In Chapter 2 we established the neuroanatomical basis for and functional interactions of key nodes comprising the corticolimbic circuit. In Chapter 3 we saw how the orderly processing of information through this circuit helps us recognize and generate adaptive reactions to the challenges we face in our environments. In this chapter, we consider how disorder within the corticolimbic circuit manifests as abnormal or maladaptive reactions to environmental challenge. Broadly, corticolimbic circuit dysfunction is most closely linked with symptoms common to mood and anxiety disorders (e.g., major depressive disorder, generalized anxiety disorder) as well as disorders of social behavior (e.g., autism spectrum disorders, antisocial personality disorder).

Consistent with the perspective we adopted in the preceding chapters, the amygdala will serve as the entry point for our study of how dysfunction within the corticolimbic circuit emerges as disordered behavior or psychopathology. In part, this amygdala-centric approach reflects the predominant focus on this structure in fMRI studies of mood and anxiety disorders as well as disorders of social behavior. This perspective, however, is not simply one of convenience. Rather, it strongly reflects the critical importance of the amygdala as the hub of the corticolimbic circuit—a hub that functions to detect stimuli in our environment and trigger adaptive reactions by channeling information through the appropriate nodes of the circuit.

As we will discover throughout this chapter, psychopathology associated with disorder of the corticolimbic circuit is quintessentially one of abnormal or maladaptive reactions to challenges, especially threat, in our environment. While the amygdala is the hub of the corticolimbic circuit through which our reactions to the environment are triggered, as well as the focus of understanding related disorders, it is only one component of the circuit. In many cases, the disorder observed in the amygdala may, in fact, reflect dysfunction in other circuit nodes, most notably the ventromedial prefrontal cortex (vmPFC) and dorsomedial prefrontal cortex (dmPFC), and the failure of these nodes to effectively integrate and regulate the bottom-up drive of the amygdala. When possible and appropriate, we will consider dysfunction in other nodes of the corticolimbic circuit as they contribute to specific forms of psychopathology.

Although at this point in time we cannot abandon the existing diagnostic nosology, and even though almost all fMRI studies are conducted in groups of individuals with DSM-defined categorical disorders (i.e., disorders defined...
by the *Diagnostic and Statistical Manual of Mental Disorders*), we will attempt to underscore the emergence of highly conserved and overlapping symptoms related to the changes occurring in the underlying corticolimbic circuit. In other words, we will begin by considering how relative increases or decreases in amygdala activity manifest as specific symptoms of psychopathology; we will then discuss categorical disorders sharing this alteration in amygdala activity and the related changes in their unique and shared symptoms.

**Amygdala Hyperactivity**

What happens when the activity of the amygdala is increased or exaggerated? As would be predicted based on the critical importance of the circuit in generating reactions to challenges we encounter in our environment, when there is amygdala hyperactivity, we become hypersensitive to these challenges. We may even perceive otherwise harmless or nonthreatening stimuli as representing threat or danger, leading to inappropriate fear and stress responses.

Such exaggerated recognition and reaction to threat and stress—real or imagined—is a hallmark symptom that unifies mood and anxiety disorders. This core symptom likely explains the substantial overlap that exists between different categorical mood and anxiety disorders, which often co-occur within individuals. This phenomenon is commonly referred to as “comorbidity.” Further, this unifying symptom is evident in the grouping of mood and anxiety disorders together under the broad label of internalizing disorders. The label *internalizing* references the general tendency of those suffering from these disorders to experience disabling levels of internal or inwardly directed distress (e.g., fear, anxiety, sadness, guilt, despair, helplessness) when confronted by threat or stressful situations. In contrast, those suffering from externalizing disorders express their distress outwardly in the form of disruptive behaviors such as crime, violence, and drug abuse. We will review some externalizing disorders, including antisocial personality disorder, later in this chapter, although most of these will be reviewed in Unit 2, on the corticostriatal circuit.

Consistent with the exaggerated recognition of and reaction to threat and stress, which manifest as internal states of distress, amygdala hyperactivity has been repeatedly observed in fMRI studies of mood and anxiety disorders. This is wholly expected, given the strong potentiating effects of amygdala activity on our physiological arousal (e.g., increased heart rate, respiration, and HPA axis activity) and our subjective awareness of these effects (e.g., through increased responsiveness of the insula). Typically, these potentiating effects are perfectly normal and, in fact, critical for adaptive responses that help us overcome the challenges we face. As we will review below, the emerging picture in mood and anxiety disorders entails not only amygdala hyperactivity but also dysfunctional activity of the medial prefrontal cortex. It is likely that a failure of the mPFC to integrate and, ultimately, regulate the amygdala further exacerbates its hyperactivity, resulting in the internalizing distress characteristic of mood and anxiety disorders. In many ways, the amygdala appears to be *shouting* in these disorders, and the PFC appears to be *not listening* to the amygdala’s call for attention.

Despite the core symptom of internal distress in response to perceived threat and stress, as well as amygdala hyperactivity, shared across mood

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**internalizing disorders** Characterized by inwardly directed distress (e.g., fear, guilt, anxiety) when confronted by threat or stressful situations.

**externalizing disorders** Characterized by outwardly directed distress in the form of disruptive or destructive behaviors (e.g., violence or substance abuse).
and anxiety disorders, the existing research is most amenable to a review of findings within specific diagnostic categories. The following sections will consider select evidence implicating corticolimbic circuit dysfunction, with a focus on amygdala hyperactivity, within the most prevalent disorders of mood, and anxiety. However, it is important to consider the shared symptoms and circuit-level features across disorders as summarized above. We will also consider evidence for amygdala hyperactivity in disorders of social behavior such as autism spectrum disorders and will highlight similarities at the level of both circuit dysfunction and symptomatology across all these disorders.

Mood Disorders

Mood disorders are characterized by a sustained disturbance in predominant internal emotional experience. As emphasized above, mood disorders involve an exaggerated reaction or hypersensitivity to threat and stress. Mood disorders are the most prevalent form of psychopathology identified in the DSM. Here we will consider the evidence for corticolimbic circuit dysfunction in the two most common mood disorders: major depressive disorder and bipolar disorders.

Major depressive disorder

Major depressive disorder (MDD), commonly referred to simply as depression, is characterized by experiencing at least one major depressive episode, or MDE. Typically, individuals experience multiple episodes leading to the diagnosis of recurrent MDD. Critically, individuals with MDD cannot have experienced any periods of manic or hypomanic states, which we will describe later, in the discussion of bipolar disorders.

An MDE must include depressed mood, or markedly diminished interest or pleasure in all (or almost all) activities most of the day, nearly every day, for at least two weeks, as indicated by either subjective report or observation made by others. An MDE must also include four or more additional symptoms, including disturbances in sleep, appetite, or physical activity; feelings of guilt and worthlessness; difficulty concentrating; and suicidal ideation (i.e., preoccupation with the idea of suicide).

More fMRI studies of amygdala activity and corticolimbic circuit function have been conducted in MDD than in any other mood or anxiety disorder. Wayne Drevets and colleagues, then at Washington University in St. Louis, conducted the first study finding abnormal amygdala function in MDD in 1992. Unlike the majority of studies now being conducted, these investigators used positron emission tomography (PET) to measure direct changes in cerebral blood flow rather than fMRI, since the latter was not commonly available at that time.

In their seminal study, Drevets and colleagues found that amygdala activity was elevated in individuals with MDD, in comparison to healthy participants, even when they were resting comfortably during a PET scan and not viewing any triggers (e.g., emotional facial expressions). Interestingly, another group of individuals who had suffered from MDD in the past but were currently in remission (i.e., asymptomatic) also exhibited elevated amygdala activity in comparison to the healthy group. This pattern suggests that amygdala hyperactivity is likely a trait marker for depression, and that

mood disorders  Characterized by sustained disturbance in internal emotional experiences and patterns of thinking, whether negative (depression) or positive (mania).

major depressive disorder (MDD)  Commonly referred to simply as depression; characterized by typically recurring major depressive episodes, with no occurrence of manic or hypomanic episodes.

major depressive episode (MDE)  Persistent depressed mood or anhedonia, typically experienced with disturbances in appetite, sleep, or activity as well as feelings of guilt, difficulty concentrating, or suicidal ideation.

depressed mood  Feeling sad, tearful, empty, or irritable; easily upset and overwhelmed by otherwise typical experiences.
it exists regardless of the presence or absence of symptoms (Figure 4.1A). In other words, amygdala hyperactivity appears to represent a risk factor for depression. The magnitude of amygdala hyperactivity in the patients with current MDD, moreover, predicted the severity of their symptoms (Figure 4.1B). Thus, even within a group of patients all meeting DSM diagnostic criteria for MDD, differences in amygdala hyperactivity predict the depth of depression.

Interestingly, while the increased amygdala activity observed by Drevets and colleagues was not in response to any specific stimulus (e.g., emotional facial expressions), most subsequent fMRI studies have found increased amygdala activity in response to a broad range of negative emotional stimuli, including prototypical facial expressions conveying threat (i.e., expressions of fear, anger, or surprise) or neutral expressions as well as other emotions, notably sadness. This pattern of generally increased amygdala activity is commonly interpreted as consistent with hypersensitivity of individuals with MDD to negative experiences, as well as their tendency to assign or experience events as negative.

Not surprisingly, hyperactivity of the amygdala is not the only disorder of the corticolimbic circuit observed in individuals suffering from depression. Increased activity is also commonly observed in the insula and dorsal anterior cingulate cortex (Figure 4.2A). While amygdala hyperactivity is reflected in the hypersensitivity of individuals to stress and threat, their greater subjective awareness of the resulting physiological changes may be reflected in hyperactivity of the insula. The dACC hyperactivity may reflect the experience of emotional conflict in patients who struggle to maintain normal relationships in the face of depressed mood.

Interestingly, in the original study by Drevets and colleagues, individuals with depression also exhibited more activity in the dmPFC than did healthy participants. In contrast to amygdala hyperactivity, which was found in both currently depressed individuals and those in remission, hyperactivity of the dmPFC was unique to those currently depressed. This pattern suggests that, while amygdala hyperactivity is a trait marker in depression, dmPFC hyperactivity may be a state marker of an MDE. That is, amygdala activity may always be higher in those vulnerable for depression, but the actual experience of an MDE follows when the dmPFC attempts but ultimately fails to effectively regulate the amygdala.

There is also evidence for increased activity in the visual thalamus, including the pulvinar, during the processing of emotional facial expressions in MDD (Figure 4.2B). This suggests the intriguing possibility that individuals at risk for MDD may have heightened primary sensory processing of threat-related

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**Figure 4.1** (A) In comparison with healthy participants, there is evidence of amygdala hyperactivity both in individuals currently suffering from depression (depressed) and in those who have a history of depression but are not currently experiencing symptoms (remitted). (B) Amygdala hyperactivity not only distinguishes an MDE, it also predicts the severity of symptoms as measured by the Hamilton Depression Rating Scale (HDRS). Note that 0 represents baseline activity in these data. (After Drevets et al., 1992.)
Disorder

Thus, trait-like amygdala hyperactivity could reflect augmented threat processing in MDD, which is likely further exaggerated by dysfunctional top-down regulation of amygdala hyperactivity via the dmPFC.

Dysregulation of communication between the amygdala and dmPFC in MDD is most clearly reflected in studies using functional connectivity, which is a measure of how strongly activity in two regions of the brain is correlated. Functional connectivity can be either positive (i.e., activity in both regions increases together) or negative (i.e., activity in one region increases while activity in the other decreases). Measures of functional connectivity do not readily allow for determination of temporal order (i.e., activity occurs first in region A and subsequently in region B) or directionality (i.e., region A is driving activity in region B). Nevertheless, functional connectivity can be used to estimate how effectively two nodes within a circuit are generally communicating information.

In healthy, nondepressed people, functional connectivity between the amygdala and both vmPFC and dmPFC is positive. This positive functional connectivity is significantly weaker in MDD and can predict the severity of depression symptoms (Figure 4.3). This weakened connectivity simultaneously suggests impairments in the capacity to integrate bottom-up arousal and effect top-down inhibition following a triggering event or stimulus.

The above fMRI data reveal that dysfunction of the corticolimbic circuit, particularly amygdala hyperactivity and decreased amygdala-mPFC functional connectivity, is a core component of MDD. Consistent with this model, MDEs often

Figure 4.2 (A) Meta-analysis of 38 fMRI studies involving viewing of emotional facial expressions reveals consistent evidence for relative hyperactivity of the amygdala (1); dACC (2); and the anterior insula (3) in MDD in comparison with healthy participants. (B) The analysis also revealed relative hyperactivity of the pulvinar nucleus of the thalamus, which relays visual information to the amygdala, in MDD. (From Hamilton et al., 2012.)

Figure 4.3 Increased severity of current depressive symptoms in MDD, seen here as a higher score on the Beck Depression Inventory-II (BDI-2), is related to weaker functional connectivity between the amygdala and the mPFC. Note that 0 represents mean connectivity in these data. (After Matthews et al., 2008.)

dmPFC: dorsomedial prefrontal cortex
vmPFC: ventromedial prefrontal cortex
follow stressful life events such as being harshly reprimanded by an angry supervisor at work, getting divorced, or even being in a car accident. Moreover, the development of depression following a stressful life event is more likely for individuals who are high in trait anxiety and dispositional negative affect, sometimes characterized as neuroticism (Figure 4.4). Such trait measures reflect the tendency to be sensitive and vigilant for threat in the environment and, as prototypical dimensional features of personality, are expressed to some degree in us all. Those individuals at risk for depression, however, have particularly high levels of trait anxiety and negative affect. Taken together, these data suggest that stressful life events and the stimuli in our environments that signal threat (e.g., angry facial expressions) trigger amygdala hyperactivity, thereby unmasking the inability of the mPFC to integrate and regulate this activity, resulting in depression, particularly in those who are more sensitive to threat generally.

A final component of understanding corticolimbic circuit dysfunction in depression arises from the growing number of pre- and posttreatment fMRI studies, which are far more numerous for MDD than for other mood or anxiety disorders. Remarkably, fMRI evidence suggests that successful treatment of MDD acts to restore order in corticolimbic circuit function. For example, selective serotonin reuptake inhibitors, or SSRIs, which are the most commonly prescribed medication in MDD, appear to simultaneously increase the functional connectivity between the amygdala and both vmPFC and dmPFC and decrease amygdala hyperactivity (Figure 4.5A). Similarly, cognitive behavioral therapy (CBT) results in decreased amygdala hyperactivity and, possibly, increased amygdala-mPFC functional connectivity (Figure 4.5B).

Finally, deep brain stimulation (DBS) has emerged as a treatment option of last resort in depressed individuals who have not responded to any other form of treatment, including SSRIs and CBT. DBS treatment in depression often targets subregions of the mPFC, particularly the subgenual anterior cingulate cortex, directly stimulating activity in this region. It is believed that such direct stimulation restores functional connectivity between the mPFC and other nodes of the corticolimbic circuit, including the amygdala. That three such disparate treatment approaches—targeting, respectively, brain

| MDD | major depressive disorder |
| SSRIs | selective serotonin reuptake inhibitors |
| vmPFC | ventromedial prefrontal cortex |
| dmPFC | dorsomedial prefrontal cortex |
| mPFC | medial prefrontal cortex |

**Figure 4.4** In both men and women, the risk of developing MDD in response to stressful experiences is greater in individuals with higher levels of negative affect and anxiety, as indexed here by the personality trait of neuroticism. (After Kendler et al., 2004.)

**neuroticism** A personality trait or disposition to experience strong negative emotions, including anxiety.
bipolar disorders (BD) are characterized by cycling between extremes of emotional reaction. Individuals with BD experience manic episodes (or in some cases hypomanic states) that can involve a number of abnormal behaviors. These include extreme “high” or euphoric feelings; excessive energy and activity; restlessness, racing thoughts, and rapid talking; denial that anything is wrong; being easily irritated or distracted; decreased need for sleep; unrealistic beliefs in one’s ability and powers; uncharacteristically poor judgment; provocative, intrusive, paranoid, or aggressive behaviors; unusual sexual drive; and abuse of drugs, particularly cocaine, alcohol, or sleeping medications. To define a manic episode, these symptoms must be present for 7 days or be severe enough to require hospitalization. Individuals with BD often also suffer from MDEs as seen in MDD. Generally, individuals with BD will alternate between manic episodes, MDEs, and periods of normal mood known as euthymia.

Compared with MDD, fMRI studies of BD are relatively few. However, a consistent picture of corticolimbic circuit dysfunction is emerging from these studies. Of particular note, Lori Altschuler and colleagues at UCLA have been examining corticolimbic circuit dysfunction across the major states of BD:

| CBT | cognitive behavioral therapy |
| BD  | bipolar disorders            |
| MDE | major depressive episode     |

chemistry, behavior, and brain electrical activity—all alleviate symptoms of depression by restoring order in the corticolimbic circuit is a strong indication of the circuit’s critical importance in the etiology of MDD.

**Bipolar disorders**

As their name implies, bipolar disorders (BD) are characterized by cycling between extremes of emotional reaction. Individuals with BD experience manic episodes (or in some cases hypomanic states) that can involve a number of abnormal behaviors. These include extreme “high” or euphoric feelings; excessive energy and activity; restlessness, racing thoughts, and rapid talking; denial that anything is wrong; being easily irritated or distracted; decreased need for sleep; unrealistic beliefs in one’s ability and powers; uncharacteristically poor judgment; provocative, intrusive, paranoid, or aggressive behaviors; unusual sexual drive; and abuse of drugs, particularly cocaine, alcohol, or sleeping medications. To define a manic episode, these symptoms must be present for 7 days or be severe enough to require hospitalization. Individuals with BD often also suffer from MDEs as seen in MDD. Generally, individuals with BD will alternate between manic episodes, MDEs, and periods of normal mood known as euthymia.

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| CBT | cognitive behavioral therapy |
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| MDE | major depressive episode     |

chemistry, behavior, and brain electrical activity—all alleviate symptoms of depression by restoring order in the corticolimbic circuit is a strong indication of the circuit’s critical importance in the etiology of MDD.

**Bipolar disorders** (BD)  Characterized by typically recurring cycles of manic episodes, euthymia, and major depressive episodes.  
**manic episodes**  Persistent feelings of euphoria, increased energy, diminished need for sleep, grandiosity, denial, and generally poor decision making.  
**euthymia**  Normal mood and affect.
manic, depressed, and euthymic. In the first of their studies published in 2005, Altshuler and colleagues reported amygdala hyperactivity in response to emotional facial expressions in individuals with BD during a manic episode. In many ways, such amygdala hyperactivity is highly consistent with the euphoria, irritability, insomnia, inattention, and distractibility that often define a manic episode.

When individuals with BD are in a depressive episode, however, there is relatively decreased amygdala activity. In addition, there is decreased activity in several prefrontal regions, including the vlPFC and dlPFC. Interestingly, the vlPFC also exhibits a relatively attenuated response in individuals during a manic episode. Moreover, a similar decrease in vlPFC activity has been documented in individuals during a euthymic, or normal, mood state. Notably, amygdala activity appears normal when individuals with BD are in a euthymic state.

When we look across these studies of BD, a striking pattern emerges. First, amygdala activity follows a state-dependent course—increased in manic, decreased in depressed, and normal in euthymic states (Figure 4.6A). Second, prefrontal cortex activation exhibits a state-independent, or trait-like, course that is decreased in all three states (Figure 4.6B). Critically, the vlPFC region exhibiting trait-like hypoactivation across manic, depressed, and euthymic states plays an important role in the downregulation of amygdala activity. In healthy participants, the vlPFC appears to exert top-down regulatory control over the amygdala (likely through the dmPFC, which has direct amygdala connections), as indexed by negative functional connectivity between the

![Figure 4.6](image-url)

**Figure 4.6** (A) Emerging fMRI research in individuals with bipolar disorders reveals state-dependent differences (blue trace) in amygdala activity, with hyperactivity during mania, hypoactivity during depression, and activity equivalent to that seen in healthy participants during euthymic states. (B) In contrast to the state-dependent patterns of amygdala activity, this research reveals state-independent vlPFC hypoactivity throughout manic, depressed, and euthymic states. The two horizontal lines indicate that in all three states, vlPFC activity in those with BD is (1) unchanging and (2) always less than the activity observed in healthy participants. As we will learn in Unit III, these patterns are consistent with abnormal or maladaptive top-down regulation of the amygdala through the prefrontal cortex. Note that 0 represents mean activity in these data. (After Hariri 2012.)
two regions. As we have seen, balance in this dynamic functional circuitry is critical for the expression of behavioral and physiological responses to provocation that are both temporally limited and contextually appropriate. Collectively, the emerging data for BD suggest that the vlPFC may not be adequately capable of regulating amygdala activity, resulting in mania.

If amygdala activity is a state-dependent phenomenon in BD and trait-like hypoactivation of regulatory prefrontal regions creates a permissive environment for the translation of amygdala hyperactivity into manic symptoms, then what could be driving amygdala hypoactivity in the depressed state? Again, the relative functioning of prefrontal regions may be key. During a depressive episode, individuals with BD exhibit increased functional connectivity between the amygdala and vlPFC. This is in contrast to the decreased functional connectivity between the amygdala and vlPFC, which can be interpreted as less top-down regulation, observed during manic episodes. Thus, it is possible that the abnormal mood states of BD reflect dysfunctional increases or decreases in connectivity between these two nodes, resulting in inappropriate regulation of the amygdala. The data suggest that these differences, not simply in the activation of brain regions (i.e., the vlPFC is hypoactive across states) but rather in the functional connectivity of distributed regions (i.e., amygdala-vlPFC connectivity is decreased in mania but increased in depression), may be particularly important for understanding changes in mood states characterizing BD.

You have probably noticed that the amygdala hypoactivity observed in individuals with BD during a major depressive episode is in stark contrast to the trait-like amygdala hyperactivity seen in individuals with MDD, which exists even when they are not currently depressed. In several important ways, the pattern of amygdala activity in BD is more consistent with the role of the amygdala in driving reactions to our environment by potentiating arousal and triggering adaptive changes in our physiology and behavior. When the amygdala is hyperactive in BD, individuals experience dramatic increases in their levels of activity and energy and also are more socially engaged (for better or worse) with their friends, family, and colleagues. When the amygdala is hypoactive, individuals with BD experience a loss of energy, are less active, and avoid or lose interest in social interactions. This difference may reflect the important role of anxiety in the development of a major depressive episode in MDD but not in BD. That is, depression in individuals with MDD represents dysfunctional underregulation of an amygdala that is hyperactive to stress and threat, while depression in individuals with BD represents dysfunctional overregulation of otherwise normal amygdala activity. These differences are further reflected in the generally higher levels of trait anxiety, negative emotionality, and comorbid anxiety disorders in MDD relative to BD.

Anxiety Disorders

Anxiety disorders are characterized by sustained mental symptoms including apprehension, fear, and general uneasiness, as well as physical symptoms including dizziness or light-headedness, chest/abdominal pain, nausea, increased heart rate, and even diarrhea. Similar to mood disorders, anxiety disorders involve an exaggerated response or hypersensitivity to threat and stress. However, with anxiety disorders there is a pronounced physical...

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**Panic attack** Overwhelming experience of fear with severe physical symptoms that can be mistaken for a heart attack.

**Panic disorder (PD)** Characterized by recurring, unpredictable panic attacks.

**Agoraphobia** Fear of places and situations where escape may be difficult.

**Anticipatory anxiety** Fear experienced only in anticipation of a threat, with no actual exposure to the threat.

Expression of this hypersensitivity not commonly observed in mood disorders. In fact, anxiety disorders are sometimes difficult to recognize because of their many physical symptoms, which result in their treatment only as physical disorders (e.g., irritable bowel syndrome).

The constellation of mental and physical symptoms common across anxiety disorders is clearly consistent with amygdala hyperactivity. This will be readily apparent as we review common forms of these disorders below. However, as with mood disorders, dysfunction in other nodes of the corticolimbic circuit is also present across anxiety disorders and, sometimes, unique to specific forms. The most prevalent forms of anxiety disorders, which we will review below, are panic disorder, generalized anxiety disorder, social anxiety disorder, and specific phobia. We will also review posttraumatic stress disorder, which was historically classified as an anxiety disorder but as of the fifth edition of the *DSM* is now considered under the new category of trauma- and stress-related disorders. We will discuss generalized anxiety disorder in a separate section later in the chapter.

**Panic disorder**

A panic attack is a discrete period of overwhelming fear that comes on abruptly. Panic attacks involve both mental and physical discomfort (with the latter sometimes interpreted by the sufferer as a heart attack because of the intense chest pain). Fortunately, these symptoms typically peak after a few minutes and subside as abruptly as they begin. Panic disorder (PD) is characterized by unexpected and recurrent panic attacks. The frequency of panic attacks varies from several times a day to only once or twice a year. Although PD specifically is uncommon, the experience of panic attacks is often present in many anxiety disorders, where they may be triggered by specific stimuli or contexts.

Individuals with PD often also have agoraphobia, which literally means “fear of the marketplace.” More broadly, agoraphobia refers to the experience of marked fear and distress when in a place or a situation that makes escape difficult, embarrassing, or impossible. Agoraphobia typically involves characteristic clusters of situations such as leaving home alone, being in crowds, going over a bridge, and using public transportation. In individuals with agoraphobia, such situations that cause fear are avoided or are endured with intense distress. Over time, individuals with agoraphobia may experience intense fear and even panic attacks when merely thinking about or imagining provocative situations, a condition referred to as anticipatory anxiety.

As you can imagine, anticipatory anxiety and agoraphobia make it difficult to conduct fMRI studies in individuals with PD. For these individuals, the mere specter of spending an hour or more inside a large magnet with only a rather small opening can trigger their fears and anxiety. Nevertheless, there have been a small number of fMRI studies in PD. Of note, viewing of emotional facial expressions does not typically produce significantly greater amygdala activity in patients with PD compared with healthy participants. There is, however, evidence for decreased activity of the prefrontal cortex, including the vmPFC, dmPFC, and vlPFC when processing negative emotional information such as threat-related facial expressions, or when undergoing fear learning. These deficits in prefrontal function suggest that PD may reflect abnormalities in the ability to integrate and regulate the bottom-up drive of the amygdala rather than an exaggerated drive directly.

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PD  panic disorder
vmPFC  ventromedial prefrontal cortex
dmPFC  dorsomedial prefrontal cortex
More remarkably, a small number of experiments have actually recorded changes in brain function during a panic attack. In the most striking of these studies, a patient with specific phobia able to reconstruct the experience of a panic attack during the scan, which involved viewing emotional facial expressions, allowing the investigators to identify corresponding changes in corticolimbic circuit function. Interestingly, at time of the patient’s first report of feeling both mentally and physically distressed, there was a corresponding increase in insula activity. Subsequently, as the patient’s anxiety and fear escalated to the point that the scan was terminated, there was a corresponding increase in amygdala activity (Figure 4.7). Such increased activity of the amygdala has been positively correlated with increased heart rate. A general pattern of decreased prefrontal activity also has been observed during spontaneous panic attacks.

Collectively, these studies suggest that panic attacks may result from an initially increased awareness of changes in our peripheral physiology as registered by the insula, which then leads to amygdala hyperactivity and subsequently further exaggeration of both mental and physical distress. This exaggerated sensitivity may persist because of an inability to integrate and control these changes associated with decreased prefrontal activity. Extending to PD, the above pattern of corticolimbic circuit disorder suggests that amygdala and insula hyperactivity may be a state feature (i.e., occurring only during panic attacks), while prefrontal cortex hypoactivity may be a trait feature (i.e., occurring always in response to negative emotional information).

**Social anxiety disorder**

Social anxiety disorder (SAD), also known as social phobia, is characterized by persistent fear and avoidance of social or performance situations without apparent justification (i.e., the individuals are not being ridiculed or threatened by others in these situations). The fear of public scrutiny leads individuals with SAD to experience embarrassment, anxiety, and situationally bound panic attacks.

**social anxiety disorder (social phobia)** Characterized by excessive or unreasonable fear of public scrutiny leading to persistent avoidance of social or performance situations and situationally bound panic attacks.
Specific phobia is characterized by excessive or unreasonable fear and avoidance of a specific place, thing, or situation. As with SAD, individuals with specific phobia often experience panic attacks when confronted by or anticipating exposure to a phobic stimulus. There are several general categories of specific phobia, with multiple exemplars in each category. These include situational phobias, such as when riding public transportation, driving, flying, and traveling through tunnels or across bridges; natural environment phobias with stimuli such as storms, heights, and water; and animal phobias including stimuli such as snakes, spiders, and dogs.

As these examples suggest, specific phobia is the clearest example of an exaggerated fear response that may once have had adaptive value (i.e., in our ancestral environments) but is generally maladaptive in modern contexts. Phobic stimuli generally do represent some form and degree of potential threat (getting bitten by a venomous snake, for example, can certainly result in death). However, they are typically encountered in contexts that effectively eliminate any real danger (e.g., most of us only encounter snakes in zoos,
where a thick plate of glass separates us from any real danger). While most of us have some initial fear response to situations and stimuli encompassing some degree of threat or danger, we (like our hiker on the trail) manage to regulate this response and resume our preferred activities. For those with specific phobia, however, such exposure is debilitating.

As we would expect, amygdala hyperactivity is clearly present in individuals with specific phobia. Interestingly, this hyperactivity is generally the largest observed among the anxiety disorders (see Figure 4.8A). While this may reflect actual neurobiological differences between the disorders, it could also be a methodological artifact because fMRI studies of specific phobia confront the patients with the stimuli they most fear (e.g., spiders in individuals with spider phobia), while fMRI studies of other anxiety disorders rely on indirect triggers (e.g., emotional facial expressions that represent conditioned stimuli). Recall from Chapter 3 that the most intense fear learning occurs when there is a perfect match between the conditioned stimulus and unconditioned stimulus. This is often the case in fMRI studies of specific phobia but not of other anxiety disorders. Consistent with this perspective, individuals with specific phobia exhibit faster amygdala activity in response to their phobic stimuli than to generally threatening stimuli.

In addition to hyperactivity of the amygdala, fMRI studies of specific phobia also document increased activity of the insula (see Figure 4.8B) and dmPFC. The former may reflect the intense physical distress experienced by phobic individuals. The latter may reflect attempts by phobic individuals to regulate their fear through top-down inhibition of the amygdala. Given the persistent amygdala hyperactivity, this effortful control is obviously ineffective. Top-down regulation of amygdala hyperactivity may be further limited by deficient integration of bottom-up amygdala drive, as suggested by relatively decreased vmPFC activity in specific phobia.

Allowing individuals to develop a tolerance for their phobic stimuli and the ability to regulate their intense fear is a hallmark of treatment in specific phobia. Such treatment almost always involves exposure therapy, wherein a patient is gradually brought into closer and closer proximity (even contact) with a phobic stimulus under carefully controlled settings where no harm can be done and with directions from the therapist about how to regulate the fear response. For example, a patient with spider phobia may be asked first to look at pictures of spiders, then to look at plastic spiders, then to hold plastic spiders, then to view a real spider in a cage, and finally to hold a real spider. This progression typically occurs slowly over many weeks and involves a great deal of input from the therapist to reassure the patient of his safety, but positive effects have been found after even a single session. Such exposure therapy is one of the most successful treatment approaches, not only in anxiety disorders but in all psychiatric disorders.

Remarkably, exposure therapy in specific phobia produces a striking normalization of the patterns of dysfunctional activity observed in individuals prior to treatment (Figure 4.9). Exposure therapy is associated with reductions in hyperactivity of the amygdala as well as the insula and dmPFC, compared with pretreatment levels in individuals with spider phobia. Moreover, decreases in amygdala and insula hyperactivity correspond to a drop in fear and anxiety levels when viewing pictures of spiders. Exposure therapy also has been associated with a relative increase in the activity of the vmPFC, which can be observed after only one treatment session. Collectively, these
posttraumatic stress disorder (PTSD) Characterized by a complex pattern of dysfunctional responses following exposure to a discrete, identifiable traumatic event or experience involving threat of death or serious bodily harm.

changes in corticolimbic circuit function following exposure therapy are highly consistent with the basic process of fear extinction and reflect the acquired capacity to actively inhibit the fear conditioning associated with the phobic stimulus. Dysfunction of fear extinction appears to be a critical feature of the final specific anxiety disorder we will consider here: posttraumatic stress disorder.

Posttraumatic stress disorder (PTSD) involves a pattern of dysfunctional responses following exposure to a traumatic event or experience involving threat of death or serious bodily harm. While the threat can be direct (i.e., something happening to you) or indirect (i.e., something you observe happening to another), diagnosis of PTSD follows if a discrete traumatic event or experience (e.g., severe weather such as a hurricane, or violent crime such as a mugging or rape) can be identified. In contrast, it is not a diagnostic necessity (and it
is often difficult) to identify a specific negative experience that preceded and possibly precipitated one of the other anxiety disorders (e.g., being bitten by a spider precipitating a specific phobia, or being publicly ridiculed precipitating SAD).

Once a traumatic event or experience is identified, the diagnosis of PTSD follows if for 30 days or longer the individual exhibits symptoms from each of four categories. The first category, **re-experiencing**, includes spontaneous memories of the traumatic event, recurrent dreams and/or flashbacks related to the event, and intense or prolonged psychological distress. Avoidance of **people and places** is a reaction to distressing memories, thoughts, feelings, or external reminders of the event. Individuals may suffer persistent and distorted negative cognitions and mood and be unable to remember key aspects of the event. This negative cognitive state can manifest in blaming of self or others, estrangement from others, and diminished interest in normal activities. The final category is that of **arousal**, including hypervigilance, sleep disturbances, and aggressive, reckless, or self-destructive behavior.

Many studies of PTSD have observed amygdala hyperactivity in response to both trauma-related imagery and more general threat-related stimuli, such as emotional facial expressions (**Figure 4.10A**; also see Figure 4.9A). This is not surprising given both the importance of the amygdala in driving arousal and subsequent reactions to threat and the hypervigilance found in individuals with PTSD. In fact, the magnitude of amygdala hyperactivity is positively correlated with the severity of PTSD symptoms (**Figure 4.10B**). In addition, studies have noted abnormal activity of the hippocampal formation and a persistent pattern of mPFC hypoactivity in response to negative stimuli including trauma-related imagery in individuals with PTSD.

**Figure 4.10** (A) Meta-analysis of 26 fMRI studies involving viewing of both trauma-related and trauma-unrelated emotional pictures reveals hyperactivity of the amygdala and dorsal ACC (yellow); and hypoactivity of the vmPFC and vlPFC (blue) in PTSD relative to healthy participants. (B) Amygdala hyperactivity to negative trauma-related imagery predicts symptom severity measured with the Clinician-Administered PTSD Scale for DSM-IV (CAPS). Note that 0 represents mean activity in these data. (A from Hayes et al., 2012; B after Browahn et al., 2010.)

| SAD | social anxiety disorder |
| mPFC | medial prefrontal cortex |
| dACC | dorsal anterior cingulate cortex |
Interestingly, the magnitude of activity in both the HF and dmPFC is inversely correlated with symptom severity (Figure 4.11). This suggests that retaining some ability to regulate bottom-up drives associated with amygdala hyperactivity and encode contextual cues may lessen the severity of PTSD symptoms. Collectively, the pattern of relative hyperactivity of the amygdala and hypoactivity in target regions within the corticolimbic circuit, notably the hippocampus and mPFC, is consistent with the trio of diagnostic symptoms in PTSD involving poorly controlled and inappropriate fear responses.

More specifically than this general pattern of corticolimbic circuit dysfunction, the trio of symptoms in PTSD aligns closely with dysfunctional fear learning. In an elegant study published in 2009, Mohammad Milad and colleagues at Harvard University examined the integrity of corticolimbic circuit function during fear learning in individuals with PTSD (Figure 4.12). In their landmark study, Milad and colleagues first completed a fear conditioning paradigm in patients with PTSD. Remarkably, there were no differences in either the strength of the fear conditioning or the activation of corticolimbic circuit nodes, including the amygdala, between these individuals and a comparison group of 15 healthy participants who had been exposed to a similar trauma but never developed PTSD or any other disorder. In other words, in patients with PTSD, fear conditioning was normal. Developing a fear response to a traumatic event and the cues and context that were associated with the event (e.g., a specific place where you were mugged or survived a hurricane) is not only normal but also highly appropriate and adaptive. The dysfunction in PTSD occurs when this normal and adaptive
fear response persists for too long and is expressed in inappropriate contexts (e.g., in a different place than where the trauma occurred). In other words, PTSD appears to be a disorder not of fear conditioning but of fear extinction.

In the second component of their fear learning study, Milad and colleagues had their participants perform a fear extinction protocol. In comparison with healthy participants, individuals with PTSD exhibited amygdala hyperactivity, suggesting that there is a failure to extinguish the conditioned fear response in PTSD. In fact, the physiological fear response in PTSD to the CS—a response that should have been extinguished in the safe context—was also greater than that of healthy participants. In addition, there was vmPFC hypoactivity in PTSD, suggesting deficits in integrating bottom-up drive from the amygdala. These patterns are consistent with the persistent fear responses and hypervigilance seen in PTSD even when cues in the environment indicate relative safety and absence of threat.

In the third and final component of their study, Milad and colleagues took fMRI scans of the participants one day following their original fear learning experience. This second-day scan was conducted to measure fear recall—the memory of fear conditioning and extinction learning. On this second day, individuals with PTSD failed to recall extinction and reduce their

Figure 4.12 Although fear conditioning occurs normally in PTSD, there is impaired fear extinction and associated abnormal corticolimbic circuit function. (A) In comparison with trauma-exposed healthy participants, individuals with PTSD show relatively decreased activity in the vmPFC and increased activity in the amygdala when learning that, in a new context, a previously fear-conditioned stimulus no longer predicts a mild electric shock. (B) Individuals with PTSD continue to exhibit corticolimbic circuit dysfunction 24 hours later during fear recall, where they exhibit relatively decreased activity in both the vmPFC and HF. This dysfunctional pattern of corticolimbic activity is consistent with the general inability to distinguish safe from threatening environments and consequent persistent expression of fear characteristic of PTSD. Note that 0 represents mean activity in these data. (After Milad et al., 2009.)
fear responses in the safe context. This failed extinction recall was manifest in the corticolimbic circuit as hypoactivity of the vmPFC and HF. Thus, key nodes of the corticolimbic circuit supporting the integration of amygdala activity (i.e., the vmPFC) and the formation of memories for specific contextually appropriate fear (i.e., the HF) were impaired in PTSD. Furthermore, the degree of this impairment in both the vmPFC and HF predicted the paucity of fear extinction. These findings support the hypothesis that fear extinction is specifically impaired in PTSD and that this impairment reflects dysfunctional integration (and subsequent regulation) of amygdala activity mediating fear conditioning, rather than dysfunctional conditioning in the first place.

RESEARCH SPOTLIGHT

One of the most important research areas in psychopathology seeks to identify and understand preexisting neurobiological factors that represent predictive markers of who will and who will not develop mental illness over time. There are many ongoing longitudinal neuroimaging studies following at-risk individuals (e.g., those with family history of a mood or anxiety disorder) with the purpose of ultimately looking back in time to identify differences in brain function that predict who will and will not become ill. However, the results of such studies are typically not available until many years after their initiation. In addition, these studies are exceedingly difficult to conduct, because of the costs associated with studying individuals over many years or even decades of life, as well as the uncertainty of successfully bringing individuals back to the laboratory for follow-up studies. Because of the explicit diagnostic requirement of discrete and identifiable exposure to a traumatic event, PTSD represents a unique opportunity to study preexisting neurobiological markers of risk in an accelerated albeit not easy manner. Such studies in PTSD generally focus on populations who are highly likely to experience a traumatic event that can be measured discretely. Military personnel, including soldiers and medics preparing for deployment to a combat zone, represent such a population and have been the focus of several ongoing studies seeking to identify patterns of corticolimbic circuit function that predict relative vulnerability and resilience to combat-related PTSD. In a prospective study of combat paramedics in the Israel Defense Forces, Admon et al. found that higher predeployment amygdala activity predicted greater postdeployment stress symptoms. Moreover, deployment was associated with changes in the functional connectivity of the HF and vmPFC. Interestingly, an increase in functional connectivity between the hippocampus and vmPFC predicted lesser stress symptoms. Thus, amygdala hyperactivity may reflect a predictive marker of sensitivity to combat-related stress, possibly by impairing the ability of the HF and vmPFC to regulate this activity when facing stressors (Figure 4.13). However, none of the paramedics in this study were diagnosed with PTSD, so the relevance of these patterns for predicting clinical disorder remains to be determined.

Figure 4.13 Research in military personnel reveals that amygdala hyperactivity prior to combat exposure predicts increased sensitivity to combat-related stress. This increased sensitivity may further reflect impairments in the ability of the HF and vmPFC to effectively regulate this amygdala hyperactivity when facing stressors. (After Admon et al., 2009, 2013.)

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Generalized Anxiety Disorder

In contrast to PTSD and the anxiety disorders reviewed above, generalized anxiety disorder (GAD) is characterized by a “free-floating” anxiety not associated with a particular object, event, or situation. In other words, there is no specific trigger resulting in fear, but rather a general and pervasive anxiety ranging from mild nervousness to continuous dread. There also is a higher degree of comorbidity between MDD and GAD than between disorders already reviewed. Interestingly, longitudinal studies suggest that the pervasive anxiety associated with GAD often precedes the development of MDD, particularly in response to stressful life events as discussed above.

As would be expected, given the high comorbidity between GAD and MDD, fMRI studies in individuals with GAD alone or comorbid GAD and MDD have shown amygdala hyperactivity (Figure 4.14A). Decreased vmPFC activity and functional connectivity between the amygdala and mPFC have also been noted in GAD. Like amygdala hyperactivity, these patterns are also consistent with those observed in MDD (Figure 4.14B). In contrast to these similarities, individuals with GAD or comorbid GAD and MDD show

**Figure 4.14** (A) During processing of emotional facial expressions, there is evidence for amygdala hyperactivity in patients with GAD only, MDD only, or comorbid for both GAD and MDD, in comparison with healthy participants. (B) The opposite pattern of relative hypo- and hyperactivity is observed for the vmPFC. Note that 0 represents mean activity in these data. (After Etkin & Schatzberg, 2011.)
decreased activity in the vlPFC not present in those with MDD only. This suggests that the pervasive anxiety that defines GAD may be related specifically to dysfunction of this regulatory region of the prefrontal cortex.

A recent study suggests that another potentially critical difference may exist in GAD in comparison with other anxiety disorders (Figure 4.15). Specifically, individuals with GAD exhibit amygdala hyperactivity when only anticipating the appearance of negative pictures but not during the actual viewing of these pictures. Interestingly, these individuals show the same hyperactivity even when the subsequent pictures are neutral. This general hyperactivity when anticipating potentially negative or aversive stimuli (even when it turns out to be neutral) is consistent with the pervasive anxiety characterizing GAD. Importantly, the localization of this hyperactivity was to the dorsal extended amygdala near the bed nucleus of the stria terminalis (BNST). This is also consistent with a general or undefined anxiety that is not in response to specific triggers.

Michael Davis and his colleagues at Emory University have provided compelling evidence that, while the amygdala is critical for fear and anxiety responses provoked by specific stimuli in our environment, the BNST is involved in maintaining these responses in the absence of such triggers. As we learned in Chapter 2, the amygdala can potentiate activity in the BNST in response to specific cues. Thus, these lines of evidence suggest the pervasive, nonspecific anxiety in GAD reflects persistent hyperactivity of the BNST (possibly after its initial activation by the amygdala) in the context of deficient prefrontal regulation.

Figure 4.15: In comparison with healthy participants, patients with GAD exhibit amygdala hyperactivity during the anticipation (seen here) but not the actual viewing of either aversive or neutral pictures. The localization of this hyperactivity is in the dorsal extended amygdala near the BNST (black circles). The histograms are the plotted data from these activation clusters. Note that 0 represents baseline activity in these data. (After Nitschke et al., 2009.)
Disorders of Social Behavior

As the previous sections reveal, corticolimbic circuit dysfunction generally and amygdala hyperactivity specifically manifest as core symptoms of exaggerated sensitivity and maladaptive responses to threat and stress in mood and anxiety disorders. Such dysfunction is also present in psychopathology not commonly categorized as mood and anxiety disorders—that is, in several conditions characterized by abnormal social interactions and behaviors, including inappropriate aggression and social withdrawal, which we will refer to broadly as disorders of social behavior. The specific categorical diagnoses we will review in the context of relative amygdala hyperactivity are antisocial personality disorder, intermittent explosive disorder, and autism spectrum disorders.

Antisocial personality disorder

Antisocial personality disorder (ASPD) is characterized by a blatant disregard for the needs, safety, and well-being of others, as well as an inability to follow moral, societal, or legal rules. ASPD is more often diagnosed in men, and these individuals are generally hypersensitive to threat and respond aggressively when they perceive themselves to be threatened (i.e., they exhibit reactive aggression). Common delinquent and antisocial acts of individuals with ASPD include assault, larceny, arson, destruction of property, reckless endangerment, and other criminal activity often leading to arrest. Although the diagnosis of ASPD is reserved for individuals 18 years of age or older, these individuals typically have a persistent history of delinquent and antisocial behaviors dating to childhood, when such behavior is diagnosed as conduct disorder (CD). A subset of individuals with ASPD also exhibit callous and unemotional (CU) traits, which involve a lack of empathy and remorse, as

antisocial personality disorder (ASPD) characterized by disregard for the needs, safety, and well-being of others, as well as an inability to follow moral, societal, or legal rules.

reactive aggression Anger or violence in response to perceived threat, especially from other individuals.

conduct disorder (CD) characterized by delinquent and antisocial behavior during childhood and adolescence. When such behavior persists beyond age 18, it may be diagnosed as antisocial personality disorder.

callous and unemotional (CU) traits Lack of empathy and remorse for the suffering of others.
Intermittent explosive disorder (IED) Characterized by hypersensitivity to threat leading to episodes of grossly inappropriate (usually violent) reactive aggression.

Amygdala hyperactivity has been observed in fMRI studies of ASPD. Some studies reporting amygdala hyperactivity have been conducted in children with CD because they represent those at-risk for later developing ASPD. In addition, there is some evidence for hypoactivity of regulatory regions of the PFC in ASPD and CD. This pattern of corticolimbic dysfunction is consistent with the hypersensitivity of some individuals with ASPD to threat, and their reactive aggression. However, as ASPD represents a heterogeneous set of disordered behaviors, the most useful fMRI studies attempt to isolate corticolimbic circuit dysfunction in specific subsets of individuals with more homogeneous symptoms (e.g., ASPD with or without CU traits). These studies, along with those in psychopaths, will be discussed in the upcoming section on amygdala hypoactivity.

Intermittent explosive disorder

Similar to some individuals with ASPD, those with intermittent explosive disorder (IED) characteristically exhibit hypersensitivity to threat and heightened levels of reactive aggression. Individuals with IED, who are typically men,

Although the inappropriate and persistent reactive aggression common to ASPD and IED represents an extreme manifestation of amygdala hyperactivity and corticolimbic circuit dysfunction, more modest forms of reactive aggression are expressed to varying degrees across all individuals. This spectrum of reactive aggression and anger more generally can be measured using a variety of self-report instruments such as the State-Trait Anger Expression Inventory (STAI) or Lifetime History of Aggression. My lab has examined the relationship between amygdala activity in response to emotional facial expressions and self-reported aggression in a normative sample of healthy adults (Figure 4.17). Analyses revealed a pattern that was remarkably similar to that reported in individuals with IED. Specifically, amygdala hyperactivity in response to angry but not fearful facial expressions uniquely predicted higher levels of trait anger, and particularly reactive anger, as measured by the STAI. However, this relationship was present only in men who also reported high levels of trait anxiety, as measured by the State-Trait Anxiety Inventory. Amygdala activity was unrelated to trait anger in women regardless of their levels of trait anxiety. Thus, these data are consistent with a role of amygdala hyperactivity in mediating reactive aggression, as only men who were more sensitive to threat (i.e., high in trait anxiety) exhibited higher reactive anger as a function of increased amygdala activity, specifically to explicit displays of threat (i.e., angry facial expressions).

Figure 4.17 For men (but not women), the propensity to experience more or less anger in contexts of reasonable provocation (e.g., when demeaned, criticized, or treated unfairly) is predicted by the magnitude of amygdala activity to angry but not fearful facial expressions. However, this association between amygdala activity and the experience of anger is present only in men who also experience high levels of trait anxiety; it is not found in those with low trait anxiety. This pattern is consistent with the role of threat-related amygdala activity in reactive aggression. Note that 0 represents mean activity in these data. (After Carré et al., 2012.)
may attack others and their possessions, causing bodily injury and property damage that is grossly out of proportion to any precipitating psychosocial stressor. For formal diagnosis, a patient must have exhibited at least three episodes of inappropriate reactive aggression during any time in his life. In contrast to individuals with ASPD, who often rationalize their aggressive behavior, those with IED typically express remorse and experience guilt after episodes of aggression.

Not surprisingly, fMRI studies of individuals with IED have shown amygdala hyperactivity as well as decreased functional connectivity between the amygdala and vmPFC. Interestingly, amygdala hyperactivity appears to be specific for stimuli that signal threat, namely angry facial expressions, and the magnitude of this hyperactivity is correlated with the number of aggressive acts committed by individuals with IED. Amygdala hyperactivity also may exist to neutral facial expressions, which may subsequently be interpreted by individuals with IED as threatening. Thus, the inappropriate reactive aggression in IED reflects a hyperactive response of the amygdala to signals of threat or potential threat, followed by a failure to effectively regulate this response through the PFC.

**Autism spectrum disorders**

*Autism spectrum disorders (ASD)* refers to a group of disorders, including autism and Asperger’s syndrome, characterized by varying degrees of social, emotional, and cognitive dysfunction. ASD is more commonly diagnosed in boys and encompasses a paucity or significant delay in the development of verbal and nonverbal language; marked social disengagement, including poor eye contact and flattened affect; stereotypical behaviors; and a hypersensitivity to sensory input. Most prominent in this constellation of symptoms in the context of corticolimbic circuit dysfunction are the deficits in social and emotional behavior that are present across the spectrum.

Many early theories suggested that ASD, and autism in particular, reflected blunting of emotional responsiveness and hyposensitivity to social input. However, recent evidence from fMRI and psychophysiological studies has led to a reconceptualization of ASD as reflecting hyperresponsiveness to social and emotional stimulation. In turn, this hyperresponsiveness leads individuals with ASD to avoid social interactions and withdraw into stereotypical patterns of familiar, nonthreatening behaviors. Consistent with this model, Temple Grandin, an accomplished research scientist who has autism and is a vocal advocate for increased understanding of ASD, describes herself as having “the nervous system of a prey species,” experiencing fear as a dominant emotional state. Such insight is uniquely valuable, as many individuals with the diagnosis, particularly autism, are cognitively low functioning and unable to articulate their internal states and experiences.

Interestingly, early fMRI studies of ASD appeared consistent with the blunted affect and social hyposensitivity models. In these studies, which required that subjects make simple perceptual decisions about objects or faces, there was a notable lack of difference in amygdala activity between healthy participants and individuals with ASD or there was significantly decreased amygdala activity in ASD. However, these early studies were critically limited by a failure to account for one of the core deficits in ASD: poor eye contact.

One of the more consistent deficits observed in ASD is gaze aversion, where patients avert their gaze from the eyes of faces and toward the mouths

**IEG** intermittent explosive disorder

**vmPFC** ventromedial prefrontal cortex

**ASD** autism spectrum disorders

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As we learned in Chapter 3, the amygdala is particularly responsive to the eyes and, moreover, the subtle differences in the presentation of the sclera associated with different emotional facial expressions. Normally, we focus our gaze on the eyes of faces, and this attentional bias contributes to eliciting amygdala activity. In the absence of this gaze bias toward the eyes, there is little to no amygdala activity. Because early fMRI studies failed to account for eye gaze, which is generally low in ASD, these studies observed a relative decrease or no difference in amygdala activity in comparison with healthy participants.

Recent studies either have worked to carefully control for differences in eye gaze between individuals with ASD and healthy participants, or the studies have employed tasks that minimize these differences. These studies consistently observe amygdala hyperactivity in those with ASD. In the first of such studies, Kim Dalton and colleagues at the University of Wisconsin found that the magnitude of amygdala activity was positively correlated with the percent of time that gaze was fixated on the eyes of facial stimuli. As expected, individuals with ASD spent less time fixating on the eyes than did healthy participants.

![Figure 4.18](image)

**Figure 4.18** Unlike healthy individuals, who focus their attention on the eyes of a face, individuals with ASD focus their attention on the mouth. (After Neumann et al., 2006.)

![Figure 4.19](image)

**Figure 4.19** (A) Amygdala activity is greater in individuals with ASD in comparison to healthy participants when they attend to the eyes of face stimuli. (B) The magnitude of amygdala activity is positively correlated with the amount of time individuals with ASD attend to the eyes. Note that 0 represents mean activity in (A) and baseline activity in (B). (After Dalton et al., 2005.)
the healthy participants. However, when Dalton and colleagues examined fMRI data only from faces where patients with ASD did fixate their gaze on the eyes, they found evidence for amygdala hyperactivity (Figure 4.19A). In fact, the magnitude of amygdala activity was positively correlated with the amount of time patients spent gazing at the eyes of the stimuli (Figure 4.19B). Additional fMRI studies in ASD have noted similar amygdala hyperactivity or amygdala activity equivalent to that of healthy participants. As would be suggested by their amygdala hyperactivity, individuals with ASD are faster in processing emotional facial expressions and have higher levels of social anxiety.

In addition to observing amygdala hyperactivity in ASD, recent studies have detected hypoactivity in the vmPFC, as well as decreased amygdala-vmPFC functional connectivity. Consistent with this pattern, there is also evidence for decreased habituation of amygdala activity in ASD, and this failure to habituate is associated with greater severity of social deficits (Figure 4.20).

These patterns of corticolimbic circuit dysfunction are highly consistent with the emerging model of ASD as representing a hypersensitivity to challenges we face from our environment. Poorly regulated amygdala hyperactivity leads to a generally anxious and fearful state, which individuals with ASD attempt to reduce by shifting their attention away from specific triggers, such as eyes, and by avoiding novel or unfamiliar places and people, which they experience as highly aversive. These biases further manifest as stereotypical or rigid patterns of behavior, which work to limit exposure to anxiety-producing and fearful contexts and triggers. A specific aversion to social interactions likely exacerbates delayed language and other cognitive abilities in individuals with ASD.

**Amygdala Hypoactivity**

Although far less commonly observed than amygdala hyperactivity, hypoactivity of the amygdala also occurs and leads to specific symptoms
of psychopathology. As would be expected, psychopathology associated with amygdala hypoactivity manifests as generally blunted affect and hyporesponsiveness to threat as well as diminished sensitivity to fear or distress expressed by others. Dysfunction in the broader corticolimbic circuit, particularly the mPFC, may also be observed in parallel with amygdala hypoactivity.

Importantly, such dysfunction does not manifest as different, nonoverlapping disorders. Rather, amygdala hypoactivity and related circuit dysfunction manifest as specific symptoms or response biases within disorders already discussed above. This is not only an indication of the substantial heterogeneity that exists within categorical diagnoses and the need to map disorder in brain circuit function onto specific symptoms or features of psychopathology, but also a critical illustration of the need to consider the stimuli and paradigms used with fMRI to probe variability in circuit function.

**Major depressive disorder**

Several fMRI studies of individuals with MDD have observed amygdala hypoactivity. Interestingly, this hypoactivity is often observed in individuals who also exhibit amygdala hyperactivity. The critical difference is to what stimuli the relative hyper- and hypoactivity of the amygdala occur. As reviewed above, amygdala hyperactivity in MDD is generally to facial expressions conveying threat such as anger and fear. This hyperactivity, which is poorly regulated by hypoactive prefrontal regions, manifests as an exaggerated sensitivity to threat, stress, and other negative experiences. There is also evidence of amygdala hyperactivity in response to facial expressions of sadness, which may reflect a mood-congruent attentional bias or sensitivity to stimuli signaling negative emotional states or social interactions. In contrast, amygdala hypoactivity has been observed to stimuli conveying positive emotion, namely, happy facial expressions (Figure 4.21).

**Figure 4.21** Individuals with MDD can exhibit differential amygdala hyper- and hypoactivity to specific emotional expressions. In this study, individuals with MDD exhibited relative hypoactivity to happy facial expressions but hyperactivity to sad facial expressions. The opposite pattern was found in healthy participants. The pattern of expression-specific amygdala hypo- and hyperactivity in MDD may reflect mood-congruent biases during an MDE (i.e., high levels of sadness and low levels of happiness). Note that 0 represents mean activity in these data. (After Suslow et al., 2010.)

mPFC   medial prefrontal cortex
MDD   major depressive disorder
MDE   major depressive episode
Moreover, the magnitude of amygdala activity in response to happy expressions is negatively correlated with the severity of depressive symptoms, suggesting that the ability to trigger responses to positive social stimuli may protect against deepening depression. Thus, in MDD there may be a specific failure to generate arousal, attention, and subsequent interest in stimuli that represent positive changes in our environment (e.g., the arrival of a close friend). This amygdala hypoactivity specifically to happy facial expressions is likely related to the anhedonia commonly experienced by individuals with MDD. While amygdala hypoactivity may contribute to anhedonia, the core dysfunction associated with this symptom is in the corticostriatal circuit and will be discussed in Unit II.

**Bipolar disorders**

As noted above, amygdala hypoactivity in BD is a state-dependent phenomenon, observed only when individuals experience a major depressive episode (see Figure 4.6A). This state-dependent hypoactivity appears to emerge through dysfunctional overregulation of what is otherwise normal amygdala activity, as indicated by the state-dependent increase in amygdala-viPFC connectivity observed only during an MDE. This overall pattern of dysfunction is consistent with the lethargy, apathy, and lack of interest in social interactions that define an MDE in individuals with BD.

**Antisocial personality disorder**

Amygdala hyperactivity is consistent with the general pattern of reactive aggression characteristic of ASPD and its developmental precursor, conduct disorder. However, amygdala hypoactivity has been observed when studies carefully work to reduce the heterogeneity of symptoms and features of ASPD. In particular, amygdala hypoactivity emerges in studies of antisocial individuals, particularly children and adolescents, who are also high in CU traits (Figure 4.22A). In addition, the amygdala activity that does exist in such individuals does not appear to properly drive activity in the vmPFC, and this diminished functional connectivity predicts greater severity of CU traits, including deficits in recognizing expressions of distress—specifically sadness and fear—and feeling less fear and less empathy for victims of aggression. Individuals high in CU traits also demonstrate reduced eye gaze, particularly to fearful facial expressions (Figure 4.22B).

Curiously, reduced eye gaze is also seen in ASD, which differs markedly with respect to both amygdala activity and social behaviors from ASPD with high CU traits. It is possible in ASD amygdala hyperactivity leads to excessive anxiety and fear, which is counteracted through averting gaze from the eyes and social withdrawal. In contrast, the amygdala hypoactivity in individuals high in CU traits may actually lead to a failure to gaze at the eyes, an inability to recognize the emotions of others, a hyposensitivity to threat, and diminished fear. These features culminate in general callousness and antisocial behavior in the absence of guilt or remorse in ASPD.

**Psychopathy**

Amygdala hypoactivity and diminished amygdala-mPFC functional connectivity are observed in the most extreme form of antisocial, callous, and unemotional behavior, referred to as psychopathy. Although no longer recognized in the DSM, psychopathy can be formally identified using an
instrumental (proactive) aggression. The purposeful and premeditated use of violence to achieve a personal goal and (unlike reactive aggression) not in response to provocation.

interview-based procedure that establishes high degrees of callousness, selfishness, narcissism, and remorseless use of others, as well as a persistent pattern of unstable relationships and antisocial behavior, established through review of case histories. Fortunately, few individuals are identified as psychopaths. The very few who are typically display instrumental, or proactive, aggression in addition to the reactive aggression commonly found in ASPD. Instrumental aggression involves the purposeful and premeditated use of violence to achieve a personal goal and is not in response to provocation.

Interestingly, a common feature of psychopaths is a failure to acquire conditioned fear responses (Figure 4.23). This deficit exists even in the presence of an explicit awareness of CS-US pairings, which is consistent with

**ASPD** antisocial personality disorder
**CS** conditioned stimulus
**US** unconditioned stimulus

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the generally high level of cognitive functioning in psychopaths. Thus, there may be relatively preserved cognitive function but impaired emotional function in psychopathy. This impaired fear conditioning is reflected in relative hypoactivity of the amygdala and interconnected corticolimbic circuit nodes, including the mPFC and insula. Collectively, the emerging data in psychopathy suggests that corticolimbic circuit dysfunction leads to deficits in the ability to recognize signals of distress, such as fearful facial expressions, and to learn conditioned fear responses. In the absence of recognizing these signals, which function to promote empathy and social affiliation as well as help us avoid danger, the intact cognitive processes in psychopaths emerge as persistent antisocial behavior and instrumental aggression.

Figure 4.23  (A) In contrast to their failure to develop a conditioned fear response as measured through changes in peripheral physiology (here, sweating), psychopaths did consciously learn which of two stimuli was paired with painful pressure (the conditioned stimulus) and rated the CS as more aversive. Note that 0 represents the baseline in these data. (B) Consistent with the failure to acquire a conditioned fear response, there was significantly decreased activity in the amygdala, mPFC, and insula of psychopaths in comparison with healthy participants. (After Birbaumer et al., 2005.)
Williams Syndrome

Although not formally a psychiatric disorder and generally reflecting multiple physical and mental symptoms, Williams syndrome includes distinct patterns of disordered social and emotional behaviors that warrant consideration in the context of corticolimbic circuit dysfunction. Most notably, individuals with Williams syndrome (which results from the partial deletion of chromosome 7) typically exhibit a marked social disinhibition and fearlessness of others. This pattern of gregarious and often indiscriminate social behavior is in stark contrast to that characterizing autism spectrum disorders, even though generally low intellectual functioning is shared by Williams syndrome and ASD.

ASD  autism spectrum disorders
ASPD antisocial personality disorder
CU  callous and unemotional
This divergence in social behavior is mirrored in the patterns of amygdala activity to facial expressions in individuals with Williams syndrome (Figure 4.25). As expected, there is amygdala hypoactivity in response to social stimuli, including facial expressions conveying threat. Interestingly, amygdala hypoactivity in response to threat predicts the degree of social fearlessness, often measured as the willingness to trust and approach strangers, in Williams syndrome. In contrast, there is evidence for amygdala hyperactivity to stimuli signaling positive emotion, such as happy facial expressions.

Critically, this fearlessness to engage in social interactions does not generalize to other stimuli. In fact, patients with Williams syndrome often exhibit higher levels of anxiety and fears, including specific phobias, than are observed in the general population, or even in other developmental disorders. Here again, the differential activity of the amygdala closely matches this aspect of the syndrome. Specifically, while there is amygdala hypoactivity in response to social threats (i.e., angry or fearful facial expressions), there is hyperactivity in response to nonsocial threats such as spiders, snakes, and snarling dogs (Figure 4.26).

Studies of functional connectivity in Williams syndrome suggest that the stimulus-specific patterns of amygdala hypo- and hyperactivity reflect abnormal patterns of top-down

![Figure 4.25](har1e_04.25.ai)

**Figure 4.25** Individuals with Williams syndrome exhibit relative amygdala hyperactivity to happy facial expressions but marked hypoactivity to fearful facial expressions. Note that 0 represents mean activity in these data. (After Haas et al., 2009.)

![Figure 4.26](har1e_04.26.ai)

**Figure 4.26** In comparison with healthy participants, individuals with Williams syndrome exhibit amygdala hypoactivity to social threat (angry and fearful facial expressions in this study) but hyperactivity to nonsocial threat (snakes, spiders, and dogs in this study). (From Meyer-Lindenberg et al., 2005.)
regulation of the amygdala by regions of the PFC. Specifically, there appears to be too little top-down regulation to nonsocial threat and too much to social threat. This pattern is consistent with the highly elaborative nature of social and emotional language seen in Williams syndrome. Such linguistic function is highly preserved in comparison not only to other developmental disorders (e.g., Down syndrome), but also to other functions (e.g., visuospatial skills) in Williams syndrome. When individuals with Williams syndrome engage in their unique and elaborate linguistic processing of social stimuli and situations, there is likely increased prefrontal activity, which could mediate top-down inhibition of otherwise heightened amygdala activity and lead to disinhibited or gregarious social behavior. The absence of such linguistic elaboration for nonsocial stimuli, in contrast, does not engage these top-down regulatory processes in the PFC, thereby allowing the expression of relatively increased amygdala activity as anxiety and fear.

Summary

Corticolimbic circuit dysfunction, manifesting as amygdala hyper- or hypoactivity, commonly emerges as psychopathology associated with mood and anxiety disorders as well as disorders of social behavior. While there are symptoms and features unique to each categorical disorder reviewed above, a shared or core dysfunction across all of these disorders is maladaptive behavioral and physiological reactions to challenges present in our environment.

Disorders characterized by heightened sensitivity to threat and stress (e.g., major depressive disorder, social anxiety disorder, specific phobia) emerge when there is amygdala hyperactivity, which is typically associated with hypoactivity of the ventromedial and dorsomedial prefrontal cortex, leading to deficient top-down integration and regulation. In contrast, disorders characterized by lessened sensitivity to threat and stress (e.g., antisocial personality disorder with callous and unemotional traits, psychopathy) emerge when there is amygdala hypoactivity, which can be associated with hyperactivity of these prefrontal regions and thus excessive top-down inhibition. Unique features of these disorders likely reflect subtle differences in the nature of dysfunctional prefrontal regulation (e.g., state-like in major depressive disorder, but trait-like in bipolar disorders) or the precise locus of dysregulated activity (e.g., amygdala in social anxiety disorder and specific phobia, but bed nucleus of the stria terminalis in generalized anxiety disorder).

Moreover, unique features also emerge as a function of differential amygdala activity in response to specific stimuli (e.g., hyperactivity in response to threatening and sad facial expressions, but hypoactivity to happy facial expressions in major depressive disorder), which likely reflect abnormal learning of specific associations between cues and outcomes. The form of such aberrant learning also contributes to the emergence of disorder-specific features (e.g., abnormal fear extinction but not fear conditioning in posttraumatic stress disorder, but abnormal fear conditioning in psychopathy).

Finally, while there is ample evidence for shared dysfunction of the corticolimbic circuit that maps onto specific symptoms across disorders, the underlying cellular, molecular, and even genetic factors ultimately leading to the observed dysfunction at the circuit level may differ considerably between disorders. While beyond the scope of this text, such unique features of disorders may be critical in the relative responsiveness of each to either pharmacological or behavioral treatment.
Literature Cited & Further Reading


treatment-resistant depression. *Cerebral Cortex*, 18: 1374–1383.


