

## MOTHER'S LITTLE HELPER

Anxiety disorders are the most prevalent form of mental illness. Schizophrenia afflicts about 1 percent of the population and depression about 15 percent, but roughly 25 percent of all adults are said to suffer from some manifestation of clinical anxiety.<sup>82</sup> Everyone is a little anxious at times, but an anxiety disorder is said to exist when day-to-day psychological functioning and interpersonal relationships are disrupted by symptoms such as worry, tension, sleep disturbances, irritability, and somatic complaints. Anxiety is not a single disorder but a spectrum of conditions that includes nonspecific or generalized anxiety, phobias, panic attacks, posttraumatic stress disorder, and obsessive-compulsive disorder.

Psychotherapy is more effective in treating anxiety disorders than any other group of mental problems.<sup>83</sup> This is true both of generalized anxiety and of the more specific conditions. The most effective forms of psychotherapy for anxiety involve behavioral and cognitive-behavioral approaches, which help the patient cope with and eliminate the unpleasant symptoms that accompany and perpetuate anxiety.

Medicinal approaches to anxiety have also been valuable.<sup>84</sup> Alcohol is the oldest and most widely used anxiety-reducing drug. Many unwind from the tensions of the working world by stopping off for “happy hour” at their favorite watering hole, or with a “cocktail hour” at home. But because alcohol is intoxicating and addictive, it is not a practical solution for severe and chronic anxiety.

The first widely used medical treatment for anxiety involved barbiturates, long-acting drugs that depress brain activity. At low doses, they reduce tension and anxiety without producing intoxication, and at higher doses, they induce sleep. However, these drugs are highly addictive, and the difference between a dose that induces sleep and one that is fatal (by suppressing breathing) is quite small. The development of a new class of anxiety drugs in the 1950s was thus welcomed.

Meprobamate was identified in the process of screening variations of mephenesin, a drug that relieved anxiety but had a very short-lasting effect. One method that drug companies used to test the value of antianxiety drugs was to give them to monkeys, which tend to be wild and aggressive in captivity. Meprobamate made them calm, less vicious. When given to humans, it reduced anxiety without producing drowsiness. This compound was then made available by prescription under the brand names Equanil and Miltown,

and came to be known, in the popular press, as “happy pills.” Though initially believed to be a safe, nonaddicting replacement for barbiturates, later reports were less favorable. Addiction did result, and sometimes medical complications occurred when the drug was stopped.

The next generation of drugs for anxiety emerged when a chemist who had worked developing dyes in Poland moved to the United States and joined a drug company. He tested a number of the compounds he had worked with in his dye research in Poland and found that one of them, and only one, was effective in calming wild monkeys. Upon further investigation, it turned out that this compound was different from all the rest. Chlordiazepoxide, as the compound was called, became the first of a new class of drugs, the benzodiazepines.

The effects of chlordiazepoxide were further tested in rats using the conflict test. The rats were made hungry, and then were allowed to obtain food by pressing a bar. However, if they pressed while a light was on, they were shocked. The light itself came to be a fear-arousing stimulus and led to outward signs of nervousness (freezing, defecation, etc.). When treated with chlordiazepoxide, though, they pressed more and were less visibly afraid even while the light was on. The drug allowed them to earn their daily bread and to be less fearful in doing so—perfect effects for a treatment of human anxiety. The conflict test in rats has, in fact, become one of the key methods for determining whether new compounds are likely to be effective in relieving anxiety in humans.

Chlordiazepoxide was sold as Librium. Then came diazepam, better known as Valium, and alprazolam, marketed as Xanax. By 1975, 15 percent of the U.S. population was said to have taken at some point a version of “mother’s little helper.” Though highly effective in relieving anxiety, and far less problematic than barbiturates and meprobamate, benzodiazepines are likewise addictive, and can be dangerous when mixed with alcohol. Judy Garland, for example, is believed to have died from this combination.

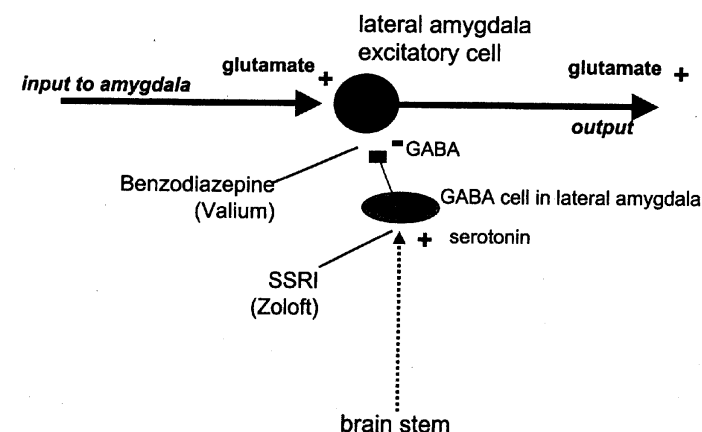
In contrast to most other drugs used to treat mental illness, all the anti-anxiety drugs work immediately. That is why a drink can calm your nerves, and why Valium and other benzodiazepines are useful in acute anxiety. In *Starting Over*, a romantic comedy from the late 1970s, the character played by Burt Reynolds is having a severe anxiety attack in Bloomingdale’s while a crowd gathers around him. Someone calls out for a Valium, and essentially the entire crowd reaches into their purses or pockets and pulls out a vial. Valium jokes are, in fact, still popular in comedies. Hugh Grant’s character in

Woody Allen's recent film *Small Time Crooks* kept running to the bathroom for a Valium when things didn't go his way.

While benzodiazepines are also useful as sleeping pills on an as-needed basis, these drugs can produce temporary memory loss after waking. There are infamous stories of businessmen taking a benzodiazepine to sleep on an overnight trip to Europe and then waking up and not being able to remember why they had flown overseas. A new class of drugs, imidazopyridines, are more useful for inducing sleep. Ambien is a prime example. Though their chemical structure is somewhat different from benzodiazepines, they work similarly (though more specifically) at the chemical level. Because these drugs have a shorter life span in the blood, and because they are not muscle relaxants, they have fewer lingering effects the next day on cognitive and behavioral functioning.

The classic antianxiety drugs work primarily by facilitating GABA inhibitory transmission in the brain, making it harder for glutamate to elicit excitation at its postsynaptic receptors. This is true for alcohol, barbiturates, and benzodiazepines (and imidazopyridines). However, each achieves its effects differently. Recall from chapter 3 that when a neurotransmitter binds to its receptor, the receptor opens, allowing electrically charged chemical ions to flow from the extracellular space into the cell. In the case of GABA receptors, the flow of chloride ions makes the inside of the cell more negative, which means that more positively charged ions have to flow into the cell through glutamate receptors to initiate an action potential. Barbiturates enhance inhibition by acting directly on GABA receptors, keeping the chloride channel open longer, allowing more negative ions to enter the cell. Alcohol has a similar effect, but at a different GABA receptor from the one affected by barbiturates. Benzodiazepines, however, work differently, as they have their own receptors, which are linked to GABA receptors. So when benzodiazepine receptors are occupied, linked GABA receptors bind GABA more easily. As a result, the same amount of GABA released from a GABA terminal will have a greater inhibitory effect on the postsynaptic cell. The benzodiazepines therefore work only at those sites where GABA is being released naturally. Imidazopyridines work like benzodiazepines, but at a more selective part of the GABA receptor, which is probably why they have fewer side effects. (Parenthetically, the fact that benzodiazepine receptors exist in the brain means that the brain also has a natural supply of benzodiazepines. It may be that calm, worry-free people have more of this chemical, and anxious people less.)

Because GABA and benzodiazepine receptors are dispersed throughout the brain, drugs that bind to them do not affect anxiety exclusively. Anxiety may



**FIGURE 10.2 ANTIANXIETY DRUGS AND THE AMYGDALA**

Two of the major types of drugs used to treat anxiety are benzodiazepines (like Valium) and selective serotonin reuptake inhibitors (SSRIs). Both may achieve anxiety relief, at least in part, through a common mechanism in the amygdala—enhancement of the inhibitory actions of the neurotransmitter GABA. Benzodiazepines directly enhance the inhibitory effects of GABA. By increasing inhibition, benzodiazepines weaken the ability of external or internal stimuli to activate the amygdala and produce fear and anxiety. SSRIs may also increase inhibition in the amygdala, though indirectly. It is known that increasing serotonin levels in the amygdala leads to an inhibition of amygdala activity, but this is achieved by exciting GABA cells, which then do the inhibiting. Since SSRIs make more serotonin available at the synapse by preventing uptake and thus breakdown, they would presumably also lead to GABA excitation and thus inhibition. This explanation works better for benzodiazepines than for SSRIs, since the former but not the latter are effective immediately in treating anxiety. Additional mechanisms, such as alteration in second messengers, are required to more fully account for the antianxiety effects of SSRIs (see earlier discussion of SSRIs and depression).

well be generated by specific networks, but drugs that treat it affect the entire brain. This accounts for some of the side effects of antianxiety drugs, such as drowsiness and muscle relaxation. Drowsiness, of course, is not considered a side effect when the drug is used for sleep induction rather than for anxiety reduction while awake.

Newer treatments for generalized anxiety are also available. Though these drugs produce fewer side effects, they have the disadvantage of not working immediately. Most of them enhance serotonin function. BuSpar (buspirone), for example, stimulates serotonin receptors (specifically serotonin 1A receptors). SSRIs, which as we've seen make more serotonin available at receptors, also appear to be helpful with these disorders.

## WORRY CIRCUITS

Where does anxiety come from? Jeffrey Gray has long believed that the anti-anxiety drugs are the key to understanding the nature of generalized anxiety, and specifically the circuits in the brain that generate anxiety.<sup>85</sup> As he argues, alcohol, barbiturates, and benzodiazepines are different drugs from a chemical point of view, and each has different side effects, but each relieves anxiety. By studying the effects of the three drugs on a variety of different behavioral tasks in rats, and identifying a set of tasks that are affected by all three drugs, a behavioral portrait of anxiety can be drawn. And if brain regions can be discovered that when damaged lead to the same effects as the anti-anxiety drugs on these “anxiety” tasks, then the neural home of anxiety might be isolated.

This research program led to a neural theory of anxiety published in 1982. Because the common effects of the anti-anxiety drugs were similar to the effects of damage to the septum and/or hippocampus, these areas were postulated to be at the core of anxiety. We’ve encountered the hippocampus frequently, but not the septum. This is a region of the forebrain—actually part of the so-called limbic system—that is intimately associated with the hippocampus and regulates some of its activity.

From a psychological point of view, the septum and hippocampus were thought of as constituting the brain’s behavioral inhibition system, a network that detects and responds to aversive stimuli, those that produce pain, punishment, failure, or loss of reward, or that elicit novelty and uncertainty. When the behavioral inhibition system is activated, ongoing behavior is inhibited (resulting, for example, in freezing), and the organism becomes aroused, attentive, and vigilant. Administering anti-anxiety drugs prevents aversive stimuli from eliciting septohippocampal arousal and vigilance, and damaging these areas reduces anxiety by eliminating the brain regions where arousal and vigilance would be elicited by aversive stimuli.

As we saw above, the classic anti-anxiety drugs work by enhancing GABA transmission. Although the drugs each affect GABA transmission by different means, they all work through GABA. A key part of Gray’s theory was that GABA neurons were the common denominator in anxiety. However, because classic anti-anxiety drugs, when administered to the hippocampus itself, proved not very effective in relieving anxiety, Gray proposed that these substances alter GABA transmission in another brain region that subsequently influences the septohippocampal system. The key area of action was proposed to be the monoamine systems in the brain stem, specifically the serotonin and

norepinephrine systems. These areas were selected on the basis of earlier studies showing that, when stimulated in rats or monkeys, they elicited anxiety-like behaviors, and that anti-anxiety drugs injected in the same areas inhibited cell activity and relieved anxiety-like behaviors.<sup>86</sup>

Before considering Gray’s theory of how anti-anxiety drugs work, let’s briefly look more closely at his conception of what anxiety is at the level of neurons. During threats, serotonin and norepinephrine cells in the brain stem are activated, and serotonin and norepinephrine are released from the terminals of these cells. Although the terminals are located in many regions of the brain, because serotonin and norepinephrine are modulators, their main effect is to alter transmission at active synapses rather than to elicit activity themselves (chap. 3). Since the septum and hippocampus are involved in processing threats, these regions would be active in the presence of threats, and serotonin and norepinephrine would enhance their synaptic processing, leading to arousal and vigilance, and anxiety.

Now for the anti-anxiety effects. The anti-anxiety drugs, as we’ve seen, enhance GABA transmission. The enhancement mainly occurs at synapses where GABA transmission is taking place, rather than at inactive synapses. Because GABA activity is often triggered in response to excitation in nearby cells, the enhancement of GABA by anti-anxiety drugs in the presence of threatening stimuli will be concentrated at those synapses processing the threat. In addition to activating cells in the septum and hippocampus, threats activate serotonin and norepinephrine cells. Gray therefore proposed that anti-anxiety drugs enhance GABA transmission at these brain stem cells, and thereby reduce the release of serotonin and norepinephrine in the forebrain. The enhanced processing that these chemicals were engendering in the septum and hippocampus will in turn be eliminated, decreasing arousal and vigilance, thereby reducing anxiety.

Although Gray’s theory was a tour de force of neuropsychological logic, it ran into trouble. First of all, it focused exclusively on GABA transmission, since this was a point of convergence between all the classic anti-anxiety drugs. The emergence of drugs that successfully treated anxiety without affecting GABA transmission therefore challenged the theory. Buspirone and SSRIs, for example, are both effective in relieving anxiety and both work at the level of receptors postsynaptic to serotonin terminals rather than at cell bodies in the brain stem. Indeed, these drugs are somewhat effective when injected directly into the hippocampus, where they selectively enhance serotonin transmission.<sup>87</sup> While this helps salvage part of the theory, it weakens the core

concept that facilitation of GABA transmission in the brain stem is key. Second, the theory did not allow a role for the amygdala, which as we've seen plays an important role in processing danger and threats.

In a recent revision of the theory, Gray and his longtime collaborator Neil McNaughton attempted to address both of these shortcomings.<sup>88</sup> Their new formulation conceives of anxiety as a psychological state emerging out of a synaptically connected network involving, among other regions, the septo-hippocampal area, amygdala, and prefrontal cortex, all modulated by brain stem monoamine systems. Although the new theory is broader in its coverage, in my opinion, it still gives the septum and hippocampus too prominent a role, at the expense of the amygdala and prefrontal cortex.

Anxiety, in my view, is a cognitive state in which working memory is monopolized by fretful, worrying thoughts. The difference between an ordinary state of mind (of working memory) and an anxious one is that, in the latter case, systems involved in emotional processing, such as the amygdala, have detected a threatening situation, and are influencing what working memory attends to and processes. This in turn will affect the manner in which executive functions select information from other cortical networks and from memory systems and make decisions about the course of action to take.

I believe that the hippocampus is involved in anxiety not because it processes threats, as Gray suggests, but instead because it supplies working memory with information about stimulus relations in the current environmental context, and about past relations stored in explicit memory. When the organism, through working memory, conceives that it is facing a threatening situation and is uncertain about what is going to happen or about the best course of action to take, anxiety occurs.

In my formulation, the amygdala plays a greater role in threat processing than the hippocampus. I have described the role of the amygdala in processing and responding to threats in earlier chapters and in *The Emotional Brain*,<sup>89</sup> and will only briefly recount it here. When sensory information about a threatening stimulus is detected by the amygdala, output connections to response-control systems in the brain stem initiate the expression of defense responses (freezing) and supporting physiological changes in the body (rises in blood pressure and heart rate, stress hormone release, and so on), some of which give rise to signals that are fed back to the brain and influence ongoing processing. Although Gray's theory did not address the question of how monoamine systems are activated by threat, one of the key ways this occurs is through direct connections from the amygdala to the monoamine cells. Thus,

during threats, serotonin and norepinephrine (and dopamine) are released in widespread forebrain areas (including the prefrontal cortex, hippocampus, and amygdala, as well as other areas). Direct connections from the amygdala to prefrontal areas (including anterior cingulate and orbital cortex) allow the detection of threats by the amygdala to directly influence working memory processing. But the prefrontal cortex and its working memory functions are also influenced through other routes, including the amygdala-initiated release of monoamines and the feedback from hormonal and other bodily responses. When the amygdala detects a threat, it triggers consequences that ultimately place working memory in a vigilant processing state, causing it to continue to attend to whatever it is occupied with at the moment, biasing thoughts, decisions, and actions. Further, output connections of the amygdala to the nucleus accumbens, as we saw in the last chapter, allow threatening stimuli to motivate the organism to avoid the source of the threat. This is an important factor, given that pathological avoidance of possible threat sources is a paramount behavioral symptom of anxiety disorders.

Up to this point in the discussion, I've not made a clear distinction between fear and anxiety. Classically, though, fear is viewed as a reaction to a specific and immediately present stimulus, whereas anxiety is a concern about what *might* happen. One possible resolution of the Gray-McNaughton theory with the amygdala theory would be if amygdala networks took care of fear and hippocampal networks took care of anxiety. This might have been an acceptable thesis some years ago, but there is now strong evidence showing that injection of benzodiazepines directly into the lateral and basal amygdala, the input stages of the amygdala, reduces anxiety behaviors in several (though not all) of the classic tasks used to test the efficacy of antianxiety drugs.<sup>90</sup> That finding is consistent with the fact that benzodiazepine receptors are concentrated in these input regions of the amygdala.<sup>91</sup> Further, atypical antianxiety drugs that target serotonin receptors also relieve anxiety in animal models when injected into the amygdala.<sup>92</sup> Both classical and atypical antianxiety drugs may therefore achieve their anxiety-reducing effects, at least in part, at the input stages of amygdala processing, making it harder for threatening stimuli to initiate activity in the amygdala, thereby preventing amygdala activation from arousing the rest of the brain.

But another theory has been proposed that distinguishes fear and anxiety in a different way. Michael Davis has performed experiments suggesting that anxiety might be a function of the bed nucleus of the stria terminalis,<sup>93</sup> a brain region that is considered an extension of the amygdala and whose output con-

nections are remarkably similar to those of the amygdala.<sup>94</sup> Because of their similar outputs, the amygdala and bed nucleus can affect many of the same target brain areas (prefrontal cortex, monoamine systems, and so on) in comparable ways and produce the same kinds of bodily responses (muscle tension, fast-beating heart, sweaty palms, tight stomach, and so on). But because the inputs to the two structures are different, they might be activated under different conditions—the amygdala in response to immediately present threats, the bed nucleus to anticipated ones. This distinction between the role of the amygdala in fear and the bed nucleus in anxiety is appealing because it potentially explains why people on antianxiety medication can be generally less worried (that is, less anxious), and still be capable of responding to an immediate threat. However, much work remains to be done to clarify the role of these two regions and their relation to the broader circuits involved in anxiety.

In summary, generalized anxiety is an aroused state of mind initiated and maintained by emotional processing. As a result, it requires, at a minimum, networks involved in arousal (monoamine systems), emotional (amygdala, perhaps including the extended amygdala), and cognitive (prefrontal cortex, hippocampus) functions. And while individual brain regions and networks make distinct contributions to the processes that together constitute anxiety, anxiety itself is best thought of as a property of the overall circuitry rather than of specific brain regions.

## THE SPECTRUM OF ANXIETY

So far, this overview has focused on free-floating or generalized anxiety. But the anxiety disorders also include phobias, panic disorder, posttraumatic stress disorders, and obsessive-compulsive disorder. These are distinct conditions with different causes and symptoms, and the treatments that work for one do not necessarily work for the others.<sup>95</sup>

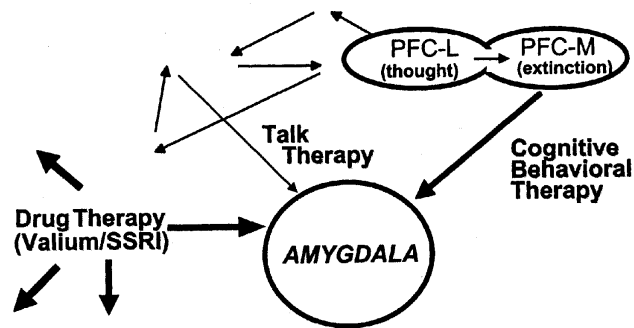
Benzodiazepines are of little help in treating the so-called simple phobias (pathologic fear of snakes, spiders, heights, and so forth). In fact, the most effective treatment for these conditions is psychotherapy, especially cognitive behavioral therapy, in which the symptoms are reduced by exposure to the feared stimulus under various conditions (see the box entitled “Cognitive Behavioral Therapy”). Another kind of phobia, social phobia, centers around a fear of being negatively evaluated by others—for example, by people with whom one works or shares interests. Some forms of social phobia involve a

### COGNITIVE BEHAVIORAL THERAPY

Therapy is a process of changing the way a patient thinks, feels, and/or acts. There are many different forms of therapy, but for the purpose of explaining what cognitive therapy is, we can contrast it with other approaches. Psychoanalysis attempts to get at the cause of the maladaptive condition, often by making unconscious (repressed) memories conscious. This is a long, slow process. Behavioral therapy, by contrast, seeks to alter maladaptive conditions (basically, bad habits) through the learning principles of behaviorist psychology, namely, reinforcement, extinction, counterconditioning, and so forth. Behavioral therapy, also known popularly as behavioral modification, focuses on observable symptoms and teaches the person to act in new ways. While fairly effective in rapidly altering certain pathologic tendencies, behavioral therapy was criticized for dealing with symptoms rather than causes, and for failing to acknowledge the importance of mental life in the initiation and maintenance of pathological conditions. Cognitive therapy, by contrast, takes as its starting point the notion that dysfunctional mental states (beliefs, attitudes, ideas) contribute significantly to psychopathology, and that the pathological conditions can be altered by helping the patient to identify and correct the beliefs. Rarely, though, does the simple realization that one has been thinking irrationally lead to improved mental health. The person has to learn new ways of thinking and acting. Many contemporary therapists blend cognitive and behavioral approaches and practice cognitive behavioral therapy (CBT), a process in which bad habits (mental and behavioral ones) supported by dysfunctional cognitions are changed. CBT has proven to be fairly effective as a treatment for a wide variety of nonpsychotic conditions, including the various anxiety disorders and depression, sometimes used alone and sometimes in conjunction with medication.

#### SELECTED READINGS

- Beck, A. T. 1991. Cognitive therapy: a 30-year retrospective. *Am. Psychol.* 46: 368–75.
- Gorman, J. M. 1996. *The New Psychiatry*. New York: St. Martin's Press.
- Hollon, S. 1999. What is cognitive behavioral therapy and does it work? *Curr. Opin. Neurobiol.* 8: 289–92.
- Zinbarg, R. E., D. H. Barlow, T. A. Brown, and R. M. Hertz. 1992. Cognitive-behavioral approaches to the nature and treatment of anxiety disorders. *Ann. Rev. Psychol.* 43: 235–67.



**FIGURE 10.3 THERAPY AND THE AMYGDALA**

Possible modes of action of three broad classes of therapy on amygdala function and dysfunction are illustrated. Classic psychotherapy (talk or insight therapy and all variations that require some conscious understanding in order to achieve a therapeutic effect) is likely to directly require the working memory functions of the prefrontal cortex. While the lateral prefrontal cortex (PFC-L) is the classic working memory area, other more medial regions (PFC-M) also appear to be involved in working memory. The absence of direct connections from the PFC-L to the amygdala may be related to why talk therapy for psychiatric conditions that involve amygdala-related conditions is relatively inefficient (in terms of the amount of time required to achieve a therapeutic effect). Behavioral therapy (including cognitive behavioral therapy) is less dependent on conscious insight and more dependent on extinction processes and on the development of new associations, skills, and habits (that is, on implicit learning). Some of these processes (especially extinction) involve the PFC-M. The direct connection of the PFC-M with the amygdala may explain why cognitive behavioral therapy is more efficient for certain fear/anxiety-related problems. Drugs can go straight to the amygdala, but they will also affect other brain regions, possibly accounting for some of the psychiatric side effects of drug therapy.

fear of being the center of attention in public. Examples of the latter include an extreme debilitating fear of public speaking or performance, and fear of eating in public or using public bathrooms. Antidepressant medications, including certain SSRIs and monoamine oxidase inhibitors, are often used in treating these conditions. Cognitive behavioral therapy is also useful. Drugs like propranolol, which reduce the bodily signs of fear (high heart rate and so forth) but that do not affect the brain directly, are sometimes used to aid in public speaking and stage fright. As with social phobia, the preferred treatment for panic disorder and posttraumatic stress disorder today is the use of an SSRI in combination with some form of psychotherapy involving anxiety management and cognitive behavioral therapy. A variety of other drugs (including monoamine oxidase inhibitors, tricyclics, and benzodiazepines) also

have some positive effects in these disorders, but the SSRIs have a better side-effect profile. Obsessive-compulsive disorder likewise responds to SSRIs to some degree.

Because the different forms of anxiety are manifested in different mental, behavioral, and physiological symptoms and often under distinct conditions (having to give a speech may have little effect on a spider phobic but will be a source of fear and anxiety to one who has a fear of public speaking), there is something unsatisfactory about the use of similar medications to treat them all. And because the preferred medications are antidepressants, rather than drugs developed for specific anxiety disorders, one can't help but feel that from the point of view of drug development and treatment, we have hardly touched these mental problems, some of which are widespread and devastating. Certainly, following the strategy of using information about effective treatments to give clues to the underlying biological disturbance is not going to reveal differences between various anxiety disorders, since the same treatment (SSRIs) is used for different anxiety disorders, as well as for depression.

Earlier, I mentioned that I am the director of the Center for the Neuroscience of Fear and Anxiety (<http://www.cns.nyu.edu/CNEA/>). This center brings together scientists at all of the major biomedical research institutions in Manhattan, including New York University (Elizabeth Phelps, Mony de Leon, and me), Rockefeller University (Bruce McEwen), Cornell University Medical College (David Silbersweig and Emily Stern), Mt. Sinai Medical School (John Morrison and Patrick Hof), and Columbia University (Jack Gorman). The research involves studies of animals and of patients with anxiety disorders. Our immediate goal is to elucidate the ways in which the brain is changed in anxiety disorders, in the hope of facilitating, over the long run, the development of more selective and more effective treatments with fewer side effects. The patient work involves the use of state-of-the-art functional MRI imaging techniques, and the animal work takes advantage of the vast arsenal of neuroscience tools that has been discussed throughout this book.

Because anxiety disorders involve alterations in the processing and/or reaction to threat and danger, and fear mechanisms are to a large extent conserved in the brains of humans and other mammals (chap. 8), research on the psychology and neuroscience of fear can inform ideas about the underlying disturbance in different anxiety disorders.<sup>96</sup> Although there have been several imaging studies of patients with anxiety disorders of various types,<sup>97</sup> the aim of our center is to use the enormous progress that has been made in elucidat-

ing the neural pathways underlying fear conditioning in animals to try and understand the nature of the brain changes that take place in anxiety disorders, especially panic disorder and posttraumatic stress disorder (PTSD).

Panic disorder and PTSD both involve alterations in the processing of threats, but the causes and symptoms are distinct.<sup>98</sup> In panic disorder, fear is expressed in the form of discrete and sudden panic attacks that arise without an obvious environmental stimulus and lead to chronic anticipatory anxiety and various degrees of avoidance behavior. Fear in panic patients has no apparent relationship to any actual threat and often involves abnormal sensitivity to uncomfortable somatic sensations. In PTSD, fear is expressed as increased sensitivity to stimuli reminiscent of an original, life-threatening traumatic event and includes flashbacks and increased startle response. Different neural mechanisms should therefore be altered in these patients.

As we've seen repeatedly, the amygdala is a key brain region in the acquisition and expression of fear elicited by stimuli associated with threatening experiences. And several studies of normal humans have now shown amygdala activation during fear conditioning, even when the conditioned stimulus is presented subliminally, that is, unconsciously.<sup>99</sup> We therefore can use fear conditioning to activate the amygdala and determine whether the pattern of activation there is altered in patients with anxiety disorders. Our expectation is that because changes in the way fear-arousing stimuli are perceived and responded to characterize all anxiety disorders, we should see increased levels of activity in the amygdala in both panic and PTSD patients.

But the amygdala is not the only area implicated in fear conditioning. As we've seen, the hippocampus is involved in processing fear-arousing situations or contexts, and the medial prefrontal cortex in the adjustment of fear reactions in response to changing environmental conditions, as in extinction (the process whereby a conditioned stimulus loses its fear-arousing properties when it no longer predicts danger). Recent studies by Liz Phelps have confirmed the role of the human hippocampus in processing contextual fear stimuli,<sup>100</sup> and we are currently testing whether activation of the human medial prefrontal cortex will be altered during extinction.

The use of fear conditioning allows us to assess whether patterns of neural activity within and between the amygdala, hippocampus, and medial prefrontal cortex differ in panic and PTSD patients from normal controls. Further, we can determine whether successful treatment (e.g., the use of SSRIs and cognitive behavioral therapy) will cause the brains of these patients to look more like those of normal controls. By testing patients after treatment

with either SSRIs or cognitive behavioral therapy alone, we should be able to determine whether the two kinds of therapy achieve their results by altering the same or different components of the circuits.

Once we have some sense of how the brains of panic and PTSD patients differ from each other and from those of normal persons, we can turn to animal studies and explore what kinds of life experiences and biological conditions might predispose the brain to change in these ways. For example, suppose we find that the amygdala is hyperactive in both panic and PTSD, but that the hippocampus and prefrontal cortex change in different ways in each condition. We could look for stressful experiences that produce these patterns of change in the rat brain. If such patterns can be identified, then the changes can be pursued at the level of synaptic alterations and explained in biological terms: as neurotransmitter actions on receptors that open channels and allow calcium to flow inside the cell and trigger kinases that phosphorylate transcription factors that induce genes to make proteins that stabilize synaptic changes. To the extent that any one of these molecular steps differs between anxiety disorders, clues about future drug development would be available.

By now you've surely noticed a trend. Neuroscientists have proposed that the prefrontal cortex, hippocampus, and amygdala are altered in some way in all forms of mental illness we've considered so far. It seems that mental disorders are giving us a message, telling us that these three brain regions are especially critical to understanding who we are and why we are that way. But we should remember that the same brain areas can be involved in different disorders for different reasons. At a fairly gross level of explanation, neural activity in a particular area might be up in one disorder and down in another. But in order for neural activity to change in this way, more basic changes have to be taking place within and between individual cells in the area in question. Since these deeper changes can be revealed only by exacting neurobiological studies, which can be done only in experimental animals, it is essential that research on psychiatric disorders in humans and basic science investigations of brain function in animals be coordinated.

We have just begun this research program, and it is too early to know just what we'll turn up. However, because of the systematic nature of the research program, we will almost certainly be able to point to differences in the brains of panic and PTSD patients, even if they are not the ones we expected. But, in many ways, unexpected findings are the most interesting, as they force thinking about problems in new ways.

## BRAINS, GENES, AND THERAPY

We've gotten all the way to the end of this chapter on biological approaches to mental illness without discussing genes. To many, especially to critics, a biological approach to mental disorders implies an emphasis on genetics. But I hope I've presented a credible alternative view. As in all other aspects of mental life, genes can predispose people in certain directions without altogether predetermining their destiny. Genes contribute to, rather than solely dictate, synaptic connectivity.

Critics such as Colin Ross and Alvin Pam are concerned that a biological approach to mental disorders implies that "the individual with behavior problems must suffer in some way from defective protoplasm, a constitutional predisposition to mental illness," and that the body or brain is responsible for mental illness rather than the family or society.<sup>101</sup> They strongly equate biological psychiatry with genetics. However, while a genetic approach to mental disorders is by definition biological in orientation, the reverse is not necessarily true: a biological approach is not exclusively or even primarily genetic. Let's first take a look at the genetic approach, and then consider the broader picture.

A massive effort is now under way to determine the extent to which genes contribute to mental illness. For example, years of research have gone into pedigree studies of families or groups of people with a tendency toward a mental disorder, and into concordance studies of identical twins, which determine the likelihood that the presence of the disorder in one predicts the disorder in the other. Schizophrenia, depression, anxiety disorders, alcoholism, and a variety of other psychiatric and neurologic conditions are being studied this way.

For illustrative purposes, consider the work on schizophrenia.<sup>102</sup> The research shows a strong correlation between the number of genes shared and the likelihood of developing the disorder.<sup>103</sup> Schizophrenia occurs in about 1 percent of the general population. In contrast, in identical twins (100 percent gene overlap), if one child has schizophrenia then there's roughly a 50 percent chance the other will develop it at some point. But in fraternal twins (50 percent gene overlap), the likelihood drops to 17 percent. In siblings (25 percent gene overlap), the figure falls to 9 percent, and in first cousins (12.5 percent gene overlap) to 2 percent. The overall picture that emerges is that schizophrenia is strongly tied to genetic factors. That is, in genetic terms, there's 50 percent concordance among identical twins. But one can view this cup as half

full or half empty—there's also 50 percent discordance. If genes fully "explained" schizophrenia, concordance would be 100 percent.

The discordance between identical twins is due to several factors.<sup>104</sup> One is that gene expression is an *epigenetic* phenomenon—it involves the interaction of the gene with environmental factors. An extreme example of epigenesis is the disease phenylketonuria (PKU), a genetic form of mental retardation that is not expressed unless the essential amino acid phenylalanine is ingested. (It is present in dairy products, avocado, certain nuts, and in the sugar substitute aspartame.) In this case, early detection and treatment can prevent the symptoms of the disease. In most genetic conditions, though, the environmental co-conspirators are not known. Another factor working against concordance is the polygenetic nature of the genetic contribution. In the days when psychiatric disorders were thought to be due to a simple imbalance in a particular brain chemical, it was plausible that the disorder might be caused by a single gene (one that makes transmitter or receptor molecules). But as we've seen, psychiatric disorders involve complex circuits in the brain, and therefore any genetic contribution is likely to involve interactions among multiple genes. Because the expression of every gene also involves interactions with environmental factors, polygenetic inheritance greatly expands the manner in which the environment can influence genetic predispositions. Further, in some cases, people with the gene for a disease show little or no evidence of having the symptoms of the disease. This is called *nonpenetrance*. In other instances, genetic diseases are variably expressed, where some family members may have the full-blown disease and others only mild symptoms. Finally, mental disorders can probably have multiple unrelated causes. It is believed, for example, that in some instances, schizophrenia can be induced by environmental factors, like brain injury or infection, in persons with little or no genetic leaning toward the disorder. So discordance between identical twins might sometimes be due to the fact that the afflicted twin acquired schizophrenia for nongenetic reasons.

Biological psychiatrists are interested in the possibility that genes contribute to mental disorders because genetic problems might in the future be fixable. A gene working overtime and thereby causing a malfunction might, with a pill, be turned down or off, and one that is sluggish might be encouraged to work harder. Whether these feats will ever be successfully accomplished is unknowable at the present. But if they are, many people are likely to be helped.

It should be noted that success or failure for one psychiatric disorder will

not predict the success or failure in treating others. Each disorder will have its own peculiar advantages and disadvantages for a genetic approach, and each has to be attacked individually. At the same time, research strategies developed for one problem may help in the pursuit of the others. With the human genome recently pronounced as “knowable,”<sup>105</sup> this kind of work is likely to expand in the coming years.

But perhaps I’m not being completely fair to the critics. One of their concerns is that a focus on genes or other aspects of biology puts too much blame on the body, discouraging mental professionals from using nondrug forms of therapy, insurance companies from paying for nondrug therapy, and patients from taking responsibility for their own healing. But these concerns, I believe, reflect a misunderstanding of the aims of biological psychiatry.

In spite of the current enthusiasm for genetic analyses of mental disorders, most biological psychiatrists view genes in a realistic way. Raymond DePaulo, a biological psychiatrist at Johns Hopkins University, expresses what is probably the most common view: “I don’t think depression is all genetic. If you can nail down one end of the tent, however, it’s easier to figure out by stretching out the rest of the tent what it should look like.”<sup>106</sup> In other words, once you know the genetic component of a disorder, it should be easier to figure out which kinds of environmental experiences interact with it to trigger the disorder and make it worse. Genes are part of the story, and if that part of the story can be interpreted, we should be better off than if we ignore it.

Experience is often considered the counterpoint to genes. But *experience* is a complex notion with many possible meanings and endless implications. As a result, the role of experience is probably going to be even more difficult to understand than the role of genes. But the more we understand about how experience changes the brain, the better off we’ll be in discovering how it contributes to mental disorders. As we’ve seen, experiences affect the brain when they are stored as synaptic changes in one or more systems during learning, which is why research on synaptic plasticity, and on learning and memory, is so important.

Where does a biological approach to mental health and mental disorders leave psychotherapy? Eric Kandel, the renowned neuroscientist, started his career as a psychiatrist. Recently, he boldly proposed a “new intellectual framework for psychiatry,” one founded on biological principles.<sup>107</sup> He argued that we are on the threshold of understanding memory and emotion systems in the brain, and that this information, combined with continued advances in molecular neuroscience, offers a wealth of opportunities for psychiatry.

As I pointed out at the beginning of this chapter, psychotherapy is fundamentally a learning process for its patients, and as such is a way to rewire the brain. In this sense, psychotherapy ultimately uses biological mechanisms to treat mental illness. This does not mean, however, that psychotherapy involves learning while drug therapy involves something else, like correction of genetically dictated chemical imbalances. Even if chemical imbalances were to account for mental disorders, the imbalance could result purely from environmental factors, like some intensely stressful experience, or from environmental events that trigger and amplify a genetic predisposition. The therapist’s job, whether using drugs or not, is to restore mental well-being. If the patient’s problem involves neural changes that are locking the brain in an aroused state, relief will come only when the aroused state is reduced, either by psychotherapy or drug therapy, or by some combination of the two. Regardless of whether the initial cause is social stress or a genetic time bomb, unless the changes in the brain that accompany the disorder can be reversed or circumvented, the problem is unlikely to dissipate.

Contemporary approaches to the treatment of mental disorders are not distinguished from older ones so much by an emphasis on drugs as by an emphasis on *effective* treatment. Jack Gorman of Columbia University, a leading biological psychiatrist, puts it this way: “In the Old Psychiatry, each clinician learned a set of techniques from one school of thought and insisted on applying them to all comers. In the New Psychiatry clinicians may still feel most comfortable with the tools of one school, but they readily admit when they don’t have the right skill for a particular patient.”<sup>108</sup> Today, psychoanalysts are willing to refer patients who need medication to a psychiatrist with skills in psychopharmacology, just as those trained in psychopharmacology increasingly send patients to a psychotherapeutic specialist. “The New Psychiatry,” according to Gorman, “is only interested in providing safe and effective treatment. If that means borrowing from different points of view to offer a patient a combination of therapies, then that is what must be done.”

Once a disorder exists, and the brain has changed, the changes have to be dealt with in some way in order for a patient to recover. Drugs can induce adaptive changes in neural circuits, or put neural circuits in a state where adaptation and learning are promoted. But there’s no guarantee that, left to its own devices, the brain will learn the right things. Patients, in other words, are likely to benefit most from drug therapy when the drug-induced adaptivity of their brains is directed in a meaningful way. This is probably best achieved by traveling down the pharmacological road to recovery with some-

