

an introduction to  
**STRESS**  
& **HEALTH**

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 **SAGE**

Los Angeles | London | New Delhi  
Singapore | Washington DC

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# 9 ANXIETY DISORDERS

## IS IT A REALITY OR AN OPINION?

In a recent episode of a television program, one of those that include the crime, the search for the bad guy, and then the trial, the defense's case was that the alleged perpetrator suffered from PTSD and as a result should not be found guilty. The prosecution lawyer, in cross-examining the expert witness, a psychiatrist, asks 'How did you diagnose this illness?'. The psychiatrist replied that he did this 'on the basis of several interviews to see whether the alleged perpetrator showed signs of PTSD', to which the prosecutor replied with something like 'So, I take it that you didn't perform any brain imaging analyses to see if there was disturbance in the brain, or any blood tests or analyses of cerebrospinal fluid that could tell us whether there were chemical imbalances? So, really, this diagnosis of yours is nothing more than an opinion, a guess. Perhaps it was an educated guess, but still just a guess'.

Although psychological disorders are thought of as diseases of the brain and so should have some biological origin, finding these underlying mechanisms hasn't been easy, and even finding the markers for these illnesses has been difficult. Unlike diabetes that can be detected on the basis of blood sugar levels, or heart problems that can be seen through different tests of varying invasiveness, to assess the presence of mental disorders we're often reliant on behavioral or cognitive symptoms. To be sure, with improved molecular, biochemical, and imaging technologies, it's just a matter of time before biological indices of various illnesses will be determined. Yet, as most illnesses represent an amalgamation of multiple disturbed processes and biological mechanisms, this won't be simple or fast. In the case of anxiety, this might be especially difficult as there are many subtypes of anxiety that differ from one another and may involve some common mechanisms and some that differ from one another.

Most of us have felt anxious at one time or another, usually in anticipation of something negative or uncertain (such as an exam, having to give an oral presentation to a group, or waiting for the results of a medical test). The anxiety most people feel is usually mild, occurs only under certain circumstances, and likely has significant adaptive value as it keeps us in a heightened state of alertness and readiness to respond. For others, it can be persistent and intense to the extent that individuals describe themselves as ‘just wanting to crawl out of their skin’. Some individuals who have suffered anxiety that was comorbid with severe depression have also indicated that the anxiety was actually as bad as, or even more disturbing than, the depression. What differentiates ‘normal’ anxiety from anxiety that requires treatment is the degree of discomfort it creates and the extent to which it affects social and workplace functioning or family interactions. Anxiety disorders may be debilitating, chronic conditions that in some individuals first appear at a very early age, possibly among individuals with a familial history of anxiety, or they may be elicited by specific events. This chapter has several core objectives regarding what the reader should learn from it:

- anxiety can be mild, reflecting a normal response to challenging or threatening situations. Alternatively, it can come in any of several disorders that call for some sort of treatment. These comprise general anxiety disorder, panic disorder, phobias, social anxiety, obsessive-compulsive disorder, and posttraumatic stress disorder. Moreover, these anxiety-related illnesses can be comorbid with depressive disorders;
- the causes for each of these disorders can be very different, and the social and biological processes associated with them are different as well;
- although each of these disorders comprises very different symptoms, and involve several different biological processes, some of them seem to have several common underlying mechanisms;
- despite the different characteristics of these disorders, they are amenable to some of the same treatments, although their effectiveness has not been particularly strong.

## SUBTYPES OF ANXIETY

‘Anxiety Disorder’ is actually a broad term that applies to several forms of abnormal and pathological anxieties or fears that affect 18% of individuals in Western societies. Although each of these illnesses is classified as an anxiety disorder, the course and etiological processes associated with them may differ appreciably from one another, and the various disorders are not necessarily responsive to the same treatments. As we’ll see, disorders that comprise anxiety and those that involve fear (e.g., phobias) are generally placed under the rubric of ‘Anxiety Disorders’, although they are actually quite different and involve different biological underpinnings. Fear has been considered as an apprehension whose onset occurs rapidly in response to a threat, and then abates quickly once the threat is removed. In this sense, the ‘fear’ response is perfectly adaptive provided that there’s an *actual* threat present. Anxiety, it seems, is more closely aligned with threats that are neither as specific nor as predictable as those that elicit fear, and because it may not be tied to specific stimuli, the course of this anxiety may be very protracted. Table 9.1 provides a summary of different types of anxiety-related disorders. We’ll deal with each independently, but as we move through these it should

become clear that despite profound differences between them, there are also several commonalities, including a core made up of common symptoms, and in some instances the same treatments are applicable. That said, the treatments available are not perfect, and there is certainly room for some refinement of the current therapeutic strategies.

TABLE 9.1 Anxiety disorders

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**Generalized anxiety disorder**, the most common anxiety disorder among adults, is characterized by persistent (at least six months) anxiety or worry that is not focused on any single subject, object, or situation.

**Panic disorder** is characterized by discrete periods involving the sudden and unpredictable onset of intense apprehension or terror accompanied by features such as shortness of breath, chest pain and palpitations, feelings of choking or smothering, and a fear of losing control. It may result in profound behavioral changes involving worry about the implications or concern about having other attacks.

**Phobias** are characterized by clinically significant anxiety (fear) elicited by certain situations, activities, things, or people, in which individuals display an excessive and unreasonable desire to avoid or escape from the feared object or situation. There are several classes of phobias, and as a group these are exceptionally common.

**Social anxiety disorder (social phobia)** comprises an intense fear of public embarrassment or humiliation (negative public scrutiny). Most often this fear is evident across situations, but can be specific to certain venues (e.g., public speaking). The severity of symptoms can be sufficiently intense to provoke social isolation.

**Obsessive-Compulsive Disorder (OCD)** comprises obsessions or intrusive thoughts that provoke anxiety and compulsions (e.g., hoarding, repeated checking, repeated behavioral acts such as hand washing, or preoccupation with sexual, religious, or aggressive impulses) that serve to alleviate the anxiety (although the compulsions aren't necessarily overt).

**Posttraumatic Stress Disorder (PTSD)** is elicited by traumatic or chronic physical or psychological stressors. It is characterized by the re-experiencing of a traumatic event, avoidance of related stimuli, and hyperarousal. In addition, PTSD is often associated with emotional numbing and cognitive disturbances. Acute Stress Disorder (ASD) comprises similar symptoms evident soon after a traumatic event (three days). It largely differs from PTSD on the basis of the number of symptoms required for a diagnosis, and is accompanied by "dissociative" symptoms.

**Separation anxiety disorder** comprises excessive and inappropriate levels of anxiety in response to being separated from a person or place. Such feelings are common in children, but are considered a disorder only when these are excessive and inappropriate.

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## GENERALIZED ANXIETY DISORDER (GAD)

This fairly common illness, whose symptoms are provided in Table 9.2, markedly influences social functioning, and has a life-time prevalence of about 5%. The appearance of GAD can occur early in life, although the onset is most common when individuals are in their twenties or early thirties and appears twice as frequently in women as in men. The development of GAD is relatively slow, but once present it may be fairly persistent. It is frequently a comorbid feature of major depression or dysthymia, as well as other anxiety disorders (panic disorder, social phobia). The frequent comorbidity between major depression and GAD raises the possibility that they share etiological processes.

There appears to be a genetic link for this disorder as it runs in families, and concordance for the presence of GAD was more frequent in monozygotic (identical) than in dizygotic twins, although to a great extent a vulnerability to GAD was tied to contextual

**TABLE 9.2** Generalized anxiety disorder (GAD) symptomatology

According to the DSM-5, GAD is characterized by:

- (1) excessive, uncontrollable, and often irrational worry about day-to-day things and events; the anxiety persists for at least six months, being present on more days than not;
- (2) an inability to or difficulty in controlling these thoughts.
- (3) In addition, three of the following symptoms must be present: restlessness (or feeling on edge), easily fatigued, difficulty concentrating, irritability, muscle tension, sleep disturbance typically involving difficulty falling asleep or staying asleep (or restless sleep).

The excessive anxiety should not be related to the use of illicit drugs and is not limited to anxiety or worry about other psychological disorders.

Beyond these core symptoms, GAD is often accompanied by physical signs that include sweating, cold clammy hands, dry mouth, headaches, muscle tension, muscle aches, nausea or diarrhea, numbness in the hands and feet, difficulty swallowing or the feeling of a lump in the throat, occasional bouts of breathing difficulty, trembling, and twitching.

For those who might have thought that an anxiety disorder is not all that serious, and really amounts to 'just a bit of anxiety', this list of symptoms lets you know how problematic it can be.

(environmental) factors. Encountering a major life stressor (e.g., a car accident, or a breast cancer diagnosis, as well as natural disasters such as earthquakes) has been implicated in the emergence of GAD. Likewise, GAD, along with PTSD, can even occur through witnessing a trauma. For instance, these disorders appeared more frequently among individuals who knew someone at the 9/11 terrorist site than among those who did not. This is not to say that GAD occurs exclusively in those who have been traumatized. Individuals who experienced high psychological job demands (excessive workload, extreme time pressures) had a two-fold risk of depressive disorders or GAD relative to those with low job demands. And added to this, early life stressors might contribute to the emergence of GAD, just as it may be a predisposing factor for depression.

## BIOLOGICAL FACTORS AND TREATMENT OF GAD

In view of the large amount of data suggesting that the amygdala and the bed nucleus of the stria terminalis are involved in anxiety and fear (Davis et al., 2010), it is thought that GAD might also involve disturbed amygdala functioning or disturbed connectivity to other brain regions that might be fundamental in processing information related to anxiety-provoking stimuli. In the latter regard, it is clear that the prefrontal cortex and hippocampus are also involved in anxiety and fear, particularly as they may contribute to an appraisal of fear-related events and also the memory of these events. For example, functional imaging studies indicated that GAD was accompanied by increased prefrontal cortical activity, which was attenuated following effective treatment of the disorder. Recent evidence concerning brain interactions has, however, put a different spin on how anxiety emerges. It was suggested that the connection that exists between the amygdala and both the prefrontal and anterior cingulate cortex, a white matter tract referred to as the uncinate fasciculus, was disturbed among GAD patients (Tromp et al., 2012). Ordinarily the anterior cingulate tells the amygdala to

calm down in the face of non-threatening stimuli, but in those with GAD this might not occur and hence elevated anxiety persists.

Admittedly, the available data concerning the brain processes specifically associated with GAD are still limited, and a unitary hypothesis regarding the development of this disorder is still a way off. For the moment, the disorder is being treated, sometimes very successfully, based on knowledge of stressor effects on biological systems and on the basis of which drugs are effective in the treatment of other anxiety disorders. When people think of anti-anxiety medications, those that likely come to mind are benzodiazepines, such as diazepam (valium), alprazolam (Xanax,) or lorazepam (Atavan), each of which is fast acting and may be an effective short-term remedy. However, these drugs are not recommended for long-term use as they may be associated with the development of tolerance, physical dependence, and withdrawal symptoms. More often, GAD is treated with SSRIs as well as the serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine (Effexor) and duloxetine (Cymbalta). These agents may be more effective than benzodiazepines as they access comorbid depression that might be present, whereas benzodiazepines typically won't (Gorman, 2003). However, SSRIs may take several weeks to modify GAD, just as there is a delay in the alleviation of depression. As well as this, the remission may be incomplete, and SSRIs and SNRIs may have some unwanted side effects. Chapter 12 covers an array of antianxiety medications and so we won't repeat these in much detail here. Suffice it to say that there are several other drugs that fall out of the usual categories that have been used in the treatment of GAD. For instance, buspirone (BuSpar), a 5-HT<sub>1A</sub> receptor partial agonist (this means the drug only partially activates the receptor, and at some doses may actually work in an opposite fashion) that also acts as a dopamine D<sub>2</sub> and  $\alpha$ -adrenergic antagonist, may be effective in treating moderate GAD. Pregabalin (Lyrica), which is used in the treatment of neuropathic pain, is also useful in the treatment of GAD, and the NE  $\beta$ -blocker propranolol (Inderal), which is primarily used for hypertension, also acts as a potent anti-anxiety treatment.

A meta-analysis conducted some years ago indicated that although pharmacological treatment and cognitive behavioral therapy (CBT) were both effective in attenuating GAD, the latter was more efficacious in several respects. Specifically, CBT was associated with having greater effects on the depression that accompanied GAD, and therapeutic gains were maintained after a discontinuation of treatment, whereas the efficacy of pharmacologic treatment diminished following medication discontinuation (Gould et al., 1997). Thus, CBT may have more long-term effects, whereas the pharmacological route appears to promote a more immediate fix. Having said this, it seems that CBT is effective to some extent in 50–60% of GAD patients (and about 30% don't gain any benefit), and other forms of behavioral therapy (e.g., relaxation or those treatments that focus on improving a tolerance for uncertainty) were about as effective.

## PANIC DISORDER

Having seen the movie *Analyze This*, with Robert De Niro and Billy Crystal, it strikes me that panic disorder is now more mainstream than it had been previously. As indicated in

**TABLE 9.3** Panic disorder symptomatology

According to the DSM-5 criteria, a panic attack is diagnosed when four of the following symptoms are present:

1. palpitations, heart pounding, or accelerated heart rate
2. sweating
3. trembling/shaking
4. sensations of shortness of breath/smothering
5. feeling choked
6. chest pain or discomfort
7. nausea or abdominal distress
8. feeling dizzy, unsteady, or light headed
9. depersonalization (person feels detached from themselves) or derealization (a feeling of unreality)
10. fear of losing control or going crazy
11. fear of dying
12. numbness or tingling sensations
13. hot flashes

Clearly, panic attacks can be pretty grim, and their anticipation can be understandably distressing.

Table 9.3, this is an anxiety disorder in which an individual may have brief attacks of intense terror and apprehension that peak within a few minutes and typically last for only a brief period (1–20 minutes), but can be longer lasting. It isn't certain what brings on the initial attack, and whether that experience leads to sensitized processes that might facilitate further attacks. It is thought that stressful life events, or appraisals of events that promote embellished perceptions of potentially stressful stimuli, contribute to the development of panic disorder. This assumption is based on reports that panic attacks are first seen following such events, as well as after physical illnesses or certain drug treatments (including illicit drugs that might have engendered negative effects).

Panic attacks are recurrent and in some people these attacks occur weekly or even daily. As a result, individuals often have ongoing concerns about having further attacks, particularly as the attack may cause them embarrassment and promote social stigma. Panic disorder is frequently comorbid with agoraphobia, and has also been reported to be comorbid with other illnesses such as bipolar disorder and alcoholism. Although panic disorder runs in families, individuals with no family history of the disorder may also suffer from panic attacks. Several genes have been identified that confer a susceptibility to panic disorder, but like many other genes that have been identified in relation to various disorders, translating this knowledge into treatment or predictive strategies has been slow in materializing (Smoller et al., 2008).

## BEHAVIORAL AND COGNITIVE VIEWS OF PANIC DISORDER

In their review of panic disorder, Schmidt and Keough (2010) indicated that cognitively-based models have been fundamental in our conceptualization of this illness. They describe three perspectives that have been particularly influential in this regard. These models comprise an emotion-based model, a cognitive perspective, and an expectancy model. The emotion-based model has it that some individuals may be disposed to overreact to stressors. This heightened

reactivity could then be related to genetic factors or adverse life events that had been encountered, including those that occurred early in life or during adolescence, and that panic will be most prominent if individuals also had the sense that events and emotions were uncontrollable and unpredictable. It was further suggested that through classical conditioning, anxiety-related arousal and panic may be associated with internal sensations (i.e., interoceptive cues), so that when these internal cues appear again, possibly as a response to reminder stimuli, a panic attack may be instigated. The second (cognitive) position also includes the perspective that feedback from the body is fundamental in the instigation of panic attacks. According to this view, certain sensations may be ‘catastrophically’ misinterpreted as being especially threatening (e.g., an elevated heart rate or feelings of indigestion may be misinterpreted as a heart attack), leading to high levels of arousal, which then promote further bodily changes and still greater perceived threat. This recurrent cycle ultimately results in a panic attack. Finally, according to the third model, anxiety is derived from the fear of symptoms re-emerging, and indeed the fear of the consequences of anxiety is greater in panic disorder patients than in most other anxiety disorders (Olatunji & Wolitzky-Taylor, 2009).

## BIOLOGICAL FACTORS RELATED TO PANIC DISORDER

Several biological processes have been implicated in subserving panic disorder. GABA is an inhibitory transmitter that acts as a brake for neuronal activity, and it is thought that anxiety emerges when the inhibitory signaling associated with GABA activity is diminished. In fact, relative to controls, patients with panic disorder exhibited lower GABA concentrations in the anterior cingulate cortex and basal ganglia (Ham et al., 2007). Moreover, cortical GABA concentrations were diminished in patients with a family history of mood and anxiety disorders, raising the possibility that genetic factors related to GABA functioning might be at play in determining a vulnerability to panic disorder.

In addition to GABA, 5-HT might contribute to panic disorder. It has been known for some time that anxiety can be induced by drugs that stimulate certain 5-HT receptors (5-HT<sub>2C</sub>/5-HT<sub>3</sub>) or reduce 5-HT<sub>1A</sub> receptor availability (Nash et al., 2008), whereas the opposite effect is elicited by treatments that antagonize the 5-HT<sub>2C</sub>/5-HT<sub>3</sub> receptors. The finding that SSRIs can be used to treat panic disorder, at least to some degree, is consistent with 5-HT involvement in panic disorder. Yet there have also been reports that SSRIs may actually elicit panic disorder symptoms, especially during the early stages of treatment. Thus, although 5-HT regulation might contribute to panic disorder, there’s much more behind this illness. Indeed, NE might also be associated with panic disorder, as the drugs that block NE receptors (particularly  $\alpha_2$  receptors) promote anxiety responses. There has also been interest in the possibility that panic disorder might be related to particular neuropeptide factors, such as CRH, AVP and one that we didn’t discuss earlier, cholecystokinin (CCK). Although CCK is more often considered as one of several gut peptides involved in digestion, reports that a low dose of CCK could induce a panic attack in patients with panic disorder is consistent with a role for this peptide in this particular anxiety disorder.

One of the difficulties associated with determining the mechanisms underlying panic disorder is the wide range of brain regions that could potentially be involved in this illness.

In response to a challenge that comprised emotionally salient cues (anxiety-provoking visual stimuli or threatening words), patients exhibited particularly elevated neuronal activity in brain regions involved in appraisal and executive processes, such as the anterior cingulate cortex, posterior cingulate cortex, orbital frontal cortex and hippocampus. As expected, following psychotherapy that diminished panic disorder symptoms, the activation patterns in some brain regions normalized (Beutel et al., 2010). However, in remitted patients (patients who purportedly had been successfully treated) tested in an emotional conflict paradigm (in which they were presented with emotionally congruent and incongruent faces and words), elevated neuronal activity was still evident in the anterior cingulate cortex, dorsal medial prefrontal cortex, and amygdala (Chechko et al., 2009). Evidently, among remitted panic disorder patients, the brain responses to emotional stimuli were still exaggerated, raising the possibility that these neuronal changes were indicative of relapse potential upon exposure to particular types of events.

## TREATMENT OF PANIC DISORDER

Both pharmacological and behavioral methods have been used to treat panic disorder, with moderate success being achieved in both cases. Positive effects were obtained through psychodynamic therapy, a psychoanalytic-like procedure that attempts to get at unconscious content and thus diminish tension. CBT has been found to be an effective treatment strategy in about 60% of panic disorder patients, and was especially effective when treatments focused on the perceived likelihood of panic, the perceived consequences of that panic, and panic-coping efficacy (Mitte, 2005). Furthermore, CBT and related treatment strategies have also been effective in attenuating some of the comorbid features of panic disorder, but in some cases (e.g., where PTSD was a comorbid condition) treating the panic did not affect the accompanying PTSD (Teng et al., 2008). Antidepressant drugs can also reduce panic disorder in some patients, but the doses required were well beyond those needed to treat depression, suggesting the involvement of different processes in these disorders. Despite the success of SSRIs (and SNRIs), it was suggested that CBT should still be considered the treatment of choice. One would think that a combination of CBT and drug treatment would produce still better results, but this was not the case (Schmidt & Keough, 2010). Likewise, there was little value in combining psychotherapy and benzodiazepine treatment.

## PHOBIAS

A phobia refers to an intense and persistent fear of certain situations, activities, things, or people, and is typically characterized by an unreasonable avoidance of this stimulus. When the fear, which is typically seen as uncontrollable, comes to interfere with daily life, a diagnosis corresponding to this type of anxiety disorder can be applied. More people seem to know about phobias because they are relatively common, and appear more often in the media, as well as in films. Estimates of the prevalence of phobias range from 8 to 18%, and are typically more common in women than in men.

For many phobic individuals the feared object or condition is not all that frequently encountered (e.g., a fear of tarantulas if you live in Canada), and thus can be readily avoided. However, other phobias might comprise daily confrontations that need to be dealt with if a reasonable quality of life is to be maintained. For instance, people with social phobias, and especially those whose phobia becomes so strong they never leave the house, have a tremendous burden to deal with. Those with fears of public speaking, which is fairly common, know that this can become incapacitating, especially when their job demands it, and being phobic about planes certainly cuts down on the good times, and might interfere with certain business ventures.

## **PHOBIA SUBTYPES**

Phobias come in several varieties, all of which are considered to reflect anxiety-related disturbances. Phobias that are specific to particular objects or situations, such as a fear of snakes, heights, enclosed spaces and so forth, are common. Most individuals with these phobias know that their fears are irrational, but this doesn't diminish the anxiety elicited by the feared object or situation. Another form of phobia entails those that involve a social component. Many of us have fears that are related to social situations, but once more we don't usually consider it a phobia unless it affects our daily functioning. Social phobias are related to a fear of public scrutiny (walking into a room and worrying that everyone is watching you, or making a public statement that results in attention being drawn to you). A social phobia may be broad (generalized social phobia) or specific to particular situations. Another fear that comprises the fear of leaving home or places where one feels safe is referred to as agoraphobia. Agoraphobia can also be tied to social phobia that is manifested when the comfort of a safe place is replaced by wide-open situations where we can be embarrassed or at least open to public appraisal and scrutiny.

## **SOCIAL ANXIETY**

Social anxiety, which has been viewed as a social phobia, is the most common of the anxiety disorders. It is characterized by emotional discomfort, fear, apprehension, or worry about social situations, interactions with others, and about being evaluated or scrutinized by other people. The fact is that many of us share some of these characteristics, and social evaluative threats (e.g., in relation to public speaking or other public performances) are especially stressful and especially common. Social anxiety frequently begins during childhood, typically waning with age, but it often persists into adolescence and adulthood (Albano & Detweiler, 2001). In children, the disorder can prove fairly incapacitating, to the extent that they end up being fearful of playing with others or speaking to teachers. How the disorder comes about is uncertain, but it is not unlikely that negative experiences in social situations (e.g., public speaking in a classroom) might have contributed to the development of this form of anxiety disorder. Once the anxiety is present, individuals may experience a confirmation bias in which they look for negative reactions from others (e.g., during public speaking the individual may focus on those in the audience who appear not to be receptive, or

those who appear critical of the oral presentation). There is also reason to believe that social anxiety disorder has biological underpinnings, as there is a modest genetic component. It might be the case that individuals inherit anxiety-related characteristics, but the disorder evolves given negative social experiences.

Exaggerated neuronal activity in the limbic (amygdala) regions might be associated with elevated attention to, and processing of, the social threats that accompany social anxiety (Miskovic & Schmidt, 2012). In view of the earlier discussion concerning the role of oxytocin in relation to social behaviors and social stressors, it's a fairly reasonable bet that disturbed levels of this hormone or its receptor might contribute to the disorder. Indeed, manipulations of oxytocin and arginine vasopressin are being advanced as possible novel targets for social anxiety disorder (Meyer-Lindenberg et al., 2011).

## TREATMENT OF PHOBIAS

It is thought that phobias develop through simple conditioning processes. Specifically, an event or stimulus occurs in conjunction with a negative feeling or emotion or other aversive stimulus. This pairing results in a classically conditioned anxiety response, so that future presentations of the conditioned stimulus will elicit the anxiety/fear response. Thus, most therapies for phobia have focused on behavioral/emotional methods to diminish (extinguish) this conditioned response. In this regard, imagery and virtual reality treatments have been used in an effort to *desensitize* the individual, typically in small steps. Likewise, CBT has been used to help individuals come to understand their negative thought patterns, and then to modify them. Gradual desensitization treatment (reducing the distress in small steps in which the feared situation or object becomes closer and closer or progressively more real) and CBT have a high success rate, provided that the patient is willing to endure the discomfort that comes with being exposed to the feared object or situation. As in the case of other phobias, the treatment of social anxiety is not especially difficult, but it does vary with individual cases. Generally speaking, CBT is the most common treatment for the disorder, and in some cases may be given in conjunction with anti-anxiety agents or SSRIs, which have also been found useful in treating social anxiety.

### FEAR OF FLYING

For years I had a fear of flying in an airplane. I don't anymore, but I think this phobia, in part, stemmed from not having control over the situation. I'm certain I would have been more comfortable if I had been actually flying the plane, even if it distressed other passengers. Actually, when I had this phobia it wasn't the plane ride that got to me, it was the days preceding the flight that were worst. In fact, once I was on the plane, and had resigned myself to certain death, an odd calmness fell over me. Of course, this didn't stop me from making deals with God (e.g., 'If I make it back alive I'm giving 10% of everything I have to charity . . . Yes, yes, yes, I know I said that before and then reneged, but this time I really, really, really mean it').

Often, when friends tried to get me to abandon the phobia (as if a person can just do so at will) they would tell me that my fear was ‘irrational’ and that more people died in car accidents within two miles of home, as if I would then just change my mind about the phobia (incidentally, if it’s so irrational, then why did so many people stop flying after 9/11?). The second frequent comment I would hear is ‘Oh, it’s all in your head’. Well that was helpful, as I had thought it was in my bladder given the sensation that flying created.

Phobias aren’t all that difficult to get rid of through procedures such as CBT. However, any plane phobic will tell you that desensitization and cognitive therapy only work so well, and it still takes some commitment on the part of the individual with the phobia.

## **OBSESSIVE-COMPULSIVE DISORDER (OCD)**

Virtually everybody who’s a fan of scary movies, and many who aren’t, knows something about obsessive-compulsive disorder (OCD). Remember the scene in *Sleeping with the Enemy* when the woman (Julia Roberts) who runs away from her abusive husband (Patrick Bergin) opens her kitchen cabinet and sees the soup cans lined up neatly in rows facing forwards? Or do you remember your high school Lit class where you were introduced to Lady Macbeth compulsively washing her hands? However, if you had been asked to classify these OCD-like behaviors, you likely wouldn’t have seen them as being an anxiety disorder.

Obsessive-compulsive disorder is considered an anxiety disorder that primarily involves repetitive obsessions (distressing, persistent, and intrusive thoughts or images) coupled with compulsions (that entail urges to perform specific acts or rituals). These components can be independent of one another, as some individuals may present with obsessions, but not the compulsive behaviors. Although OCD sounds fairly unusual, its lifetime prevalence is 2%. However, not everyone who exhibits obsessive or compulsive features should be considered to be suffering from the disorder. Some people may be just a little more obsessive or quirky (i.e., it’s a personality style), but wouldn’t be classified as being ill.

Obsessions refer to recurrent and persistent thoughts that are difficult to shake. Initially, obsessive thoughts present weakly or are largely unformed, creating discomfort or anxiety until the obsession has been dealt with. The relief may be transient, and when obsessive thoughts again emerge, the behaviors that diminish anxiety will again be emitted and reinforced by the reduction of anxiety. As these thoughts become more formed, individuals might become preoccupied with particular notions, such as someone close to them becoming infected by a disease or dying, or that certain objects have important characteristics that are ‘meaningful’. Still other obsessive thought can take the form of conspiracies, or sexual characteristics, and in a severe form the obsessions may be delusional.

**IS IT REALLY ALL THAT ODD?**

At first blush obsessive-compulsive behaviors do seem rather strange. Why would anyone engage in these behaviors? Is there anything even remotely rewarding about them that might promote their frequent repetition? For that matter, does it become stranger still when the behavior involves self-injurious acts such as hair pulling (trichotillois) or the repeated cutting of body parts? Many of us will have had the experience of being bugged by leaving something undone, and when finally we do whatever it is to get rid of what had been gnawing at us, there's a sense of relief. Can you remember as a kid playing a game in which you touched every sign on the way to school (or had to step on every sidewalk crack)? If you missed one you had to go back and 'get it', since not doing so ate away at you. The relief was tangible when it was done, even though you knew it was dopey. Perhaps the person with OCD is taking this to an extreme and it's rewarding to 'scratch that itch'. Alternatively, certain behaviors, particularly those that involve self-injury, cause the release of certain brain chemicals (e.g. dopamine, endorphins) that provide a high, thereby reinforcing the behavior. This would be all the more dramatic if, after the act is done, the initial tension that was accompanied by an elevated heart rate turned to bradycardia that might signal relief.

Self-injurious behaviors aren't all that uncommon. It's frequently seen in animals under some conditions. Dogs, for example, will repeatedly lick at themselves to the extent that they might create open wounds or infection (hotspots). Likewise, hair pulling, self-biting, or feather pulling are observed across many species. Often, these behaviors occur in animals that are kept in penned conditions, including caged zoo animals (they might also exhibit OCD-like behaviors in the form of repeated pacing back and forth). It might be that the isolation and loneliness triggered these behaviors if for no other reason than to create a degree of stimulation that was followed by a relief from boredom.

The behaviors that comprise OCD vary appreciably across individuals, and may include behaviors such as hoarding, aggressive or sexual impulses, repeated checking (e.g., whether the door is locked, the stove is off), hair pulling, or hand washing. Added to this, some individuals will display ritualistic behaviors (locking doors and checking and rechecking in a specific sequence; making sure that they take a certain number of steps between their front door and the sidewalk, and restarting the process when the number is wrong; touching certain objects when entering a room or when leaving). Such behaviors would obviously appear abnormal to others, and social alienation may then develop, aggravating an already bad situation. Moreover, the OCD-affected person will realize that their behaviors are unusual, and this too creates distress and anxiety. Perhaps for this reason, the compulsive component of OCD might not be manifested as overt compulsions, but instead individuals may go through mental compulsive rituals.

### PIGEONS AND BASEBALL PLAYERS

You might recall B.F. Skinner's description of superstitious behaviors in pigeons responding to a particular schedule of reinforcement. Having been adventitiously reinforced shortly after adopting a particular posture or behavior, they continued to adopt these behaviors or postures. Next time you watch a baseball game, see whether some of the batters go through their own rituals (touch one shoulder, then the other, scrape their left foot on the ground, then the right, then the left, and the right once more, followed by three movements of the bat – no wonder the game takes so long), and when interrupted how they go through the ritual again. I'm not suggesting that baseball players are necessarily affected by OCD, but they sure remind me of pigeons.

### BIOLOGICAL FACTORS RELATED TO OCD

The view was offered that OCD is produced by a complicated loop comprising the frontal cortical brain regions involved in executive functioning and decision making (i.e., the anterior cingulate cortex, ventromedial, dorsolateral, and lateral-orbital cortex) that link to those associated with reward processes (the nucleus accumbens, caudate). Neurons in these regions, in turn, activate the thalamus and the basal ganglia, which are connected to several brain regions, including the cortex. This loop has been implicated in routine behaviors and habits, as well as in decision making regarding the selection of which of several behaviors to emit when there are several options (Milad & Rauch, 2012). In recent years there have been reformulations of this view of OCD. Fundamental to this perspective has been that the lateral and medial orbitofrontal cortex (lOFC and mOFC) are responsible for processing information with a negative or a positive valence, respectively. The lOFC is viewed as essential for both responding to punishment and escaping from danger, and might contribute to the repetitive or ritualized behaviors characteristic of OCD. The importance of the mOFC comes from reports that this region is essential for the extinction of fear memories (Milad et al., 2007). Ordinarily, when a fear-producing situation is encountered repeatedly and found to be safe, the fear response may extinguish, an outcome that involves the inhibition of neuronal activity within the ventromedial PFC. It was suggested that OCD may stem from a failure of the mOFC to properly inhibit the ventromedial PFC in response to danger cues, thus resulting in the OCD-related fears being sustained. As a result, although the excessive activation of the ventromedial PFC and the OFC might contribute to OCD, the real culprit might be the mOFC which isn't doing its job of controlling (inhibiting) functioning in these other cortical regions.

As crucial as the lOFC and mOFC are for OCD, the story doesn't end there, as it seems that the anterior cingulate cortex may be involved in OCD. This brain region has been mentioned several times in the context of other disorders (such as depression), and it seems that some of its functions, namely identifying cognitive conflict, error monitoring, and decision making, also play into OCD. Ordinarily, when we are placed in a situation where dual and inconsistent messages are received, or when we must interpret messages where one signal tells us to 'go' and another tells us to 'stop', and especially when interference comes from

external sources, the anterior cingulate cortex appears to be activated as it is necessary for decision making. However, hyper-activation of the anterior cingulate cortex was evident when individuals presenting with OCD were placed in decision-making situations (Page et al., 2009). Thus, it was suggested that this brain region might be having difficulty in making appropriate appraisals and decisions, so that we end up with improper feedback that might lead to repeated behavioral responses.

To some extent this formulation is reminiscent of a proposition advanced by Woody and Szechtman (2011) in which the existence of a ‘security motivation system’ was proposed to explain the appearance of OCD. Essentially, they suggested that we ordinarily have a ‘feeling of knowing’ (they use the term ‘yedasentience’, a combination of Hebrew and Latin) that is essential for us to end a task and move on to other activities. If this signal or its reception is not operating properly, then the OCD symptoms will persist. Have you ever had the worry after leaving home of ‘Did I turn off the iron (or stove)?’ or ‘Did I shut the garage?’. This feeling might haunt you all day (some of us more than others), unless you go back and check. I suspect that the person with OCD might be affected in this way all or much of the time.

#### FINDING INFORMATION IN ODD PLACES

Parkinson’s disease, which occurs owing to degeneration of DA neurons within the substantia nigra (although other factors are also involved), is typically treated with drugs that increase DA functioning. However, these drugs don’t just cause DA to increase in the substantia nigra, but also affect DA in brain regions associated with reward processes. It has been reported that other disorders that fall in the impulsive-compulsive spectrum sometimes emerge following the treatment with DA acting agents. These secondary effects include compulsive shopping, binge eating, hypersexuality, compulsive hobbying, compulsive computer use, and gambling. These characteristics are most notable in patients with an early onset of the disorder, those with a history of use of recreational drugs, and novelty-seeking personality characteristics. These findings are obviously in line with suggestions that DA plays a pivotal role in reward processes, and the behaviors observed could simply be a reflection of the elevated DA in some brain regions making certain behaviors seem to be more rewarding (e.g., gambling). These findings might also suggest a role for DA in compulsive behaviors or those with impulse control disturbances.

#### TREATMENT OF OCD

It is difficult to determine whether there is any single best treatment of OCD as the symptoms can vary appreciably from one individual to the next, and it is possible that the mechanisms involved may also vary with features of the illness (e.g., does repeated checking involve processes akin to those involved in hoarding?). Some success has been achieved with CBT and with ‘exposure and response prevention’ (ERP) in which patients learn, in gradual steps, to tolerate the anxiety that occurs when they do not engage in the compulsive behavior. Yet another approach has been to alter the associations that are normally made in

response to obsessive thoughts. For instance, an individual who is obsessed with not touching anything ‘contaminated by germs’ might be ‘taught’ to appraise external objects less negatively by having them pair the thought of these objects with neutral thoughts or emotions.

High doses of SSRIs have also been used to treat OCD, although it may take a relatively lengthy period for positive effects to appear. It seems that targeting glutamate, a neurotransmitter known to be involved in learning and memory, might also provide positive outcomes (Marazziti et al., 2010). As well here, studies in animals have pointed to the DA mechanism, probably involving the nucleus accumbens, in maintaining repeated checking (Dvorkin et al., 2010). Yet given the breadth of symptoms associated with OCD, the possibility was expressed that each symptom dimension might involve different mechanisms and diverse etiological processes, and that (once again) the most effective treatment strategies will necessarily be tailored for individual patients.

## POSTTRAUMATIC STRESS DISORDER (PTSD)

Posttraumatic stress disorder (PTSD) has received growing levels of attention, particularly as it affects a fairly substantial portion of individuals who encounter traumatic experiences, and because we hear about it more often in relation to soldiers returning from combat missions. Most of us will encounter traumatic events at one time or another, and the incidence of PTSD is as high as 10% in the USA. The *DSM-IV* had described PTSD as occurring in response to an intense stressor that involves actual or threatened death, injury, or learning about an unexpected or violent death, and that the individual’s response must comprise intense fear, helplessness, or horror. In recent years, the criteria regarding fear, helplessness and horror have been disputed, as symptoms of PTSD may emerge even in the absence of these extreme emotional responses. Thus, the *DSM-5* criteria for PTSD were recalibrated to take into consideration the factors that lead to PTSD, including nontraumatic stressors, the time-line for the appearance of PTSD, and expansion of the symptoms that comprise the disorder (see Table 9.4). In addition, within the *DSM-5* PTSD is no longer present in the section dealing with anxiety, but was instead placed in a category of ‘Trauma and stressor-related disorders’. However, it’s been left in this chapter on anxiety because it shares many characteristics with other disorders of this class, although as we’ll see, it is also quite different from other anxiety-related disorders.

PTSD is usually considered in the context of individuals who experienced any of numerous natural disasters (earthquake, hurricane, tsunami), as well as war experiences, car accidents, rape, being held hostage, medical complications, being told about a severe medical condition, bullying and common assault, witnessing traumatic events (e.g., abuse). In addition, PTSD symptoms can be instilled by chronic stressors, such as chronic racial discrimination (Matheson & Anisman, 2012), and symptoms of PTSD even developed when the stressor was a distal one (i.e., when individuals were not directly confronted with the trauma), as occurred among US residents following the 9/11 terrorist attacks (Silver et al., 2002).

A diagnosis of PTSD is made when symptoms persist for six months or more. However, when the *DSM-IV* was first released a syndrome referred to as Acute Stress Disorder (ASD)

**TABLE 9.4** Posttraumatic stress disorder (PTSD) symptomatology

The *DSM-5* diagnostic symptoms associated with PTSD include several changes from the *DSM-IV*. The section below is from [www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=165#](http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=165#).

- A. Exposure to actual or threatened death, serious injury, or sexual violation, or witnessing others experience these traumatic event. Trauma experiences can also comprise learning of trauma experienced by a close friend/relative, or repeated exposure to details (consequences) regarding the traumatic event (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse), but not through exposure that occurs through electronic media, television, movies, or pictures.
- B. Presence of one or more of the following intrusion symptoms:
  1. intrusive distressing memories of the traumatic event(s) of an involuntary nature that occur spontaneously or in response to specific cues
  2. recurrent dreams in which the content or affect is related to the traumatic event(s)
  3. dissociative reactions in which individuals feel as if the traumatic event(s) are recurring (flashbacks): in its extreme form individuals may experience loss of awareness of their current surroundings
  4. reminders of the trauma elicit intense or prolonged psychological distress or physiological reactions
- C. Persistent avoidance of stimuli associated with the trauma. These behaviors comprise:
  1. avoidance of distressing thoughts, or feelings associated with the traumatic event(s)
  2. avoidance of reminders of the events (people, places, conversations, activities, objects) that promote distress
- D. Disturbed cognitions and mood manifested by two or more of the following:
  1. disturbed recall of an important aspect of the event(s) for reasons other than head injury or drug intake
  2. exaggerated, persistent negative perspectives or expectations about oneself, others, or the world
  3. persistent and distorted self- or other-blame regarding the cause or consequences of the traumatic event(s)
  4. a strong, persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame)
  5. anhedonia
  6. feelings of detachment or estrangement from others
  7. persistent failure to experience positive emotions (e.g., psychic numbing)
- E. Marked arousal and reactivity associated with the traumatic event(s) that began or became worse following the traumatic event. Arousal and reactivity are reflected by two or more of the following:
  1. irritability or aggressiveness
  2. reckless or self-destructive behavior
  3. hypervigilance
  4. hyperarousal or an exaggerated startle response
  5. concentration difficulties
  6. sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep)

was introduced, which has been maintained in the *DSM-5*, but has been moved to the ‘Trauma and stressor-related disorders’ category. It is not unusual for symptoms such as intense emotional reactions to appear soon after a catastrophic stressor, but they typically diminish with time. If symptoms are present three days after the trauma, then it may be categorized as ASD, provided that a series of other symptoms are present as well. Although many of the symptoms of ASD and PTSD are very similar, ASD is also accompanied by ‘dissociative’ symptoms. Of five potential dissociative features, a diagnosis of ASD requires the presence of three of the following: (a) a sense of numbing, absence of emotional responses or detachment, (b) reduced awareness of surroundings, or feeling as if in a daze,

(c) derealization, wherein individuals experience altered perception or experience of the external world so that it seems unreal, (d) depersonalization, in which individuals have the feeling of watching themselves act, but lack control over the situation – the world is dreamlike, less real, or lacking in significance, and (e) dissociative amnesia characterized by memory gaps in which individuals are unable to recall information concerning events of a traumatic or stressful nature.

As in the case of PTSD, those with ASD may repeatedly re-experience the event through either recurrent images, thoughts, dreams, illusions, flashbacks, as well as the feeling that they're reliving the traumatic experience, or distress that occurs in response to trauma reminders. They may also display avoidance of stimuli that arouse recollections of the trauma, and symptoms of anxiety and/or arousal are present, characterized by poor sleep, irritability, impaired concentration, hypervigilance, motor restlessness, and hyper-reactivity. At the time that ASD was introduced as an independent disorder, it was thought that the dissociative symptoms might predict whether or not PTSD would subsequently be present. However, it turned out that many individuals with ASD don't continue with PTSD symptoms, and conversely, it is not unusual for those without ASD to later develop PTSD (Bryant et al., 2011).

## VULNERABILITY AND RESILIENCE

Although most of us will encounter a traumatic experience at some time, only a relatively small number will develop PTSD. This raises the question concerning which factors make individuals vulnerable to the effects of traumatic experiences, and which variables contribute to resilience. To a considerable extent, the vulnerability factors outlined earlier concerning other stressor-related pathologies are also pertinent to the development of PTSD. In this regard, factors related to appraisals of the trauma (i.e., perceived level of threat) and post-trauma elements (i.e., the response to the trauma) predicted the emergence of PTSD. In addition, some pretrauma features (psychiatric history, being abused, or experiencing trauma as a child, as well as being separated, divorced, or widowed) and some peritrauma variables (i.e., events that occur soon after the traumatic event) contributed to the emergence of PTSD, as did a constellation of psychosocial factors, including the coping strategies used and perceived social support (King et al., 1998). It also appeared that those people who score highly on a neuroticism scale (i.e., constant worriers who exhibit chronic anxiety and tend to overreact to daily negative experiences that most people take in their stride) were particularly likely to develop PTSD in response to trauma.

An important predictor of PTSD is that of having previously experienced multiple traumas (Suliman et al., 2009). It seems that a traumatic event may prime (sensitize) biological systems so that responses to later traumatic experiences are exaggerated. This view, however, is not universally accepted, as PTSD might be more likely to develop among individuals who encountered a previous trauma or multiple traumatic events *provided* that these experiences resulted in PTSD at that time (Breslau & Peterson, 2010). In effect, the initial trauma might be disclosing which individuals are most likely to develop PTSD, or it might be that the initial trauma increases the vulnerability to later PTSD only if it affected those circuits responsible for the emergence of PTSD. It also appears that mental health status prior to a trauma

experience may be related to whether or not PTSD will emerge. By example, among soldiers returning from Afghanistan, those with prior trauma experiences or modest mental health problems prior to deployment were at elevated risk for PTSD stemming from war experiences. And further to this same point, trauma experiences, including abuse or neglect in childhood, have long-lasting effects on the ability to cope with stressors in adulthood, and might thus favor the development of PTSD. Furthermore, those individuals who experienced childhood trauma, interpersonal violence, or a secondary anxiety or affective disorder were least likely (or took longer) to remit from PTSD (Chapman et al., 2011).

The way in which individuals appraise and cope with stressors may also be related to the development of PTSD features. An avoidant strategy that favors compartmentalization of the stressor actions may be beneficial, given that the memory of an event and the cues that stimulate these memories are particularly effective in aggravating the symptoms. Furthermore, greater use of emotional avoidance and lower levels of emotional expression were accompanied by increased PTSD symptom severity. As a result, while emotional expression is often viewed as a poor coping method, encouraging this strategy might have positive effects in relation to PTSD (Hassija et al., 2011), and as well as this, the extent to which individuals separate emotional responses from the cognitive representation of the event (cognitive-emotional distinctiveness) may be related to the appearance of PTSD symptoms. In addition to these methods of coping influencing PTSD development, the negative effects of trauma events were most pronounced among individuals with low social support, and it was further observed that social support was found to be associated with a reduction in maladaptive cognitive coping methods (i.e., worry, self-punishment) and the use of avoidant coping (e.g., social and non-social avoidance coping) strategies, which might otherwise favor PTSD symptoms (Bennett et al., 2009). It was thus suggested that interventions that target maladaptive coping strategies (worry, self-punishment, and social avoidance), and those that encourage social support and understanding from others, might be effective in diminishing PTSD symptoms.

### THINKING OF PTSD IN THE CONTEXT OF OTHER ILLNESSES

One of the predictors of PTSD is whether individuals had experienced a psychological disorder prior to the most recent traumatic experience. In line with these findings, it was reported that women with a history of a mood disorder were more likely to exhibit PTSD in response to a later trauma than were women without a history of mental health problems. This finding might reflect the possibility that certain people are particularly vulnerable to a range of mental health disturbances. Alternatively, it might be that mental health problems, like an earlier trauma, might result in the sensitization of biological systems, so that these individuals would be more vulnerable to a subsequent stressor-promoted pathology.

Regardless of the source of these outcomes, given that severe illnesses, such as cancer, may lead to PTSD, it might be useful for oncologists to determine an individual's previous psychiatric history before beginning therapy. Of course, the oncologist's primary duty is to treat the cancer, but if it's the case that stressful events influence disease progression, then it is possible that the

treatment might be more successful if precautions were taken to deal with the mental health issues related to the trauma rather than just focusing on the cancer. In fact, in a study of women who had been surgically treated for breast cancer, in which some received psychological intervention to reduce distress, improve their moods, alter health behaviors, and adhere to cancer treatment and care, the probability of recurrence and death within an eleven-year window was appreciably reduced, relative to women who had not received the psychological intervention (Andersen et al., 2008).

## NEUROANATOMICAL UNDERPINNINGS OF PTSD

As stressors give rise to multiple biological changes, any of these might potentially contribute to the evolution and maintenance of PTSD. Indeed, the primary symptoms of PTSD are fairly diverse and it is not only possible, but also very likely, that many of these behaviors involve one or more different neuronal mechanisms. In addition, PTSD is often comorbid with other pathological conditions that might be secondary to immune, HPA, or autonomic disturbances related to PTSD, making it evermore difficult to identify which processes underlie the disorder and which are related to the comorbid conditions.

## PTSD AS A DISTURBANCE OF MEMORY PROCESSES

The finding that hippocampal atrophy was associated with PTSD gave rise to the view that it was the traumatic event that led to this outcome; however, it was subsequently demonstrated that a reduced hippocampal size was present in the co-twin of individuals suffering PTSD following a war experience, even though they had neither been traumatized nor suffered PTSD (Pitman et al., 2006). Thus, having a relatively small hippocampus might increase the vulnerability to PTSD rather than be a consequence of the disorder. This may well be, but reduced hippocampal volume was also associated with more chronic PTSD relative to that evident among individuals who had shown symptom remission, thereby implicating hippocampal volume in sustaining PTSD symptoms (Apfel et al., 2011).

The hippocampus is intimately related to short-term memory processes, and may be fundamental when memory is retrieved from storage. Neurons in this brain region are exceptionally plastic (interconnections are readily influenced by environmental or experiential factors), making it a potential contributor to the adverse effects of trauma. If the hippocampal disturbances are, in fact, related to PTSD, then it would be appropriate to consider whether memory processes are involved in this disorder. After all, having been traumatized by a particular event it would be perfectly understandable to react strongly to stimuli subsequently experienced that were relevant to the trauma. For example, a woman who is assaulted in a dark parking lot might subsequently be afraid of dark parking lots, which certainly might be a highly adaptive response. But what if this response generalizes to all dark places, all parking lots (even in daylight), or flat open spaces, or places where there are

lots of cars, such as shopping center lots? Obviously, this over-generalization might be maladaptive, and may disturb the individual's quality of life. This also raises an odd sort of paradox concerning memory related to traumatic events. When a memory is focused and accurate, strong responses should be evident to the primary aversive stimulus, and moderate generalization should be expected. If, in contrast, the memory of an event is vague, then individuals might not respond just to the primary aversive stimulus, but might also respond to events that were modestly reminiscent of the original stressor. PTSD-affected individuals seem to react very strongly to cues highly reminiscent of the original trauma, but also react to relatively vague cues as if the memory had not been well entrenched. Given the involvement of the hippocampus in memory processes, some sort of disturbance in memory functioning might contribute to these dual responses in those with PTSD.

When an animal or human is exposed to cues associated with a previous trauma, a recollection of that event, together with biological responses, will be elicited. It also appears, however, that memory processes may be activated even when cues are stressful but also entirely distinct from the previously encountered experience (Jezek et al., 2010). Essentially, stressful stimuli might be capable of energizing the memory processes related to a previous event not because they are reminders of that event, but because they engage the same neural circuits that are activated by stressors. From this perspective, PTSD might not be related to disturbed memory as we might ordinarily think of it, but to generalized biological responses to stressors, without necessarily assuming impairments regarding the memory of the initial trauma. Alternatively, PTSD may be a disorder of forgetting in that the normal extinction of fear responses does not occur readily.

## PTSD IN RELATION TO NONASSOCIATIVE PROCESSES

Yet another perspective of PTSD is that the disorder might reflect a failure of our recovery system(s). Ordinarily, most individuals ought to react strongly to traumatic events, but with the passage of time or appropriate coping responses being used, this 'damage' should heal. However, in some individuals, a failure of recovery in the biological systems may result in the PTSD syndrome emerging. As much as the data might point to memory processes being tied to PTSD, it might also be considered that these 'apparent' memory changes could involve other types of processes that were not of an associative nature, but instead involved the brain regions that govern attention or decision making. Beyond the involvement of the hippocampus, the prefrontal cortex might also be a key player in PTSD. In this regard, subtle impairments of response inhibition, and regulation of the attention mechanisms involving this brain region, may act as risk factors for PTSD (Aupperle et al., 2011). In fact, the anterior cingulate cortex, like the hippocampus, is reduced in size among patients with PTSD (Woodward et al., 2006). Based on a twin study it was suggested that this was not a genetically endowed reduction of the anterior cingulate cortex, but was dependent on PTSD being present (Kasai et al., 2008). As described earlier, the PFC, and specifically the anterior cingulate cortex, is exceptionally reactive to stressors and is important in our appraisal of events and decision making. Thus, the suggestion that this region might be involved in a syndrome such as PTSD is intuitively appealing.

Functional imaging studies indicated that among PTSD patients activation of the medial PFC response was diminished upon the presentation of aversive stimuli, such as pictures and the sound of combat, as well as in response to narratives of a negative nature that were unrelated to the trauma experience, for example, scripts containing traumatic imagery or images of fearful faces, as well as a test that elicited an emotional response unrelated to the trauma (e.g., Bremner et al., 2004; Gold et al., 2011). However, following successful treatment of the disorder, the PFC activation to stressful stimuli was found to normalize. In effect, among individuals with PTSD frontal cortical functioning was altered, not just for reminder stimuli, but for all sorts of stressor images, suggesting that aberrant behavioral responses could be expected among these individuals in response to any number of stressor events that might be encountered.

The PFC, amygdala, and hippocampus appear to be involved in the regulation of emotional memories. As such, beyond the PFC and hippocampus, aspects of the amygdala might contribute to PTSD. In fact, vague cues that were related to a traumatic experience influenced amygdala functioning (Liberzon & Sripada, 2008), suggesting that affected individuals were hyper-alert or hyper-responsive to even the mildest stimuli (at a nonconscious level) relevant to the trauma experience. In effect, the axis comprising the PFC, amygdala, and hippocampus, representing appraisals, emotional responses, and memory processes respectively, is critically involved in PTSD, and this circuitry might define re-experiencing, emotional reactivity, and fear (avoidance), which comprise the specific characteristics of the syndrome.

## BIOCHEMICAL DETERMINANTS OF PTSD

Assessing the neurochemical and hormonal mechanisms underlying PTSD is fairly difficult as individuals might not only differ in the symptoms expressed, but also the neural circuitry activated may vary as a function of the specific stressor encountered. Moreover, given the limitations concerning what can be analyzed in human brain tissue, the conclusions that can be drawn regarding the biochemical underpinnings of PTSD are limited. A good deal of the evidence regarding the mechanisms subserving PTSD comes from studies assessing the effectiveness of drug treatments in attenuating the disorder, but even here it is uncertain whether the treatments are masking symptoms or actually getting at the mechanism(s) responsible for the illness. In the ensuing section we'll examine the contribution of several neurochemical and hormonal processes to PTSD. The intent isn't simply to provide a catalogue of these biological processes. However, we simply don't know to what extent each of these factors contributes to the specific symptoms that characterize PTSD, and so with the understanding that different factors might subserve the varied symptoms, we'll cover some of the main players implicated in this disorder.

In assessing the biological processes of PTSD, researchers have often relied on animal models of disorders, but as discussed earlier, it is frequently questionable whether complex human pathologies can be simulated in rodents, and this is true of PTSD. It is fairly simple to assess some behaviors that are characteristic of PTSD, such as hyperarousal (e.g., by evaluating startle responses to sudden noise) or the avoidance of particular stimuli. It is

another matter to evaluate whether rodents are 're-experiencing' the trauma. In some studies attempts were made to strengthen traumatic memories by exposing rodents to cues reminiscent of an earlier trauma (Anisman, 2011). This had interesting experimental and clinical implications, but reminders of an event might be distinctly different from spontaneously 're-experiencing' that event.

A second difficulty comes from the fact that stressors, especially traumatic-like stressors, might not only elicit PTSD, but also produce general anxiety and depression, and the paradigms used to assess the behavioral changes that are thought to reflect PTSD are frequently the very same tests that are used to assess anxiety and depression. Because of this, it's uncertain whether the studies are actually tapping into PTSD, depression, anxiety-related features, or some combination of these syndromes. The predictive validity of the models is also compromised, as the treatments used to attenuate the behavioral disturbances in PTSD (e.g., SSRIs) are likewise effective for other anxiety disturbances and depression. Finally, most people who encounter traumatic events adapt to the situation through behavioral and biochemical processes. Typically, adaptation (the disappearance of symptoms) occurs within a matter of weeks; however, in about 15% of individuals adaptation does not occur, and PTSD symptoms are still present long after the trauma. In animal studies it is essential to understand what governs these individual differences, and why the pathology persists over time, and perhaps even increases in intensity in some instances.

## NOREPINEPHRINE AND SEROTONIN

Despite the limitations, there have been several promising animal models of PTSD. One of these capitalizes on animals' natural responses to predators (e.g., rats' responses to a cat or even to the scent of cat urine) (Cohen et al., 2011). A second involves exposure to a single prolonged stressor comprising several different insults, followed by re-exposure to reminder stimuli every four days over the ensuing three weeks. When later tested in behavioral paradigms these mice showed an exaggerated startle response, mimicking the reactivity associated with PTSD (Olson et al., 2011). Of particular interest here was that these mice were also more resistant to extinction of the fear response, engaged in less social interaction, and were unusually aggressive toward an intruder. Moreover, these animals also exhibited increased neuronal activation, especially within brain regions such as the locus coeruleus, central amygdala, and the bed nucleus of the stria terminalis, all of which are regions in which stressors ordinarily increase the activity of NE neurons. Significantly, the effects of the traumatic stressor could be modified by a drug treatment that disrupted NE functioning, thus implicating NE in PTSD-like characteristics in mice.

Studies in humans likewise implicated NE functioning in PTSD. For instance, among individuals with PTSD, NE accumulation in urine was elevated, and increased NE receptor sensitivity was detected in the brain. Added to this, in a prospective analysis of high-risk individuals (e.g., police officers), the increased utilization of peripheral NE was predictive of those who later developed PTSD symptoms following a critical incident (Apfel et al., 2011b). Finally, treatments that attenuated NE functioning had an ameliorative effect on this disorder in some individuals.

In addition to NE, PTSD was also accompanied by variations of 5-HT functioning. In animal models the expression of the 5-HT<sub>1A</sub> receptor at the dorsal raphe nucleus was increased, which would have the effect of diminishing 5-HT release at the PFC and hippocampus (Luo et al., 2011). Further, as alluded to earlier, among those carrying the short allele of the 5-HTT gene, PTSD was more common if individuals had also encountered both a childhood and adult trauma (Xie et al., 2009). Essentially, these findings suggest that several risk factors might need to come together for PTSD to emerge, and for some individuals 5-HT functioning might be a critical element in this mix. Obviously, however, PTSD and depression have unique behavioral characteristics and it will be necessary to identify their unique neurochemical signatures.

## CRH AND CORTICOIDS

CRH might play a role in PTSD just as it does in other anxiety-related illnesses. For instance, when a CRH<sub>1</sub> receptor antagonist was administered to rodents either before a traumatic experience comprising exposure to a predator or 30 minutes later, during the period when memory was being consolidated, the subsequent anxiety induced by the stressor (measured days later) was markedly diminished. As such, CRH<sub>1</sub> receptors might be involved in either the initiation or consolidation of traumatic memories that feed into PTSD. There is also good reason to believe that corticosterone (cortisol) plays an essential role in the development and/or manifestation of PTSD. As an example, following the retrieval of a memory (e.g., having animals respond to stressor cues to encourage a previous memory to come forward), administration of a glucocorticoid receptor antagonist diminished the memory of this test. Thus, when the memory of an aversive event was retrieved, it was susceptible to disruption by a glucocorticoid manipulation (Taubenfeld et al., 2009). It should be underscored here that for the drug to have the effect that it did, it was essential that it be administered once the memory was retrieved (we'll come back to this shortly, and the significance of this will become more apparent).

In addition to such findings, interesting corticosterone (cortisol) changes have been associated with PTSD that may be important for analyses of the processes leading to PTSD. In Chapters 3 and 4 we learned that an elevated release of cortisol from the adrenal gland is a prototypical response to stressful situations. Thus, it might be expected that PTSD would be accompanied by elevated levels of this hormone, possibly acting in an adaptive capacity. However, this might not occur in response to chronic stressors or among individuals who experienced trauma that led to PTSD. On the contrary, with the appearance of pronounced PTSD symptoms cortisol levels are comparable to, or even fall below, those of individuals who show no symptoms (Yehuda, 2002). Furthermore, PTSD is associated with a change in the diurnal pattern of cortisol secretion, so that the normal daily fluctuations become flattened (i.e., the morning cortisol levels are lower, and evening cortisol levels are elevated) (Michaud et al., 2008). This might represent a fundamental adaptive response to strong or chronic stressors, as excessive or prolonged cortisol release might promote the loss of hippocampal corticoid receptors, so that the message necessary to regulate cortisol secretion might become disturbed (hippocampal function is necessary to inform the hypothalamus to

cease the release of CRH and ultimately cortisol secretion), leading to yet more adverse consequences (McEwen & Gianaros, 2011).

One might think that once HPA functioning is down-regulated, individuals might be at risk for pathology as they might not have the biological resources necessary to contend with further stressors. In a series of interesting studies Heim and Nemeroff provided important information regarding the processes related to trauma effects that have clear clinical implications (Heim et al., 2010). Specifically, when depressed women who had previously been traumatized (abused) were challenged with CRH, which ordinarily causes the release of ACTH from the anterior pituitary gland, the ACTH response was muted. These data are clearly consistent with the view that the HPA system was down-regulated. However, when these women were placed in a Trier Social Stress Test (public speaking) that was usually accompanied by feelings of shame and elevated cortisol, they exhibited a particularly exaggerated HPA response, relative to controls (Heim & Nemeroff, 2002). It was similarly observed that among women who had experienced dating abuse, high levels of PTSD were accompanied by lower cortisol levels relative to abused women who showed only moderate PTSD symptoms. However, when these women were provided with reminders of their abusive experiences, an especially marked increase of cortisol levels was instigated in those women with the highest levels of PTSD (Matheson & Anisman, 2012).

So what might be accounting for these unusual ACTH or cortisol changes? As already indicated, HPA activity might be down-regulated among traumatized individuals as an excessive cortisol release might leave those individuals at risk of adverse outcomes. However, this down-regulation might itself be maladaptive as the cortisol changes might be necessary to deal with certain stressors. Therefore, it might be advantageous for HPA functioning to be generally diminished, but when certain brain regions are activated (e.g., the prefrontal cortex, amygdala) in response to *relevant* stressor cues, this activation might serve to over-ride the otherwise down-regulated HPA system.

## GABA AND NPY

As GABA has been implicated in anxiety, it's not at all surprising that it might also contribute to PTSD. GABA, it will be recalled, is an inhibitory transmitter that puts the brakes on some neuronal processes, and it is possible that when GABA levels in certain brain regions are low, the lack of inhibition allows for the persistence of the neuronal functioning that is part of a fear or PTSD-like state (i.e., the fear response does not extinguish). Support for GABA involvement in PTSD has come from findings such as those indicating that among combat veterans, PTSD was accompanied by a reduced number (or binding) of benzodiazepine receptors, which are tied to GABA functioning (Geuze et al., 2008). It was further demonstrated that GABA levels in blood were diminished in those with PTSD, and it was suggested that its levels might be used as a biomarker to predict illness vulnerability (Vaiva et al., 2004). Unlike the effects of NE and glucocorticoid manipulations, however, administering a benzodiazepine after the trauma event did not deter the emergence of the pathology. In fact, in an animal model, treatment with a benzodiazepine shortly after trauma exacerbated

the adverse effects of a later stressor (Matar et al., 2009). Hence, GABA might serve in some capacity in maintaining PTSD, but it is less likely that altered GABA functioning was directly responsible for the development of PTSD. As already indicated, it is possible that it plays some sort of role in sustaining PTSD that is already present. In this regard, a synthetic analogue of GABA, pregabalin, which is marketed as Lyrica, was found to have positive effects in animal models (e.g., Zohar et al., 2008) as well as in accident-related PTSD in humans (Pae & Patkar, 2009). This compound, which is more commonly used in the treatment of fibromyalgia and some seizure conditions, seems to have its effects by altering GABA uptake, although there are a variety of other as yet unidentified processes that might contribute to its effects.

Neuropeptide Y (NPY) might also contribute to stressor-provoked behavioral disturbances. This peptide is associated with stress responses, and studies in animals also revealed that following a predator-odor, the anxiety and hyper-reactivity elicited were accompanied by a reduction in the expression of NPY in the hippocampus and amygdala. Of particular significance was the finding that those animals that showed highly disrupted behavior were also those that exhibited symptom amelioration following the administration of NPY directly into the brain (Cohen et al., 2012). Likewise, when NPY was administered intranasally to rats prior to a prolonged stressor, the subsequent development of PTSD-like symptoms was diminished (Serova et al., 2013). Predictably, nasal spray containing NPY is currently being assessed as a method to ameliorate PTSD in humans.

Assuming that the stressor-provoked behavioral disturbances are related to PTSD, these findings are in line with the perspective that NPY plays a mediating role for PTSD, and hence NPY might serve as a therapeutic target for this disorder. A gene polymorphism on the promoter gene for NPY has been associated with exaggerated HPA responses following early adversity (Witt et al., 2011), but it is likely still too early to determine whether this polymorphism is related to PTSD.

Summarizing briefly, there is ample reason to believe that both NE and HPA functioning are associated with PTSD. However, there are other processes that need to be evaluated more thoroughly before we can assume that these systems are not tied to this disorder. Good candidates to start with are various 5-HT receptors and NPY (Krystal & Neumeister, 2009), and possibly GABA/glutamate functioning. In their very interesting review, Sah and Geraciotti (2013) made an impressive case concerning the involvement of NPY in PTSD, particularly as they tied NPY to specific features that comprise this syndrome. Like GABA, it is thought that NPY acts as a brake to prevent or diminish the effects of stressors in the promotion of CRH and NE release within the amygdala, and in this way is the controller for the development of stress-related pathology, particularly fear-related symptoms, such as avoidance and hyper-reactivity.

It should also be considered that stressful events, through their actions on glucocorticoids, might promote a cascade of intraneuronal changes leading to epigenetic modifications of gene expression of the processes that serve as an access route to the hippocampus. As these epigenetic changes can persist throughout an individual's life, they may be rendered vulnerable to pathology in the future.

### LEARNING FROM THE HEART

Type 2 ryanodine receptors (RyR2) comprise channels (much like those we saw when discussing the GABA receptor) that regulate calcium levels in neurons. Research conducted by Marks and his associates had indicated that stressors could result in a leakage of calcium in the heart and other muscles, culminating in heart failure and arrhythmias. It likewise seems that when mice are chronically stressed, the RyR2 receptors within the hippocampus destabilize and become leaky, just as they had in the heart. Interestingly, these mice exhibit marked behavioral disturbances that were indicative of memory and learning problems like those associated with PTSD. Significantly, in mice that had been pretreated with a drug to prevent calcium leakage, the stressor-induced behavioral disturbances were not evident. Likewise, in mice that had been genetically engineered so that leaking would not occur, behavioral impairments were prevented (Liu et al., 2012). These findings raise the possibility of a new therapeutic target for PTSD.

A skeptic would suggest that every time we think we've got a grip on things, another potential process for PTSD is offered. Maybe so, but this tells us that PTSD is a complex disorder, and the symptoms of the illness might involve many interlocking mechanisms. What struck me about this study is that it borrowed from previously investigated processes associated with heart problems and applied these to another stress-related psychological disturbance.

### SENSITIZED RESPONSES AND EPIGENETIC FACTORS IN RELATION TO PTSD

There are several puzzling features regarding the temporal dynamics of PTSD. Why would the emergence of PTSD become more pronounced with the passage of time following a traumatic experience? Likewise, why would an individual who seemed to have dealt well with a traumatic event develop PTSD at some later time? These issues can be addressed from a psychodynamic perspective or one that involves brain biological processes. From the psychodynamic side it can be argued that the distress associated with trauma might, in some individuals, result in persistent rumination and replaying of events that cumulatively have disastrous consequences, much like chronic stressors can have such effects. This view is in line with the position that stressors may result in permanent changes in the characteristics of neurons so they are more readily triggered by appropriate stimuli, and especially by reminders of the adverse event. In effect, neurons might become sensitized, so that with repeated trauma or even reminders of the trauma, a progressively greater propensity toward pathology might develop. In discussing animal models of PTSD, it was pointed out that a single strong stressor followed by intermittent reminder cues resulted in anxiety-related behavioral changes, and that reminder cues were necessary for this long-lasting outcome to occur. These reminder cues might have their effects by strengthening the neuronal network associated with the emotional memories regarding the trauma, or alternatively, they might prevent the time-related dissipation of emotional trauma memories that might otherwise occur.

**DANGER: BRAIN AT WORK**

Individuals often make the mistake of assuming that once a traumatic or exceptionally distressing event is over, so are the distress and the accompanying biological changes, and consequently they should start to recover. We even have expressions that speak to this, such as ‘Time heals all wounds’. Time might allow for some wounds to heal in some individuals, or it might remove them from the surface. For others, time moves ever so slowly, and the trauma memories linger and so do their psychological and physical consequences. Parents who have lost a child, individuals who experienced the horrors of warfare, or survivors of genocidal efforts don’t simply forget. Some might never speak about their experiences (a conspiracy of silence), whereas others can’t stop speaking about it. Although the majority of individuals go on with life, their traumatic memories are often just below the surface, and their effects can reemerge over time.

It’s odd that so many people gain some sort of pleasure in deriding Sigmund Freud, despite the enormous contributions he made to brain sciences, including his thoughts on defense mechanisms and other processes that are still considered to be useful. He had postulated, among many other things, that early experiences might mark individuals for life, although he didn’t understand how this came about from a biological perspective. After all, he didn’t have the luxury of knowing about the workings of neurochemical systems. In an interesting paper, McFarlane (2010) reminded me of a notion attributed to Freud, namely that traumatic memory represents a causative ‘agent still at work’. Essentially, traumatic memories can be exceedingly aversive, and replaying incidents and ruminating about these events might encourage the development of PTSD.

What makes these reports particularly interesting is that they focus on the evolution of PTSD symptoms that might occur with the passage of time and upon reexposure to relevant contextual stimuli. As discussed earlier, exposure to a strong, uncontrollable stressor may result in the sensitization of norepinephrine neuronal activity so that responses to later similar or dissimilar stressors are exaggerated and might serve to promote behavioral disturbances (Anisman et al., 2003). These sensitization effects are not limited to NE, having been observed with respect to 5-HT, GABA, and BDNF activity within regions such as the prefrontal cortex, and sensitization was reported with respect to neuroendocrine and cardiac hormone responses, as well as growth factors such as BDNF. It has been suggested that sensitized effects such as these are responsible for the recurrence of depressive illness and could contribute to PTSD, especially as the sensitized responses become progressively greater with multiple traumatic episodes (Anisman et al., 2008).

In addition to sensitized responses of this sort, stressful events may engender epigenetic changes so that the functioning of certain genes is turned off. Traumatic experiences, especially if they occur early in life, might engender epigenetic changes that will influence responses to stressors later in life (Szyf, 2009), and might thus increase vulnerability to PTSD. Although this is certainly a possibility, there are currently limited data showing that epigenetic factors are tied to PTSD in humans, but patterns of hypermethylation were seen

in US service members that had previously been deployed to Afghanistan. Those individuals who exhibited PTSD symptoms could be distinguished from controls with respect to their genetic and epigenetic profiles. It was of particular significance that individuals with PTSD could also be distinguished from one another on the basis of epigenetic differences, which seemed to depend upon whether or not they had also encountered adverse early life experiences. In effect, it is possible that events in childhood may promote epigenetic changes that result in vulnerability to PTSD and to the development of particular symptoms (Mehta et al., 2013). There have also been reports on rodents suggesting this possibility. Of particular relevance was the finding that BDNF gene methylation within the hippocampus, but not the prefrontal cortex or amygdala, was also affected by the adult stressor treatment, implicating an epigenetic process related to memory processes, but not fear/anxiety, in the provocation of a PTSD-like state (Roth et al., 2011).

## TREATMENT OF PTSD

There has been an assortment of treatments used to treat PTSD, including family or interpersonal therapy, trauma management therapy, mindfulness training, imagery training (rehearsal) and virtual reality treatments, acceptance and commitment therapy, and various pharmacological approaches. We'll limit our discussions here to some of the most prominent treatments (see also Chapter 12), especially those that point to potential processes underlying PTSD. A detailed review of treatment strategies is available in Cukor et al. (2009).

Several types of psychotherapy and behavioral therapy have been used in the treatment of PTSD. One of the more useful has been individualized CBT (Bisson et al., 2007). Indeed, CBT was effective in treating PTSD (together with depression and complicated grief) that had been elicited by a terrorist attack even when ongoing threats of terrorism persisted (Bryant et al., 2011). In contrast to individual CBT, stress management/relaxation and group CBT were less successful, and still other therapies (e.g., supportive therapy/nondirective counseling, psychodynamic therapies, and hypnotherapy) were generally reported to be entirely ineffective. Although CBT has been the treatment of choice for PTSD, it may be especially pertinent that CBT was least effective in those individuals who carried the short allele for 5-HTT (Bryant et al., 2010), and so it might be useful to screen an individual's genotype, and then on this basis determine the most suitable form of treatment.

A form of behavioral therapy, namely that of prolonged exposure (PE), has been widely used in the treatment of PTSD. This approach focuses on efforts to extinguish emotional and cognitive responses to danger cues that had not been properly extinguished previously, so that individuals continued to exhibit excessive responses to cues that might signal danger. In the course of treatment, the danger cues are reintroduced (using imagery or actual exposure to cues), thereby resulting in habituation and extinction to these stimuli. Significantly, during the therapy sessions individuals also repeatedly retell their trauma experiences and engage emotionally with these. Eventually, the memories and cues that had elicited these powerful emotional and physiological responses might no longer have these strong effects.

A particular form of therapy, eye movement desensitization and reprocessing (EMDR), is at first blush a bit flaky and, predictably, has not been easily accepted as a method of treatment.

Yet there is some evidence supporting its effectiveness (Seidler & Wagner, 2006). Over the course of several sessions, patients are asked to focus on a vivid image of the traumatic event, during which the therapist has the patient conduct various eye movements (e.g., following a finger that moves across their visual field), as well as stimulating other senses. Essentially, it is thought that the memory of the trauma (which has been activated during the session) will be associated with other, less threatening stimuli, so that the traumatic memory and the emotions ordinarily elicited by these memories will be dissociated from one another. Sounds strange, but if it works, then why not use it? Besides, as we'll see shortly, there is actually a scientifically-based reason for why this treatment might work.

Given the profound neuronal changes that are elicited by stressors, and especially traumatic events, it would be expected that pharmacotherapy would be a main line for treatment to ameliorate the symptoms of PTSD. In fact, SSRIs have been widely used to treat this disorder. Indeed, the main pharmacological methods of treatment of PTSD have been certain SSRIs or SNRIs (e.g., Davis et al., 2006). Unlike depression, however, where a combination of CBT and an SSRI provoked a better outcome than either treatment alone, this did not seem to be the case regarding PTSD (Hetrick et al., 2010), although it is uncertain whether the combination therapy would have long-term benefits, particularly with respect to the impact of subsequent traumatic encounters.

As PTSD is accompanied by variations of HPA functioning, there has been an interest in determining whether the treatments that affect HPA activity might be beneficial in attenuating the disorder. It was particularly noteworthy that although the manipulation of cortisol didn't have much of an effect on individuals who presented with PTSD symptoms, a high dose cortisol treatment administered within six hours of the trauma could prevent the emergence of PTSD. Regardless of the mechanism by which glucocorticoids introduced their beneficial effects, these data point to the possibility that a 'window of opportunity' exists following a trauma experience, during which the protracted adverse effects can be diminished (Zohar et al., 2011).

Based on the findings that stressful experiences have significant autonomic effects and also influence brain NE activity, there has been considerable attention devoted to the possibility that  $\alpha$ - and  $\beta$ -adrenergic antagonists might be useful in treating PTSD. In this regard, drugs that diminish NE release, such as  $\alpha_2$  agonists (clonidine), or block  $\alpha_1$  and  $\beta$  receptors (such as prazosin and propranolol, respectively), attenuate symptoms of PTSD (Krystal & Neumeister, 2009). For instance, the  $\alpha_1$  adrenergic antagonist prazosin reduced some symptoms associated with PTSD, such as trauma-related nightmares and insomnia. This contrasts with propranolol, which is said to be efficacious in alleviating the emotional content associated with traumatic memories. As a result, it was suggested that the combined use of prazosin and propranolol might be particularly effective in treating PTSD (Shad et al., 2011).

As with behavioral changes, the augmented physiological responses associated with PTSD were diminished if the  $\beta$ -adrenergic antagonist propranolol was administered soon after the trauma (Pitman et al., 2002). It had been suggested that when memories were already consolidated and were in long-term storage, they were fairly resistant to being altered. However, when memories were fresh (i.e., not yet thoroughly consolidated), they

might be less resistant to disruption, and hence treatments that modified NE activity during the period soon after a trauma would be effective in altering the course of PTSD (McIntyre et al., 2011). It was likewise suggested that when memories were recalled, they might also be more vulnerable to being changed, so that the emotional responses associated with a memory and the recall of the events might actually be dissociated from one another and then reconsolidated in this new form (Johansen et al., 2011; Nader et al., 2000). In line with this, if a fear memory in rodents was reactivated by reminder cues, disrupting NE activity within the lateral amygdala, the animals' fear recall was subsequently impaired. Similarly, PTSD symptoms were attenuated among individuals in whom PTSD had already developed and were treated with propranolol shortly after these individuals recalled (retrieved) these memories. However, there have also been reports indicating that propranolol was ineffective in limiting the development of PTSD in either animal models or humans (e.g., Cohen et al., 2012). Thus, firm conclusions will have to await data that might be relevant to whether there are certain individuals or conditions that are more or less amenable to this treatment approach, or whether  $\beta$ -blockers would be effective when combined with other therapeutic treatments. Regardless of the most efficacious drug treatment in disrupting reconsolidation and hence limiting PTSD, it should be considered that the eye movement desensitization and reprocessing (EMDR) described earlier might have its beneficial effects by affecting memory during reconsolidation. Perhaps eye movements that cause brain activity changes while recalling events have the effect of confusing or dissociating memories of events from the emotional responses associated with these events.

Another promising strategy to treat PTSD has involved the manipulation of glutamate activity, which is fundamental to learning and memory processes. Studies in animals indicated that D-cycloserine (Seromycin), which acts as a partial N-methyl-D-aspartate (NMDA) glutamate receptor agonist, facilitates fear extinction (Ledgerwood et al., 2005). It turned out that D-cycloserine has promising effects in the treatment of PTSD, particularly when used in combination with CBT or exposure (extinction) therapy. Once again, however, D-cycloserine isn't effective in all patients, and, it is important to determine whether there are predictors that can be informative as to the optimal treatment strategy for any given individual.

### **A BROAD CAVEAT CONCERNING TEMPORAL CHANGES IN PTSD**

One final point needs to be considered, which is applicable not just to PTSD, but also to anxiety disorders and depression, as well as drug addictions. The evolution of PTSD seems to involve dynamic neurochemical systems, and it is possible that those neurochemical systems activated soon after trauma might not be identical to those that are present during later phases and during chronic PTSD. Therefore, it is possible that the effectiveness of treatment strategies might similarly vary over the different phases of the disorder. Particular treatments, such as cortisol or NE antagonists, might be effective when administered during a window of opportunity soon after the traumatic experience. Other treatments or treatment combinations (e.g., cognitive behavioral therapy in combination with an SSRI or D-cycloserine), in

contrast, might be most effective in ameliorating the symptoms once PTSD is established. Still other treatments might be especially useful in limiting memory reconsolidation that is otherwise strengthened by reminder cues. Finally, if sensitization of neurochemical changes is fundamental in the development and strengthening of PTSD symptoms, then it may be propitious to establish strategies that target the sensitized mechanisms. Essentially, the view being proposed here is in line with the suggestion that multi-targeted approaches may ultimately be needed to limit the emergence of PTSD or treat the disorder once it is established. More than this, however, is that the treatment or treatment combinations necessary at one phase might not be the most useful at a second phase in the disorder's development.

## CONCLUSION

The various subtypes of anxiety and PTSD share several common features, although in some respects they are very different from one another (contrast, for instance, the characteristics of OCD, GAD, and PTSD). Likewise, the presumed biological processes for these disorders may be biochemically heterogeneous, and although they share some biological features there are likely several differences as well. It is similarly the case that the most efficacious treatments vary across conditions, although it should be said that in some instances the headway in developing good treatment strategies has been limited. Given the biological and behavioral complexity of anxiety disorders, as well as the frequent comorbid conditions that occur, effective treatment may have to await a broad-scale endophenotypic approach such as that advocated for other psychological conditions.

Although it is broadly acknowledged that anxiety disorders affect a large portion of individuals, other than PTSD, these disorders don't seem to be given the attention (or financial support for research) that's needed. Having champions for various causes has been extremely helpful for the support of individuals with a particular pathology. Heart disease, juvenile diabetes, immune-related disorders, cancer of one sort or another, Lou Gehrig's disease, Parkinson's disease, Alzheimer's, and others, have all received public and private support. To a great extent, GAD, OCD, and phobias are still waiting their turn. That said, anxiety-related disorders represent a tremendous burden on individuals and their families as well as the health system. As with many of the illnesses we've discussed, anxiety is highly comorbid with other conditions, and thus its toll goes well beyond that attributed to the primary anxiety condition.

## SUMMARY

- Several anxiety disorders have been identified that are not only distinguishable based on their overt symptoms, but also involve different etiological processes and life-time trajectories.
- The various anxiety disorders likely involve both common and different brain processes and neural circuits.

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- Diverse underlying mechanisms are likely responsible for the various anxiety disorders. Particular attention in this regard has focused on 5-HT, NE, CRH, and GABA, but depending on the specific condition being considered, the involvement of these factors may vary over the course of the illness.
- Because the symptoms of depression, PTSD, and other anxiety disorders are shared, it has been a challenge to create animal models that distinguish between these illnesses, making it that much more difficult to establish treatment strategies. However, it has become increasingly apparent that individualized treatment strategies will eventually be needed for the treatment of anxiety, just as these have been called for in the case of depressive disorders.