have a genetic susceptibility (see Jaruskog, Miyamoto, & Lieberman, 2007;
Discovery of the First Antischizophrenic Drugs

The first major breakthrough in the study of the biochemistry of schizophrenia was the accidental discovery in the early 1950s of the first antischizophrenic drug, chlorpromazine. Chlorpromazine was developed by a French drug company as an antihistamine. Then, in 1950, a French surgeon noticed that chlorpromazine given prior to surgery to counteract swelling had a calming effect on some of his patients, and he suggested that it might have a calming effect on difficult-to-handle psychotic patients. His suggestion proved to be incorrect, but the research it triggered led to the discovery that chlorpromazine alleviates schizophrenic symptoms: Agitated patients with schizophrenia were calmed by chlorpromazine, and emotionally blunted patients with schizophrenia were activated by it. Don’t get the idea that chlorpromazine cures schizophrenia. It doesn’t. But it often reduces the severity of schizophrenic symptoms enough to allow institutionalized patients to be discharged.

Shortly after the antischizophrenic action of chlorpromazine was first documented, an American psychiatrist became interested in reports that the snakeroot plant had long been used in India for the treatment of mental illness. He gave reserpine—the active ingredient of the snakeroot plant—to his patients with schizophrenia and confirmed its antischizophrenic action. Reserpine is no longer used in the treatment of schizophrenia because it produces a dangerous decline in blood pressure at the doses needed for the treatment.

Although the chemical structures of chlorpromazine and reserpine are dissimilar, their antischizophrenic effects are similar in two major respects. First, the antischizophrenic effect of both drugs is manifested only after a patient has been medicated for 2 or 3 weeks. Second, the onset of this antischizophrenic effect is usually associated with motor effects similar to the symptoms of Parkinson’s disease: tremors at rest, muscular rigidity, and a general decrease in voluntary movement. These similarities suggested to researchers that chlorpromazine and reserpine were acting through the same mechanism, one that was related to Parkinson’s disease.

Dopamine Theory of Schizophrenia

Paradoxically, the next major breakthrough in the study of schizophrenia came from research on Parkinson’s disease. In 1960, it was reported that the striatums (caudates plus putamens) of persons dying of Parkinson’s disease had been depleted of dopamine (Ehringer & Hornykiewicz, 1960). This finding suggested that a disruption of dopaminergic transmission might produce Parkinson’s disease, and, because of the relation between symptoms of Parkinson’s disease and the antischizophrenic effects of chlorpromazine and reserpine, that antischizophrenic drug effects might be produced in the same way. Thus was born the dopamine theory of schizophrenia—the theory that schizophrenia is caused by too much dopamine and, conversely, that antischizophrenic drugs exert their effects by decreasing dopamine levels.

Lending instant support to the dopamine theory of schizophrenia were two already well-established facts. First, the antischizophrenic drug reserpine was known to deplete the brain of dopamine and other monoamines by breaking down the synaptic vesicles in which these neurotransmitters are stored. Second, drugs such as amphetamine and cocaine, which can trigger schizophrenic episodes in healthy subjects, were known to increase the extracellular levels of dopamine and other monoamines in the brain.

An important step in the evolution of the dopamine theory of schizophrenia came in 1963, when Carlsson and Lindqvist assessed the effects of chlorpromazine on extracellular levels of dopamine and its metabolites (substances that are created by the breakdown of another substance in cells). Although they expected to find that chlorpromazine, like reserpine, depletes the brain of dopamine, they didn’t. The extracellular levels of dopamine were unchanged by chlorpromazine, and the extracellular levels of its metabolites were increased. The researchers concluded that both chlorpromazine and reserpine antagonize transmission at dopamine synapses but that they do it in different ways: reserpine by depleting the brain of dopamine and chlorpromazine by binding to dopamine receptors. Carlsson and Lindqvist argued that chlorpromazine is a receptor blocker at dopamine synapses—that is, that it binds to dopamine receptors without activating them and, in so doing, keeps dopamine from activating them (see Figure 18.1 on page 470). We now know that many psychoactive drugs are receptor blockers, but chlorpromazine was the first to be identified as such.

Carlsson and Lindqvist further postulated that the lack of activity at postsynaptic dopamine receptors sent a feedback signal to the presynaptic cells that increased their release of dopamine, which was broken down in the synapses. This explained why dopaminergic activity was reduced while extracellular levels of dopamine stayed about the same and extracellular levels of its metabolites were increased. Carlsson and Lindqvist’s findings led to an important revision of the dopamine theory of schizophrenia:
Rather than high dopamine levels, the main factor in schizophrenia was presumed to be high levels of activity at dopamine receptors.

In the mid-1970s, Snyder and his colleagues (Creese, Burt, & Snyder, 1976) assessed the degree to which the various antischizophrenic drugs that had been developed by that time bind to dopamine receptors. First, they added radioactively labeled dopamine to samples of dopamine-receptor–rich neural membrane obtained from calf striatums. Then, they rinsed away the unbound dopamine molecules from the samples and measured the amount of radioactivity left in them to obtain a measure of the number of dopamine receptors. Next, in other samples, they measured each drug’s ability to block the binding of radioactive dopamine to the sample, the assumption being that the drugs with a high affinity for dopamine receptors would leave fewer sites available for the dopamine. In general, they found that chlorpromazine and the other effective antischizophrenic drugs had a high affinity for dopamine receptors, whereas ineffective antischizophrenic drugs had a low affinity. There were, however, several major exceptions, one of them being haloperidol. Although haloperidol was one of the most potent antischizophrenic drugs of its day, it had a relatively low affinity for dopamine receptors.

A solution to the haloperidol puzzle came with the discovery that dopamine binds to more than one receptor subtype—five have been identified (Hartmann & Civelli, 1997). It turns out that chlorpromazine and other effective antischizophrenic drugs had a high affinity for dopamine receptors, whereas ineffective antischizophrenic drugs had a low affinity. There were, however, several major exceptions, one of them being haloperidol. Although haloperidol was one of the most potent antischizophrenic drugs of its day, it had a relatively low affinity for dopamine receptors.

This discovery of the selective binding of butyrophenones to D₂ receptors led to an important revision in the dopamine theory of schizophrenia. It suggested that schizophrenia is caused by hyperactivity specifically at D₂ receptors, rather than at dopamine receptors in general. Snyder and his colleagues (see Snyder, 1978) subsequently confirmed that the degree to which neuroleptics—antischizophrenic drugs—bind to D₂ receptors is highly correlated with their effectiveness in suppressing schizophrenic symptoms (see Figure 18.2). For example, the butyrophenone spiroperidol had the greatest affinity for...
D₂ receptors and the most potent antischizophrenic effect.

Although the evidence implicating D₂ receptors in schizophrenia is strong, it has become apparent that the D₂ version of the dopamine theory of schizophrenia cannot explain several key findings. Appreciation of these limitations has led to the current version of the theory. This version holds that excessive activity at D₂ receptors is a factor in the disorder but that there are other, as yet unidentified, causal factors. The major events in the development of the dopamine theory are summarized in Table 18.1.

### TABLE 18.1 The Key Events That Led to the Development and Refinement of the Dopamine Theory of Schizophrenia

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 1950s</td>
<td>The antischizophrenic effects of both chlorpromazine and reserpine were documented and related to their parkinsonian side effects.</td>
</tr>
<tr>
<td>Late 1950s</td>
<td>The brains of recently deceased Parkinson’s patients were found to be depleted of dopamine.</td>
</tr>
<tr>
<td>Early 1960s</td>
<td>It was hypothesized that schizophrenia was associated with excessive activity at dopaminergic synapses.</td>
</tr>
<tr>
<td>1960s and early 1970s</td>
<td>Chlorpromazine and other clinically effective neuroleptics were found to act as receptor blockers at dopamine synapses.</td>
</tr>
<tr>
<td>Mid-1970s</td>
<td>The affinity of neuroleptics for dopamine receptors was found to be only roughly correlated with their antischizophrenic potency.</td>
</tr>
<tr>
<td>Late 1970s</td>
<td>The binding of existing antischizophrenic drugs to D₂ receptors was found to be highly correlated with their antischizophrenic potency.</td>
</tr>
<tr>
<td>1980s and 1990s</td>
<td>It became clear that the D₂ version of the dopamine theory of schizophrenia cannot account for all of the research findings.</td>
</tr>
</tbody>
</table>

**Neural Basis of Schizophrenia: Limitations of the Dopamine Theory**

The following are four key discoveries about the neural bases of schizophrenia that cannot be explained by the D₂ version of the dopamine theory. These discoveries suggest that although overactivity at D₂ receptors plays a role in schizophrenia, other important factors are yet to be identified.

**Receptors Other Than D₂ Receptors Are Involved in Schizophrenia** Neurotransmitters other than dopamine have been linked to schizophrenia, including glutamate (Javitt & Coyle, 2004; Tuominen, Tiihonen, & Wahlbeck, 2005), GABA (Lewis, Hashimoto, & Volk, 2005), and serotonin (Sawa & Snyder, 2002). Much of the evidence implicating serotonin and glutamate comes from the study of hallucinogenic drugs such as *lysergic acid diethylamide* (LSD) and *phencyclidine* (PCP). Both LSD and PCP produce psychological symptoms similar to those of schizophrenia by acting on serotonergic and glutaminergic transmission (see González-Maeso & Sealfon, 2009).

Compelling evidence that D₂ receptors are not the sole mechanism underlying schizophrenia came from the development of *atypical neuroleptics* (antischizophrenic drugs that are not primarily D₂ receptor blockers). For example, *clozapine*, the first atypical neuroleptic for the treatment of schizophrenia, has an affinity for D₁ receptors, D₄ receptors, and several serotonin receptors, but only a slight affinity for D₂ receptors.

Clozapine has some promising therapeutic properties. It is often effective in treating patients with schizophrenia who have not responded to *typical neuroleptics*, and it does not produce parkinsonian side effects. Unfortunately, the therapeutic utility of clozapine is limited because it produces a severe blood disorder in some patients who use it (see Wong & Van Tol, 2003); however, a number of other atypical neuroleptics are in wide use.

**It Takes Weeks of Neuroleptic Therapy to Alleviate Schizophrenic Symptoms** As you have already learned, it takes several weeks of neuroleptic therapy to alleviate schizophrenic symptoms. However, neuroleptics effectively block activity at D₂ receptors within hours. This time difference indicates that the blockage of D₂ receptors is not the specific mechanism by which the neuroleptics have their therapeutic effect. It appears that blocking D₂ receptors triggers some slow-developing compensatory change in the brain that is the key factor in the therapeutic effect.

**Schizophrenia Is Associated with Widespread Brain Damage** With the development of neuroimaging techniques in the 1960s, reports of brain pathology in patients with schizophrenia accumulated rapidly. The first generation of studies reported enlarged ventricles and fissures (see Figure 18.3 on page 472), which indicated reduced brain size. Subsequent studies focused on specific cortical areas and subcortical structures. A recent meta-analysis reported reduced volume in 50 different brain regions (see
Kubicki et al., 2007). Schizophrenia-related brain damage occurred in both gray and white matter, and was most consistently observed in the temporal lobes (see Honea et al., 2005). Figure 18.4 illustrates the amount of gray matter loss documented by structural MRIs in various cortical areas of a group of teenagers with schizophrenia (Thompson et al., 2001). Similarly, post-mortem studies of schizophrenic brains have found widespread neuron loss and abnormalities of neuron structure and circuitry in many parts of the brain (see Walker et al., 2004).

Two things about the pattern of brain damage observed in many patients with schizophrenia are problematic for the dopamine theory: One is that there is little evidence of specific structural damage to dopaminergic circuits (see Egan & Weinberger, 1997; Nopoulis et al., 2001); the other is that the dopamine theory provides no rationale for the diffuse pattern of brain damage that is typically observed.

Because schizophrenia is believed to be a neurodevelopmental disorder, many studies have assessed the development of brain damage in patients with schizophrenia. Three important findings have emerged—see the meta-analyses of Steen and colleagues (2006) and Vita and colleagues (2006):

- Extensive brain damage exists when patients first seek medical treatment and have their first brain scan.
- Subsequent brain scans reveal that the brain damage has continued to develop.
- Damage to different areas of the brain develops at different rates (Vidal et al., 2006).
Neuroleptics Are Only Marginally Effective  If the 
D₂ version of the dopamine theory of schizophrenia were 
correct, then typical neuroleptics should be effective 
treatments for all cases of schizophrenia. They aren’t. It is 
important to remember that just because a drug has been 
proven to have statistically significant beneficial effects, 
that doesn’t mean that these effects are large.

To put this point in perspective, consider the results of 
a meta-analysis that re-evaluated all of the studies that 
had compared the effectiveness of the neuroleptic chlor-
promazine to that of a placebo (Adams et al., 2005). The 
analysis revealed that there were clear beneficial effects 
only when chlorpromazine was administered for more 
than 6 months and that, even then, only about 1 in 7 pa-
tients was helped substantially.

Neuroleptics are also marginally effective in the sense that 
even when they do have beneficial effects, they tend to act on 
only some symptoms of schizophrenia—contradicting the 
dopamine theory, which predicts that neuroleptics should 
 improve the entire condition. In general, neuroleptics are 
much more effective in treating positive symptoms of 
schizophrenia than they are in treating negative symp-
toms (Murphy et al., 2006).

Patients often stop taking typical neuroleptics because 
of the motor side effects. There was great optimism when 
the atypical neuroleptics were introduced because they 
did not produce the movement disturbances associated 
with typical neuroleptics. However, it has become appar-
ent that the atypical neuroleptics have their own array of 
side effects, including diabetes, weight gain, and problems 
with fat regulation (e.g., Melkersson & Dahl, 2004). As a 
result, according to another meta-analysis, patients are 
just as likely to refuse to keep taking atypical neuroleptics 
as typical neuroleptics (Leucht et al., 2004). Indeed, in 
one 18-month comparison of patients who had been pre-
scribed atypical or typical neuroleptics, the overall 
dropout rate was 74% (Lieberman et al., 2005).

The Case of P.S., the Weeping 
Widow

P.S. was a 57-year-old widow and mother of four. She was 
generally cheerful and friendly and known for her metic-
ulous care of her home and children. She 
took great pride in having reared her 
children by herself following the death 
of her husband 14 years earlier.

For no apparent reason, her life began to change. She 
suddenly appeared more fatigued, less cheerful, and 
much more lackadaisical about her housework. Over the ensu-
ning weeks, she stopped going to church and cancelled all 
of her regular social engagements, including the weekly 
family dinner, which she routinely hosted. She started to 
spend all her time sleeping or rocking back and forth and 
sobbing in her favorite chair. She wasn’t eating, bathing, 
or changing her clothes. And her house was rapidly be-
coming a garbage dump. She woke up every morning at 
about 3:00 A.M. and was unable to get back to sleep.

Things got so bad that her two children who were still 
living with her called her oldest son for advice. He drove

Sleep disturbances and thoughts of suicide are common. 
When this condition lasts for 
more than 2 weeks, these peo-
ple are said to be suffering 
from clinical depression, or 
 major depressive disorder. The case of P.S. introduces you 
to some of the main features of clinical depression.
from the nearby town where he lived. What he found reminded him of an episode about 10 years earlier, when his mother had attempted suicide by slitting her wrists.

At the hospital, P.S. answered few questions. She cried throughout the admission interview and sat rocking in her chair wringing her hands and rolling her head up towards the ceiling. When asked to explain what was bothering her, she just shook her head no.

She was placed on a regimen of antidepressant medication. Several weeks later, she was discharged, much improved (Spitzer et al., 1983).

**Major Categories of Affective Disorders**

Depression is an **affective disorder** (any psychiatric disorder characterized by disturbances of mood or emotion). **Mania**, another affective disorder, is in some respects the opposite of depression; it is characterized by overconfidence, impulsivity, distractibility, and high energy. Affective disorders are also commonly known as **mood disorders**.

During periods of mild mania, people are talkative, energetic, impulsive, positive, and very confident. In this state, they can be very effective at certain jobs and can be great fun to be with. But when mania becomes extreme, it is a serious clinical problem. When mania is full-blown, the person often awakens in a state of unbridled enthusiasm, with an outflow of incessant chatter that careens nonstop from topic to topic. No task is too difficult. No goal is unattainable. This confidence and grandiosity, coupled with high energy, distractibility, and a leap-before-you-look impulsiveness, result in a continual series of disasters. Mania often leaves behind it a trail of unfinished projects, unpaid bills, and broken relationships.

Many depressive patients experience periods of mania. Those who do are said to suffer from **bipolar affective disorder**. Those depressive patients who do not experience periods of mania are said to suffer from **unipolar affective disorder**. Depression is often further divided into two categories. Depression triggered by a negative experience (e.g., the death of a friend, the loss of a job) is called **reactive depression**; depression with no apparent cause is called **endogenous depression**.

In most countries, the probability of suffering from clinical depression during one’s lifetime is about 10%. Women tend to be diagnosed with unipolar affective disorder about twice as frequently as men (see Altemus, 2006; Bale, 2006; Hyde, Mezulis, & Abramson, 2008)—but the reason for this is unclear. There is no sex difference in the incidence of bipolar affective disorder. A high rate of suicide among the clinically depressed is well documented, and the lifetime rate that is often reported is 15%, which is based on a 1970 meta-analysis (Guze & Robins, 1970). Because this high figure seemed to be inconsistent with their experiences at the Mayo Clinic, Bostwick and Pankratz (2000) re-examined the 1970 meta-analysis and spotted a major methodological flaw. They then conducted a more accurate meta-analysis and found that the lifetime risk of suicide in an individual diagnosed with clinical depression is about 5%.

Affective disorders attack children, adolescents, and adults. Indeed, it has been suggested that bipolar affective disorders that first appear in childhood, adolescence, and adulthood may constitute three different subgroups with different symptoms and causes (Carlson & Meyer, 2006). In adults, affective disorders are associated with heart disease (Frasure-Smith & Léspérance, 2005; Miller & Blackwell, 2006); in adult women, these disorders are associated with bone loss (Eskandari et al., 2007).

**Causal Factors in Affective Disorders**

Genetic factors contribute to differences among people in the development of affective disorders. Twin studies of affective disorders suggest a concordance rate of about 60% for identical twins and 15% for fraternal twins, whether they are reared together or apart. Although there are many exceptions, there is a tendency for affected twins to suffer from the same type of disorder, unipolar or bipolar; and the concordance rates for bipolar disorders tend to be higher than those for unipolar disorders. No particular gene has been linked to affective disorders (see Berton & Nestler, 2006).

Most of the research on the causal role of experience in affective disorders has focused on the role of stress in the etiology of depression. Indeed, depression is often described as a stress-related disorder (Bale, 2005). However, good evidence linking stress to affective disorders is sparse. Several studies have shown that stressful experiences can trigger attacks in people already suffering from depression (e.g., Brown, 1993), but there is little evidence showing that stress can increase the susceptibility to affective disorders in the healthy—even childhood sexual abuse appears to have only a slight effect on the development of depression in adulthood (see Nelson et al., 2002). Rather than depression, extreme stress tends to produce **posttraumatic stress disorder**, which you will learn more about later in this chapter.

There are two affective disorders whose cause is more apparent because of the timing of the attacks. One is **seasonal affective disorder** (SAD), in which attacks of depression and lethargy typically recur every winter (Lam et al., 2006). Two lines of evidence suggest that the attacks are triggered by the reduction in sunlight. One is that the incidence of the disorder is higher in the northern United States (9%) than in Florida (1.5%), where the winter days are longer and brighter (Modell et al., 2005). The other is that **light therapy**...
is often effective in reducing the symptoms (Lam et al., 2006). The second affective disorder with an obvious cause is **postpartum depression**, the intense, sustained depression experienced by some women after they give birth. The diagnosis of postpartum depression requires that the depression last for at least 1 month. It normally lasts no longer than 3 months. Although estimates vary, the disorder seems to develop following about 10% of deliveries.

**Discovery of Antidepressant Drugs**

Four major classes of drugs have been used in the treatment of affective disorders (see Berton & Nestler, 2006): monoamine oxidase inhibitors, tricyclic antidepressants, selective monoamine-reuptake inhibitors, and mood stabilizers.

**Monoamine Oxidase Inhibitors** Iproniazid, the first antidepressant drug, was originally developed for the treatment of tuberculosis, for which it proved to be a dismal flop. However, interest in the antidepressant potential of the drug was kindled by the observation that it left patients with tuberculosis less concerned about their disorder. As a result, iproniazid was tested on a mixed group of psychiatric patients and seemed to act against clinical depression. It was first marketed as an antidepressant drug in 1957.

Iproniazid is a monoamine agonist; it increases the levels of monoamines (e.g., norepinephrine and serotonin) by inhibiting the activity of **monoamine oxidase (MAO)**, the enzyme that breaks down monoamine neurotransmitters in the **cytoplasm** (cellular fluid) of the neuron. **MAO inhibitors** have several side effects; the most dangerous is known as the **cheese effect** (see Youdim, Edmonson, & Tipton, 2006). Foods such as cheese, wine, and pickles contain an amine called **tyramine**, which is a potent elevator of blood pressure. Normally, these foods have little effect on blood pressure, because tyramine is rapidly metabolized in the liver by MAO. However, people who take MAO inhibitors and consume tyramine-rich foods run the risk of strokes caused by surges in blood pressure.

**Tricyclic Antidepressants** The **tricyclic antidepressants** are so named because of their antidepressant action and because their chemical structures include three rings of atoms. **Imipramine**, the first tricyclic antidepressant, was initially thought to be an antischizophrenic drug. However, when its effects on a mixed sample of psychiatric patients were assessed, it had no effect against schizophrenia but seemed to help some depressed patients. Tricyclic antidepressants block the reuptake of both serotonin and norepinephrine, thus increasing their levels in the brain. They are a safer alternative to MAO inhibitors.

**Selective Monoamine-Reuptake Inhibitors** In the late 1980s, a new class of drugs—the selective serotonin-reuptake inhibitors—was introduced for treating clinical depression. **Selective serotonin-reuptake inhibitors (SSRIs)** are serotonin agonists that exert agonistic effects by blocking the reuptake of serotonin from synapses—see Figure 18.5.
Fluoxetine, which is marketed as Prozac, was the first SSRI to be developed. Now there are many more (e.g., Paxil, Zoloft, Luvox, Remeron). Prozac’s structure is a slight variation of that of imipramine and other tricyclic antidepressants; in fact, Prozac is no more effective than imipramine in treating depression. Nevertheless, it was immediately embraced by the psychiatric community and has been prescribed in many millions of cases. The remarkable popularity of Prozac and other SSRIs is attributable to two things: First, they have few side effects; second, it is claimed that they act against a wide range of psychological disorders in addition to depression. Because SSRIs are so effective against disorders that were once considered to be the exclusive province of psychotherapy (e.g., lack of self-esteem, fear of failure, excessive sensitivity to criticism, and inability to experience pleasure), they have had a major impact on psychiatry and clinical psychology.

In 2003, there was an indication that SSRIs might increase suicide rates, and U.S. and European public health agencies issued warnings. However, increased suicide rates in SSRI users were not observed in subsequent studies (e.g., Bridge et al., 2007; Simon et al., 2006; Tiibonen, 2006). As a result of the premature warning from governmental agencies, SSRI prescriptions decreased, and suicide rates increased markedly between 2003 and 2005 (Gibbons et al., 2007).

The success of the SSRIs spawned the introduction of a similar class of drugs, the selective norepinephrine-reuptake inhibitors (SNRIs). These (e.g., Reboxetine) have proven to be as effective as the SSRIs in the treatment of depression. Also used against depression are drugs (e.g., Wellbutrin, Effexor) that block the reuptake of more than one monoamine neurotransmitter.

Mood Stabilizers Antidepressant drugs have a major drawback: They often act against depression in bipolar patients by triggering bouts of mania. This led to the development of a new class of drugs for the treatment of bipolar affective disorders—the mood stabilizers. Mood stabilizers are drugs that act against depression without increasing mania or, conversely, act against mania without increasing depression (Bourin & Prica, 2007). The mechanism by which mood stabilizers work is unknown (see Gould & Einat, 2007), but for some reason these drugs are also effective in the treatment of epilepsy.

Lithium, a simple metallic ion, was the first drug found to act as a mood stabilizer. The discovery of lithium’s antimania action is yet another important pharmacological breakthrough that occurred by accident. John Cade, an Australian psychiatrist, mixed the urine of manic patients with lithium to form a soluble salt; then he injected the salt into a group of guinea pigs to see if it would induce mania. As a control, he injected lithium into another group. Instead of inducing mania, the urine solution seemed to calm the guinea pigs; and because the lithium control injections had the same effect, Cade concluded that lithium, not uric acid, was the calming agent. In retrospect, Cade’s conclusion was incredibly foolish. We now know that at the doses he used, lithium salts produce extreme nausea. To Cade’s untrained eye, his subjects’ inactivity may have looked like calmness. But the subjects weren’t calm; they were sick. In any case, flushed with what he thought was the success of his guinea pig experiments, in 1954 Cade tried lithium on a group of 10 manic patients, and it seemed to have a therapeutic effect. There was little immediate reaction to Cade’s report—few scientists were impressed by his scientific credentials, and few drug companies were interested in spending millions of dollars to evaluate the therapeutic potential of a metallic ion that could not be protected by a patent. It was not until the late 1960s that lithium was found to treat mania without increasing depression.

Effectiveness of Drugs in the Treatment of Affective Disorders About 2 billion dollars is spent in the United States each year by the Medicaid program on antidepressants (Chen et al., 2008). But how effective are antidepressants? Numerous studies have evaluated the effectiveness of antidepressant drugs against unipolar affective disorder. Hollon, Thase, and Markowitz (2002) compared the efficacy of the various pharmacological treatments for depression. The results were about the same for MAO inhibitors, tricyclic antidepressants, and selective monoamine-reuptake inhibitors: About 50% of clinically depressed patients improved. This rate seems quite good; however, the control group showed a 25% rate of improvement, so only 25% of the depressed group were actually helped by the antidepressants.

In 2008, the news about the benefits of antidepressants got a lot worse. Kirsch and colleagues (2008) conducted a meta-analysis of all the evaluation studies of the four most commonly prescribed antidepressants that were on record with the U.S. Food and Drug Administration. They found that the antidepressants did not produce improvements that were significantly greater than those produced by placebos in patients who were mildly or moderately depressed. In the severely depressed, the improvements were slight. The meta-analysis indicated that antidepressants work, but mostly through the placebo effect—overall, the placebos were 82% as effective as the actual drugs.

The effectiveness of mood stabilizers in the treatment of bipolar affective disorder was reviewed by Bourin and Prica (2007), who concluded that the ideal mood stabilizer does not exist—an ideal mood stabilizer would effectively stop attacks of depression or mania without triggering the alternative condition and then keep subsequent attacks from recurring. Although the evidence is sparse, they concluded that lithium and carbamazepine (an anti-epileptic drug) are best for treating mania, and lamotrigine (another anti-epileptic drug) is best for treating depression.
Brain Pathology and Affective Disorders

Numerous MRI studies of the brains of bipolar patients have been published. Reductions in overall brain size (e.g., Frazier et al., 2005) and in the size of many different brain structures (e.g., amygdala, cingulate cortex, or prefrontal cortex) have been reported (e.g., Savitz & Drevets, 2009; Delbello et al., 2004). However, the pattern of results is inconsistent: A particular brain structure found to be reduced in size in some studies is often found to be of normal size in others (McDonald et al., 2004). This suggests that not all patients diagnosed as having bipolar affective disorder by current criteria suffer from the same disorder (see Fountoulakis et al., 2008).

However, there are two structures that are found to be abnormal in many structural and functional brain-imaging studies of affective disorders: the amygdala (e.g., Gotlib & Hamilton, 2008; Savitz & Drevets, 2009) and the anterior cingulate cortex (Fountoulakis et al., 2008; Greicius et al., 2007). Even the connections between these two structures appear to be disturbed in patients with affective disorders (e.g., Matthews et al., 2009; Wang et al., 2009). Figure 18.6 illustrates the loss of tissue in the anterior cingulate cortex and the amygdala in a group of healthy volunteers who are genetically disposed to developing depression.

Theories of Depression

The search for the neural mechanisms of affective disorders has focused on clinical depression. However, the fact that depression and mania often occur in the same patients—that is, in those with bipolar affective disorder—suggests that the mechanisms of the two are closely related. None of the prominent theories of depression deals adequately with its relation to mania.

Monoamine Theory of Depression

One prominent theory of clinical depression is the monoamine theory. The monoamine theory of depression holds that depression is associated with underactivity at serotonergic and noradrenergic synapses. The theory is largely based on the fact that monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin-reuptake inhibitors, and selective norepinephrine-reuptake inhibitors are all agonists of serotonin, norepinephrine, or both.

Other support for the monoamine theory of depression has been provided by autopsy studies (see Nemeroff, 1998). Norepinephrine and serotonin receptors have been found to be more numerous in the brains of deceased clinically depressed individuals who had not received pharmacological treatment. This implicates a deficit in monoamine release: When an insufficient amount of a neurotransmitter is released at a synapse, there are usually compensatory increases in the number of receptors for that neurotransmitter—a process called up-regulation.
Overall, support for the monoamine theory of depression is weak. Although the theory is based on the fact that monoamine agonists are used to treat depressed patients, few depressed patients benefit substantially from them.

**Diathesis–Stress Model of Depression**  A second theory of depression is the *diathesis–stress model*. According to this theory (see Gillespie & Nemeroff, 2007; Pariante & Lightman, 2008), some people inherit a diathesis (a genetic susceptibility), which is incapable of initiating the disorder by itself. The central idea of the diathesis–stress model is that if susceptible individuals are exposed to stress early in life, their systems become permanently sensitized, and they overreact to mild stressors for the rest of their lives.

Support for the diathesis–stress model of depression is largely indirect: It is based on the finding that depressed people tend to release more stress hormones (see Gillespie & Nemeroff, 2007). For example, depressed individuals synthesize more hypothalamic corticotropin-releasing hormone and release more adrenocorticotropic hormone from the anterior pituitary and more glucocorticoids from the adrenal cortex.

Although there has been some evidence that individuals who have experienced early stress (e.g., sexual abuse) are more likely to suffer from depression later (see Carpenter et al., 2004; Nelson et al., 2002), this evidence is not convincing because it is based on the recollections of patients, which cannot be confirmed (Monroe & Reid, 2008). Moreover, there is no evidence of excessive early stress in the lives of the majority of depressed patients.

**Treatment of Depression with Brain Stimulation**

Perhaps the most exciting recent advance in the study of affective disorders was the demonstration that chronic brain stimulation through an implanted electrode (see Figure 18.7) has a significant therapeutic effect in depressed patients who had repeatedly failed to respond to conventional treatments. The results were striking: 60% showed substantial improvements, 35% were...
largely symptom free, and the improvements were maintained for at least 1 year (the duration of the study). However, a careful double-blind evaluation of the effectiveness of the procedure must be performed before it can be recommended for wider use.

18.3 Anxiety Disorders

Anxiety—chronic fear that persists in the absence of any direct threat—is a common psychological correlate of stress. Anxiety is adaptive if it motivates effective coping behaviors; however, when it becomes so severe that it disrupts normal functioning, it is referred to as an anxiety disorder. All anxiety disorders are associated with feelings of anxiety (e.g., fear, worry, despondency) and with a variety of physiological stress reactions—for example, tachycardia (rapid heartbeat), hypertension (high blood pressure), nausea, breathing difficulty, sleep disturbances, and high glucocorticoid levels.

The Case of M.R., the Woman Who Was Afraid to Go Out

M.R. was a 35-year-old woman who developed a pathological fear of leaving home. The onset of her problem was sudden. Following an argument with her husband, she went out to mail a letter and cool off, but before she could accomplish her task, she was overwhelmed by dizziness and fear. She immediately struggled back to her house and rarely left it again, for about 2 years. Then, she gradually started to improve.

Her recovery was abruptly curtailed, however, by the death of her sister and another argument with her husband. Following the argument, she tried to go shopping, panicked, and had to be escorted home by a stranger. Following that episode, she was not able to leave her house by herself without experiencing an anxiety attack. Shortly after leaving home by herself, she would feel dizzy and sweaty, and her heart would start to pound; at that point, she would flee home to avoid a full-blown panic attack.

Although M.R. could manage to go out if she was escorted by her husband or one of her children, she felt anxious the entire time. Even with an escort, she was terrified of crowds—crowded stores, restaurants, or movie theaters were out of the question.

Five Classes of Anxiety Disorders

There are five major classes of anxiety disorders:

- **Generalized anxiety disorders** are characterized by stress responses and extreme feelings of anxiety that occur in the absence of any obvious precipitating stimulus.
- **Phobic anxiety disorders** are similar to generalized anxiety disorders except that they are triggered by exposure to particular objects (e.g., birds, spiders) or situations (e.g., crowds, darkness). M.R., the woman who was afraid to go out, suffered from a common phobic anxiety disorder: agoraphobia. **Agoraphobia** is the pathological fear of public places and open spaces.
- **Panic disorders** are characterized by rapid-onset attacks of extreme fear and severe symptoms of stress (e.g., choking, heart palpitations, shortness of breath); they are often components of generalized anxiety and phobic disorders, but they also occur as separate disorders.
- **Obsessive-compulsive disorders** are characterized by frequently recurring, uncontrollable, anxiety-producing thoughts (obsessions) and impulses (compulsions). Responding to them—for example, by repeated compulsive hand washing—is a means of dissipating the anxiety associated with them.
● **Posttraumatic stress disorder** is a persistent pattern of psychological distress following exposure to extreme stress, such as war or being the victim of sexual assault (McNally, 2003; McNally, Bryant, & Ehlers, 2003; Newport & Nemeroff, 2000).

**Etiology of Anxiety Disorders**

Because anxiety disorders are often triggered by identifiable stressful events and because the anxiety is often focused on particular objects or situations, the role of experience in shaping the disorder is often apparent (see Anagnostaras, Craske, & Fanselow, 1999). For example, in addition to having agoraphobia, M.R. was obsessed by her health—particularly by high blood pressure, although hers was in the normal range. The fact that both her grandmother and her father suffered from high blood pressure and died of heart attacks clearly shaped this component of her disorder.

Like other psychiatric disorders, anxiety disorders have a significant genetic component—heritability estimates range from 30% to 40% in various studies (Leonardo & Hen, 2006). The concordance rates for various anxiety disorders are substantially higher for identical twins than for fraternal twins. However, the timing and focus of anxiety disorders often reflect the particular experiences of the patient (see Gross & Hen, 2004). No specific genes have yet been linked to anxiety disorders (Gordon & Hen, 2004).

**Pharmacological Treatment of Anxiety Disorders**

Three categories of drugs are effective against anxiety disorders: benzodiazepines, serotonin agonists, and antidepressants.

**Benzodiazepines** Benzodiazepines such as chlordiazepoxide (Librium) and diazepam (Valium) are widely prescribed for the treatment of anxiety disorders. They are also prescribed as hypnotics (sleep-inducing drugs), anticonvulsants, and muscle relaxants. Indeed, benzodiazepines are the most widely prescribed psychoactive drugs; approximately 10% of adult North Americans are currently taking them. The benzodiazepines have several adverse side effects: sedation, ataxia (disruption of motor activity), tremor, nausea, and a withdrawal reaction that includes rebound anxiety. Another serious problem with benzodiazepines is that they are highly addictive. Consequently, they should be prescribed for only short-term use (see Gray & McNaughton, 2000). The behavioral effects of benzodiazepines are thought to be mediated by their agonistic action on GABA<sub>α</sub> receptors.

**Serotonin Agonists** The serotonin agonist buspirone is widely used in the treatment of anxiety disorders. Buspirone appears to have selective agonist effects at one subtype of serotonin receptor, the 5-HT<sub>1A</sub> receptor. Its mechanism of action is not totally understood, but it does not function as an SSRI. The main advantage of buspirone over the benzodiazepines is its specificity: It produces anxiolytic (anti-anxiety) effects without producing ataxia, muscle relaxation, and sedation, the common side effects of the benzodiazepines. Buspirone does, however, have other side effects (e.g., dizziness, nausea, headache, and insomnia).

**Antidepressant Drugs** One of the complications in studying both anxiety disorders and depression is their comorbidity (their tendency to occur together in the same individual)—in one study of patients with unipolar or bipolar affective disorder, over half had also been previously diagnosed with an anxiety disorder (Simon et al., 2004). The comorbidity is thought to exist because both disorders involve a heightened emotional response to stress (Morilak & Frazer, 2004). Consistent with the comorbid relationship are the observations that antidepressants, such as the SSRIs, are often effective against anxiety disorders, and anxiolytic drugs (anti-anxiety drugs) are often effective against depression.

**Animal Models of Anxiety**

Animal models have played an important role in the study of anxiety and in the assessment of the anxiolytic potential of new drugs (see Gray & McNaughton, 2000; Green, 1991; Treit, 1985). A weakness of these models is that they typically involve animal defensive behaviors, the implicit assumption being that defensive behaviors are motivated by fear and that fear and anxiety are similar states (see McNaughton & Zangrossi, 2008). Three animal behaviors that model anxiety are elevated-plus-maze performance, defensive burying, and risk assessment.

In the elevated-plus-maze test, rats are placed on a four-armed plus-sign-shaped maze that is 50 centimeters above the floor. Two arms have sides and two arms have no sides, and the measure of anxiety is the proportion of time the rats spend in the enclosed arms, rather than venturing onto the exposed arms (see Pellow et al., 1985).

In the defensive-burying test (see Figure 5.27), rats are shocked by a wire-wrapped wooden dowel mounted on the wall of a familiar test chamber. The measure of anxiety is the amount of time the rats spend spraying bedding material from the floor of the chamber at the source of the shock with forward thrusting movements of their head and forepaws (see Treit et al., 1993).

In the risk-assessment test, after a single brief exposure to a cat on the surface of a laboratory burrow system, rats flee to their burrows and freeze. Then, they engage in a variety of risk-assessment behaviors (e.g., scanning the surface from the mouth of the burrow or exploring the surface in a cautious stretched posture).
before their behavior returns to normal (see Blanchard, Blanchard, & Rodgers, 1991; Blanchard et al., 1990). The measures of anxiety are the amounts of time that the rats spend in freezing and in risk assessment.

The elevated-plus-maze, defensive-burying, and risk-assessment tests of anxiety have all been validated by demonstrations that benzodiazepines reduce the various indices of anxiety used in the tests, whereas nonanxiolytic drugs usually do not. However, a potential problem with this line of evidence stems from the fact that many cases of anxiety do not respond well to benzodiazepine therapy. Therefore, existing animal models of anxiety may be models of benzodiazepine-sensitive anxiety rather than of anxiety in general, and thus the models may not be sensitive to anxiolytic drugs that act by a different (i.e., a non-GABAergic) mechanism. For example, the serotonin agonist buspirone does not have a reliable anxiolytic effect on subjects performing on the elevated-plus-maze test.

Neural Bases of Anxiety Disorders

Like current theories of the neural bases of schizophrenia and depression, current theories of the neural bases of anxiety disorders rest heavily on the analysis of therapeutic drug effects. The fact that many anxiolytic drugs are agonists at either GABA<sub>A</sub> receptors (e.g., the benzodiazepines) or serotonin receptors (e.g., buspirone, Prozac, and Paxil) has focused attention on the possible role in anxiety disorders of deficits in both GABAergic and serotonergic transmission.

There is substantial overlap between the brain structures involved in affective and anxiety disorders. Indeed, the amygdala and the anterior cingulate cortex, which you have just learned have been implicated in affective disorders, have also been implicated in anxiety disorders. This is hardly surprising given the comorbidity of affective and anxiety disorders, the effectiveness of some drugs (e.g., SSRIs) against both, and the fact that both are primarily disturbances of emotion.

Although the amygdala and the anterior cingulate cortex have been implicated in both affective and anxiety disorders, the patterns of evidence differ. With affective disorders, you have already seen that there seems to be shrinkage to these structures; however, with anxiety disorders, there appears to be no gross damage. Most of the evidence linking the amygdala and the anterior cingulate cortex to anxiety disorders has come from functional brain-imaging studies in which abnormal activity in these areas has been recorded during the performance of various emotional tasks (see Bishop, 2007; Kim & Whalen, 2009; Melcher, Falkai, & Gruber, 2008; Nitschke et al., 2009). For example, Figure 18.9 illustrates increased functional MRI activity in the amygdala of patients with spider phobias when they viewed photographs of spiders.

Tourette Syndrome

Tourette syndrome is the last of the four psychiatric disorders discussed in this chapter. It differs from the first three (schizophrenia, affective disorders, and anxiety) in the specificity of its effects. And they are as interesting as they are specific. The case of R.G. introduces you to Tourette syndrome.

The Case of R.G.—Barking Mad

When R.G. was 15, he developed tics (involuntary, repetitive, stereotyped movements or vocalizations). For the first week, his tics took the form of involuntary blinking, but after that they started to involve other parts of the body, particularly his arms and legs.

R.G. and his family were religious, so it was particularly distressing when his tics became verbal. He began to curse repeatedly and involuntarily. Involuntary cursing is a common symptom of Tourette syndrome and of several other psychiatric and neurological disorders (Van Lancker & Cummings, 1999). R.G. also started to bark like a dog. Finally, he developed echolalia: When his mother said, “Dinner is ready,” he responded, “Is ready, is ready.”
Prior to the onset of R.G.’s symptoms, he was an A student, apparently happy and with an outgoing, engaging personality. Once his symptoms developed, he was jeered at, imitated, and ridiculed by his schoolmates. He responded by becoming anxious, depressed, and withdrawn. His grades plummeted.

Once R.G. was taken to a psychiatrist by his parents, his condition was readily diagnosed—the symptoms of Tourette syndrome are unmistakable. Medication eliminated 99% of his symptoms, and once his disorder was explained to him and he realized he was not mad, he resumed his former outgoing manner (Spitzer et al., 1983).

Many people with Tourette syndrome experience no symptoms other than tics. Thus, if their friends, family members, and colleagues are understanding and supportive, these people can live happy, productive lives—for example, Tim Howard (shown in the photo) is goalkeeper for both the American national team and Everton Football Club, a team in the English Premier Division.

What Is Tourette Syndrome?

Tourette syndrome is a disorder of tics (involuntary, repetitive, stereotyped movements or vocalizations) (Gerard & Peterson, 2003). It typically begins early in life—usually in childhood or early adolescence—with simple motor tics, such as eye blinking or head movements, but the symptoms tend to become more complex and severe as the patient grows older. Common complex motor tics include hitting, touching objects, squatting, hopping, twirling, and sometimes even making lewd gestures. Common verbal tics include inarticulate sounds (e.g., barking, coughing, grunting), coprolalia (uttering obscenities), echolalia (repetition of another’s words), and palilalia (repetition of one’s own words). The symptoms usually reach a peak after a few years, and they often gradually subside as the patient matures.

Tourette syndrome develops in approximately 0.7% of the population and is three times more frequent in males than in females. There is a major genetic component: Concordance rates are 55% for identical twins and 8% for fraternal twins (see Pauls, 2001).

Some patients with Tourette syndrome also display signs of attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, or both (Sheppard et al., 1999). For example, R.G. was obsessed by odd numbers and refused to sit in even-numbered seats.

Although the tics of Tourette syndrome are involuntary, they can be temporarily suppressed with concentration and effort by the patient. The effect of suppression has been widely misunderstood. A study published in 2004 by Marcks and colleagues found that 77% of medical professionals believed that tic suppression is inevitably followed by a rebound (that the tics become even worse following a period of suppression). However, this has proven not to be the case (Himle & Woods, 2005; Meidinger et al., 2005)—see Figure 18.10.

Imagine how difficult it would be to get on with your life if you suffered from an extreme form of Tourette syndrome—for example if you frequently made obscene gestures and barked like a dog. No matter how polite, intelligent, and kind you were inside, not many people would be willing to socialize with, or employ, you (see Kushner, 1999).

Neuropathology of Tourette Syndrome

Because Tourette syndrome is a well-defined disorder with clearly observable symptoms, its neuropathology is more amenable to study than that of the other disorders that you have encountered in this chapter. Still, there are impediments: for example, the lack of an animal model and the lack of a strong link to any particular gene. The greatest difficulties in studying Tourette syndrome are attributable to the fact that symptoms often subside as people age. Because Tourette patients are rarely under care for the syndrome when they die, few postmortem studies of
Tourette syndrome have been conducted. Consequently, the study of the disorder’s neuropathology is based almost exclusively on brain-imaging studies, which are difficult to conduct because of the requirement that the patients remain motionless. As a result, many brain-imaging studies of Tourette syndrome have focused on adult patients in whom the tics have largely subsided. This makes it difficult for researchers to identify the neural mechanisms of tic production (see Gerard & Peterson, 2003).

Most research on the cerebral pathology associated with Tourette syndrome has focused on the caudate. Patients with this disorder tend to have smaller caudate nuclei, and when they suppress their tics, fMRI activity is recorded in both prefrontal cortex and caudate nuclei (see Albin & Mink, 2006; Gerard & Peterson, 2003). Presumably, the decision to suppress the tics comes from the prefrontal cortex, which initiates the suppression by acting on the caudate nuclei. Although most studies of the neuropathology associated with Tourette syndrome have focused on the caudate nuclei, the brain damage appears to be more widespread. A recent MRI study of children with Tourette syndrome (Sowell et al., 2008) documented thinning in sensorimotor cortex that was particularly prominent in the areas that controlled the face, mouth, and larynx (voice box)—see Figure 18.11 on page 484.

Treatment of Tourette Syndrome

Although tics are the defining feature of Tourette syndrome, treatment typically begins by focusing on other aspects of the disorder. First, the patient, family members, friends, and teachers are educated about the nature of the syndrome. Second, the treatment focuses on the ancillary emotional problems (e.g., anxiety and depression). Once these first two steps have been taken, attention turns to treating the symptoms.

The tics of Tourette syndrome are usually treated with neuroleptics (the D₂ receptor blockers that are used in the treatment of schizophrenia). Neuroleptics can reduce tics by about 70%, but in practice their benefits are only modest because patients often refuse, or are not allowed by their parents, to take them because of the adverse side effects (e.g., weight gain, fatigue, and dry mouth).

The success of D₂ receptor blockers in blocking Tourette tics is consistent with the current hypothesis that the disorder is related to an abnormality of the basal ganglia–thalamus–cortex feedback circuit. The efficacy of these drugs especially implicates the striatum (caudate plus putamen), which is the target of many of the dopaminergic projections into the basal ganglia. The binding of extracellular D₂ receptors was found to be reduced in the brains of a group of adult Tourette patients who had never taken D₂-receptor-blocking medication (Gilbert et al., 2006).

P.H. is a scientist who counsels Tourette patients and their families. He also has Tourette syndrome, which provides him with a useful perspective.

The Case of P.H., the Neuroscientist with Tourette Syndrome

Tourette syndrome has been P.H.’s problem for more than three decades (Hollenbeck, 2001). Taking advantage of his position as a medical school faculty member, he regularly offers a series of lectures on the topic. Along with students, many other Tourette patients and their families are attracted to his lectures.

Encounters with Tourette patients of his own generation taught P.H. a real lesson. He was astounded to learn that most of them did not have his thick skin. About half of them were still receiving treatment for psychological wounds inflicted during childhood.

For the most part, these patients’ deep-rooted pain and anxiety did not result from the tics themselves. They derived...
from being ridiculed and tormented by others and from the self-righteous advice repeatedly offered by well-meaning "clods." The malfunction may be in a patient’s striatum, but in reality this is more a disorder of the onlooker than of the patient.

Last year, I received an e-mail from a professor of biological sciences at Purdue University. He came across this text because it was being used in his department’s behavioral neurobiology course. He thanked me for my coverage of Tourette syndrome but said that he found the case study “a bit eerie.” The message began with “From one case study to another,” and it ended “All the best, P.H.”

Clinical Trials: Development of New Psychotherapeutic Drugs

Almost daily, there are news reports of exciting discoveries that appear to be pointing to effective new therapeutic drugs or treatments for psychiatric disorders. But most often, the promise does not materialize. For example, almost 50 years after the revolution in molecular biology began, not a single form of gene therapy is yet in widespread use. The reason is that the journey of a drug or other medical treatment from promising basic research to useful reality is excruciatingly complex, time-consuming, and expensive. Research designed to translate basic scientific discoveries into effective clinical treatments is called translational research.

So far, the chapter has focused on early drug discoveries and their role in the development of theories of psychiatric dysfunction. In the early years, the development of psychotherapeutic drugs was largely a hit-or-miss process. New drugs were tested on patient populations with little justification and then quickly marketed to an unsuspecting public, often before it was discovered that they were ineffective for their original purpose.

Things have changed. The testing of experimental drugs on human subjects and their subsequent release for sale are now strictly regulated by government agencies.

The process of gaining permission from the government to market a new psychotherapeutic drug begins with the synthesis of the drug, the development of procedures for synthesizing it economically, and the collection...
(2) establishing the testing protocol, and (3) final testing (see Zivin, 2000). The average duration and cost of each phase, based on estimates by Adams and Brantner (2010), are summarized in Figure 18.12 on page 486.

**Screening for Safety**  The purpose of the first phase of a clinical trial is to determine whether the drug is safe for human use and, if it is, to determine how much of the drug can be tolerated. Administering the drug to humans for the first time is always a risky process because there is no way of knowing for certain how they will respond. The subjects in phase 1 are typically healthy paid volunteers. Phase 1 clinical trials always begin with tiny injections, which are gradually increased as the tests proceed. The reactions of the subjects are meticulously monitored, and if strong adverse reactions are observed, phase 1 is curtailed.

**Establishing the Testing Protocol**  The purpose of the second phase of a clinical trial is to establish the conditions under which the final tests are likely to provide a clear result. For example, in phase 2, researchers hope to discover which doses are likely to be therapeutically effective, how frequently they should be administered, how long they need to be administered to have a therapeutic effect, what benefits are likely to occur, and which patients are likely to be helped. Phase 2 tests are conducted on patients suffering from the target disorder; the tests usually include placebo-control groups (groups of patients who receive a control substance rather than the drug), and their designs are double-blind—that is, the tests are conducted so that neither the patients nor the physicians interacting with them know which treatment (drug or placebo) each patient has received.

**Final Testing**  Phase 3 of a clinical trial is typically a double-blind, placebo-control study on large numbers—often, many thousands—of patients suffering from the target disorder. The design of the phase 3 tests is based on the results of phase 2 so that the final tests are likely to demonstrate positive therapeutic effects, if these exist. The first test of the final phase is often not conclusive, but if it is promising, a second test based on a redesigned protocol may be conducted. In most cases, two independent successful tests are required to convince government regulatory agencies. A successful test is one in which the beneficial effects are substantially greater than the adverse side effects.

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**TABLE 18.2 Phases of Drug Development**

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<thead>
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<th>BASIC RESEARCH</th>
<th>HUMAN CLINICAL TRIALS</th>
<th>SELLING TO THE PUBLIC</th>
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<tbody>
<tr>
<td>Discovery of the drug, development of efficient methods of synthesis, and testing with animal models</td>
<td>Phase 1: Screening for safety and finding the maximum safe dose</td>
<td>Application to begin marketing and reviews of results of clinical trials by government agency</td>
</tr>
<tr>
<td>Application to begin clinical trials and the review of basic research by government agency</td>
<td>Phase 2: Establishing most effective doses and schedules of treatment</td>
<td>Recovering development costs and continuing to monitor the safety of the drug</td>
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<tr>
<td>Phase 3: Clear demonstrations that the drug is therapeutic</td>
<td>Application to begin marketing and reviews of results of clinical trials by government agency</td>
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<tr>
<td>Source: Adapted from Zivin (2000).</td>
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Controversial Aspects of Clinical Trials

The clinical trial process is not without controversy, as is clear from the following major focuses of criticism and debate (Zivin, 2000).

Requirement for Double-Blind Design and Placebo Controls In most clinical trials, patients are assigned to drug or placebo groups randomly and do not know for sure which treatment they are receiving (see Woods et al., 2001). Thus, some patients whose only hope for recovery may be the latest experimental treatment will, without knowing it, receive the placebo. Drug companies and government agencies concede that this is true, but they argue that there can be no convincing evidence that the experimental treatment is effective until a double-blind, placebo-control trial is complete. Because psychiatric disorders often improve after a placebo, a double-blind, placebo-control procedure is essential in the evaluation of any psychotherapeutic drug.

The Need for Active Placebos Conventional wisdom has been that the double-blind, placebo-control procedure is the perfect control procedure to establish the effectiveness of new drugs, but it isn’t (see Salamone, 2000). Here is a new way to think about the double-blind placebo-control procedure. At therapeutic doses, many drugs have side effects that are obvious to people taking them, and thus the participants in double-blind, placebo-control studies who receive the drug can be certain that they are not in the placebo group. This knowledge may greatly contribute to the positive effects of the drug, independent of any real therapeutic effect. Accordingly, it is now widely recognized that an active placebo is better than an inert placebo as the control drug. Active placebos are control drugs that have no therapeutic effect but produce side effects similar to those produced by the drug under evaluation.

Length of Time Required Patients desperately seeking new treatments are frustrated by the amount of time needed for clinical trials (see Figure 18.12). Therefore, researchers, drug companies, and government agencies are striving to speed up the evaluation process, without sacrificing the quality of the procedures designed to protect patients from ineffective treatments. It is imperative to strike the right compromise (see Benderly, 2007).

Financial Issues The drug companies pay the scientists, physicians, technicians, assistants, and patients involved in drug trials. Considering the millions these companies spend and the fact that only about 22% of the candidate drugs entering phase 1 testing ever gain final approval (see Figure 18.13), it should come as no surprise that the companies are anxious to recoup their costs. In view of this pressure, many have questioned the impartiality of those conducting and reporting the trials (see Fisher, 2006). The scientists themselves have often complained that the sponsoring drug company makes them sign an agreement that prohibits them from publishing or discussing negative findings without the company’s consent.

Another financial issue is profitability—drug companies seldom develop drugs to treat rare disorders because such treatments will not be profitable. Drugs for which the market is too small for them to be profitable are called orphan drugs. Governments in Europe and North America have passed laws intended to promote the development of orphan drugs (see Maeder, 2003). Also, the massive costs of clinical trials have contributed to a translational bottleneck (Hyman & Fenton, 2003)—only a small proportion of potentially valuable ideas or treatments receive funding for translational research.

Targets of Psychopharmacology Hyman and Fenton (2003) have argued that a major impediment to the development of effective psychotherapeutic drugs is that the effort is often aimed at curing disease entities as currently

FIGURE 18.12 The cost and duration of the three phases of drug testing on human volunteers.
conceived—for example, as defined by DSM-IV-TR. The current characterizations of various psychiatric disorders are the best they can be, based on existing evidence; however, it is clear that most psychiatric disorders, as currently conceived, are likely clusters of disorders, each with a different pattern of brain pathology. Thus, effective new drugs are likely to benefit only a proportion of those patients who have been given a particular diagnosis, and thus their effectiveness might go unrecognized. Hyman and Fenton recommend that drug development should focus on treating specific, readily monitored symptoms, rather than on treating general psychiatric disorders as currently conceived.

Effectiveness of Clinical Trials

Despite the controversy that surrounds the clinical trial process, there is no question that it works. A long, dismal history tells of charlatans who make unfounded promises and take advantage of people at the time when they are least able to care for themselves. The clinical trial process is the most objective method ever devised to assess the efficacy of a treatment. It is expensive and slow, and in need of constant refinements, and oversight, but the process is trustworthy. (Zivin, 2000, p. 75)

Certainly, the clinical trial process is far from perfect. For example, concerns about the ethics of randomized double-blind, placebo-control studies are often warranted. Still, the vast majority of those in the medical and research professions accept that these studies are the essential critical test of any new therapy. This is particularly true of psychotherapeutic drugs because psychiatric disorders often respond to placebo treatments and because assessment of their severity is subjective and can be greatly influenced by the expectations of the therapist.

Everybody agrees that clinical trials are too expensive and take too long. But one expert responds to this concern in the following way: Clinical trials can be trustworthy, fast, or cheap; but in any one trial, only two of the three are possible (Zivin, 2000). Think about it.

It is important to realize that every clinical trial is carefully monitored as it is being conducted. Any time the results warrant it, changes to the research protocol are made to reduce costs and the time required to deliver an effective treatment to patients in need—particularly to the patients in the placebo-control group.

Conclusion

The chapter, and indeed the book, ends with the case of S.B., who suffers from bipolar affective disorder. S.B.’s case is appropriate here because S.B. benefited greatly from the clinical trial process and because S.B.’s case demonstrates the value of a biopsychological education that stresses independent thinking and the importance of taking responsibility for one’s own health. You see, S.B. took a course similar to the one that you are currently taking, and the things that he learned in the course enabled him to steer his own treatment to a positive outcome.

The Case of S.B., the Biopsychology Student Who Took Control

I met S.B. when he was a third-year undergraduate. S.B. is a quiet, pleasant, shy person; he has an unassuming manner, but he is kind, knowledgeable, and intelligent, with broad interests. For example, I was surprised to learn that he was a skilled artist, interested in medical illustration, so we chatted at length about the illustrations in this book.

I was delighted to discover that S.B.’s grades confirmed my positive impression of him. In addition, it soon became apparent that he had a real “touch” for research, so I invited him to become my graduate student. He accepted and was truly exceptional. As you can tell, I am very proud of him.

S.B. is now going to describe his case to you in his own words. I wanted to tell you a bit about him myself so that you would have a clear picture of his situation. As you are about to discover, S.B.’s view of himself, obscured by a black cloud of depression, bears little relation to reality.

As an undergraduate student, I suffered from depression. Although my medication improved things somewhat, I still...
felt stupid, disliked, and persecuted. There were some positives in my undergraduate years. Dr. Pinel was very good to me, and I liked his course. He always emphasized that the most important part of his course was learning to be an independent thinker, and I was impressed by how he had been able to diagnose his own brain tumor. I did not appreciate at the time just how important these lessons would be.

A few months after beginning graduate school, my depression became so severe that I could not function. My psychiatrist advised me to take a leave of absence, which I did. I returned a few months later, filled with antipsychotics and antidepressants, barely capable of keeping things together.

You can appreciate how pleased I was 2 years later, when I started to snap out of it. It occurred to me that I was feeling better than I had ever felt. My productivity and creativity increased. I read, wrote, and drew, and new ideas for experiments flooded into my head. Things were going so well that I found that I was sleeping only 2 or 3 hours a night, and my brain was so energized that my friends sometimes begged me to talk more slowly so that they could follow what I was saying.

But my euphoria soon came to an abrupt end. I was still energetic and creative, but the content of my ideas changed. My consciousness was again dominated by feelings of inferiority, stupidity, and persecution. Thoughts of suicide were a constant companion. As a last resort, I called my psychiatrist, and when she saw me, she immediately advised at the time just how important these lessons would be.

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4. Judge people by what they do, not by what they say. Discuss this recommendation with respect to Tourette syndrome.

5. Tourette syndrome is a disorder of onlookers. Explain and discuss.

6. Clinical trials are no more than excessive government bureaucracy. The prescription of drugs should be left entirely to the discretion of physicians. Discuss.

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**Key Terms**

- Psychiatric disorders (p. 467)
- DSM-IV-TR (p. 467)

**18.1 Schizophrenia**
- Positive symptoms (p. 468)
- Negative symptoms (p. 468)
- Chlorpromazine (p. 469)
- Reserpine (p. 469)
- Haloperidol (p. 470)
- Phenothiazines (p. 470)
- Butyrophenones (p. 470)
- Neuroleptics (p. 470)
- Clozapine (p. 471)

**18.2 Affective Disorders: Depression and Mania**
- Clinical depression (major depressive disorder) (p. 473)
- Affective disorders (p. 474)
- Mania (p. 474)
- Mood disorder (p. 474)
- Bipolar affective disorder (p. 474)
- Unipolar affective disorder (p. 474)
- Reactive depression (p. 474)
- Endogenous depression (p. 474)
- Seasonal affective disorder (SAD) (p. 474)
- Postpartum depression (p. 475)
- Iproniazid (p. 475)
- MAO inhibitors (p. 475)
- Cheese effect (p. 475)
- Tricyclic antidepressants (p. 475)
- Imipramine (p. 475)

**18.3 Anxiety Disorders**
- Anxiety (p. 479)
- Anxiety disorder (p. 479)
- Generalized anxiety disorders (p. 479)
- Phobic anxiety disorders (p. 479)
- Agoraphobia (p. 479)
- Panic disorders (p. 479)
- Obsessive-compulsive disorders (p. 479)
- Posttraumatic stress disorder (p. 480)

**18.4 Tourette Syndrome**
- Tics (p. 482)

**18.5 Clinical Trials: Development of New Psychotherapeutic Drugs**
- Translational research (p. 484)
- Clinical trials (p. 485)
- Active placebos (p. 486)
- Orphan drugs (p. 486)
- Translational bottleneck (p. 486)

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**Quick Review**

Test your comprehension of the chapter with this brief practice test. You can find the answers to these questions as well as more practice tests, activities, and other study resources at www.mypsychlab.com.

1. The first antischizophrenic drug was
   a. clozapine.
   b. iproniazid.
   c. chlorpromazine.
   d. imipramine.
   e. haloperidol.

2. When clinical depression alternates with periods of mania, the disorder is termed
   a. major depressive disorder.
   b. bipolar affective disorder.
   c. endogenous depression.
   d. reactive depression.
   e. postpartum depression.

3. Lithium is classified as a
   a. mood stabilizer.
   b. monoamine oxidase inhibitor.
   c. tricyclic antidepressant.
   d. SSRI.
   e. both a and c

4. Because the tics of Tourette syndrome seem to be associated with activity in the caudate nuclei, they have been treated with
   a. D₄ receptor blockers.
   b. tricyclic antidepressants.
   c. SSRIs.
   d. benzodiazepines.
   e. phenobarbital.

5. Research designed to develop effective clinical treatments from basic scientific discoveries is termed
   a. phase 1 research.
   b. phase 2 research.
   c. phase 3 research.
   d. translational research.
   e. orphan research.