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Abstract

Posttraumatic stress disorder (PTSD) is a psychiatric condition that emerges in some people after experiencing a serious traumatic event like sexual assault, natural disaster, accidents, or combat. Symptoms may include recurrent memories or bad dreams about the event, avoidance of any reminders of the event, negative changes to mood and thinking, and hyperarousal including increased startle, difficulty concentrating, and trouble sleeping. Descriptions of PTSD have existed for centuries and across different cultures, but PTSD was often viewed with skepticism. Largely through the efforts of neuroscientists over the past few decades, objective biological evidence for PTSD began to emerge and the reality of PTSD is no longer in doubt. This chapter reviews some of that biological evidence. Theoretical understanding of PTSD and its treatment is largely based in rodent models of Pavlovian fear conditioning, and studies of individuals with PTSD have shown increased conditioned fear, decreased extinction of that learned fear, and decreased ability to recall safety learning. These abnormalities are reflected in the neurocircuitry of PTSD. Individuals with PTSD exhibit functional abnormalities in emotion and memory-related structures such as the dorsal and rostral anterior cingulate cortex, amygdala, hippocampus, and insula. In general, structures involved in the expression of fear and defensive behaviors are hyper-responsive in PTSD while structures that inhibit fear are hypo-responsive. Interestingly, some functional brain abnormalities are actually vulnerability factors that pre-date the triggering traumatic event, as opposed to acquired characteristics of PTSD diagnosis. Inherited genetics may contribute to PTSD vulnerability as well, but one of the most profound PTSD vulnerability factors is a prior history of trauma. The chapter ends with a brief description of epigenetic mechanisms that may explain how environmental experience could confer long-lasting biological effects such as changes in the sensitivity to the stress hormone cortisol.

Keywords

Amygdala • Anterior cingulate cortex • Anxiety disorder • Reinstatement • Spontaneous recovery • Renewal • Exposure therapy • HPA axis • Glucocorticoid receptor • FKBP5 • Epigenetics • Psychophysiology • Positron emission tomography (PET) • Medial prefrontal cortex • Functional magnetic resonance imaging (fMRI) • Extinction • Fear conditioning • Hippocampus • PTSD • Posttraumatic stress disorder • Trauma
Brief History

It has been called by many different names, but Posttraumatic stress disorder (PTSD) has existed for thousands of years and across human societies (e.g., Abdul-Hamid and Hughes 2014; Jones 2006). The Mahabharata compilation of Indian epics describe PTSD-like symptoms in soldiers fighting wars that took place more than 5000 years ago, and the Buddhist Jakata stories of 2400 years ago tell of a monk suffering frightful mental images and emotional numbing. Writings on clay tablets from the Assyrian period (1250–612 BCE) in ancient Mesopotamia (now Iraq) describe soldiers with trouble sleeping and nightmares, low mood, and repetitive thoughts that they could not control. The ancient Mesopotamians believed that these soldiers were haunted by the ghosts of the enemies they had killed. In ancient Greece, Homer’s epic poem The Iliad, written in the ninth century BCE about a war said to have taken place in the thirteenth or twelfth century BCE, describes soldiers with symptoms that we might now call PTSD, including survivor’s guilt, dissociation, and suicide. Also in ancient Greece but 400 years after Homer, the physician Hippocrates described PTSD-like symptoms in two female patients with unending fear and depression and in male patients with frightening battle dreams. While Homer ascribed such symptoms to a goddess’ spell, Hippocrates is often credited with being the first person to hypothesize that diseases were not because of magic or gods but were rather caused naturally, reflecting an imbalance of bodily fluids. A soliloquy by Lady Percy in William Shakespeare’s play Henry IV, written in the late 1500s, described how intrusive memories of war steal sleep and pleasure. All through eighteenth-century Europe, the term “nostalgia” was used to describe the anxiety, dread, depression, and exhaustion suffered by soldiers on foreign soil because it was believed that these symptoms arose from the homesickness of being away as opposed to the psychological trauma of war itself. In the mid-nineteenth century, the new railroad systems in Europe and the United States offered the first opportunity for large numbers of people to travel together over land at relatively high speeds. But these railroads were not very safe, and passengers faced deadly accidents with relative frequency – and railroad companies found themselves legally liable for their passengers’ safety. When accident survivors with PTSD-like symptoms sought compensation, doctors found diagnosis challenging because the patients were often physically unhurt or had only minor injuries that seemed disproportionate to the resulting disability. A diagnosis of “railway spine” was created, reflecting a theory that the symptoms were caused by impact shaking and damaging the spinal cord. Similarly, during World War 1, PTSD-like symptoms in soldiers were referred to in the United States and Europe as “shell shock” because doctors believed that exploding bombs caused the symptoms by doing damage to the nervous system. It is true that experiencing crash impact or being near an explosion can cause a brain injury, and we now know that brain injury during a traumatic experience increases the likelihood of PTSD. But in reality, these symptoms probably reflected the psychological experience of almost being killed or seeing the violent death of others, rather than only the physical impact of a crash or explosion.
In World War 1, if the same symptoms were instead ascribed to the poison gas used in trench warfare across Europe, the diagnosis was “gas hysteria.” In World War 2, US soldiers with PTSD were said to have “battle fatigue” or “old sergeant syndrome” or “traumatic war neurosis.”

Along with the lack of understanding came the lack of appropriate treatment and, often, mistreatment of traumatized people who were accused of weakness of character or even malingering. A combination of ignorance and machismo dominated the issue. While visiting a field hospital in Italy in 1943, US General George Patton slapped a young soldier who had been hospitalized for “battle fatigue,” shouting, “I won’t have the hospitals cluttered up with these sons of bitches who haven’t got the guts to fight. Send that yellow son of a bitch back to the front line.” After the war, treatment of traumatized veterans was not much better. Even if doctors had sympathy for veterans who showed the symptoms of what we now call PTSD, science and medicine did not understand what was happening in their brains and bodies nor how to treat it. For a brief period after WW2, “gross stress reaction” was an official diagnosis for the response to traumatic stressors such as battle, but it was thought that this response should only last up to a few weeks. “Gross stress reaction” was soon dropped as an official diagnosis, possibly because WW2 had been over for several years, and it was not considered that these symptoms could last for years or that stressors other than combat could cause psychiatric pathology in civilians. After the US government’s invasion of Vietnam, drafted soldiers once again showed the same general set of symptoms seen in soldiers since ancient India and Mesopotamia. This time, however, the condition would be given a permanent name that would not be forgotten between major military conflicts, for the simple reason that scientists and doctors began comparing combat trauma to other types of trauma.

We know the most about the history of combat-related PTSD because many history books discuss the experiences of male soldiers, but women are about twice as likely to experience PTSD as men. This may be partially due to subtle biological differences between women and men, but is largely explained by the fact that women are much more likely than men to experience rape and sexual abuse, which have a relatively high likelihood of causing PTSD regardless of sex. Progress in understanding began when symptoms caused by rape, then referred to as “rape trauma syndrome,” were compared to symptoms caused by combat (Keane et al. 2006). After the Vietnam War, veterans and their families demanded that the US government recognize and treat the symptoms that so many of them were experiencing after returning home, sometimes called a “delayed stress reaction.” Scientists and doctors noticed that combat veterans had symptoms that were similar to the symptoms experienced by rape survivors. This is why the name PTSD now emphasizes that such symptoms may emerge after “traumatic stress” of any kind and not just combat. However, even after PTSD became an “official” diagnosis in the United States in 1980, for many years, political and medical establishments still viewed it with skepticism. This is largely due to the fact that, at the time, PTSD was thought of almost entirely in psychological terms and psychological symptoms were considered to be easy to fake for ulterior motives. Veterans were again accused of attempting to garner government benefits meant for physically injured veterans by faking their
psychological symptoms (indeed, it was referred to by some skeptical doctors as “compensation neurosis”). Through the efforts of research scientists, objective biological evidence for PTSD began to emerge, and the reality of PTSD could no longer be ignored (Pitman et al. 2012). This chapter will discuss some of that biological evidence. An emphasis will be given to how the neurocircuitry of PTSD is based in animal fear conditioning and extinction research and the implication for clinical presentation and treatment. There will also be a discussion of traits in PTSD that go beyond the fear conditioning and extinction model, including discussion of genetic and neuroendocrine biomarkers. The chapter will conclude with information about the emerging field of epigenetics, followed by a brief summary of the future directions that the next generations of scientists will take PTSD research.

What Is PTSD?

Post-traumatic stress disorder (PTSD) is a psychiatric condition that emerges in some individuals who have experienced a particularly distressing event such as rape, combat, natural disaster, assault, accident, kidnapping, serious injury, or torture (APA 2013). PTSD can result from directly experiencing such an event, witnessing it happen to another person, or hearing about it happening to a loved one. The more directly experienced and more severe a traumatic event is, the more likely it is to lead to PTSD. Some types of trauma like rape or torture, which are acts of deliberate human cruelty, cause particularly high rates of PTSD (Mehta and Binder 2012; Keane et al. 2006).

There are four general types of psychological symptoms, and diagnosis is made based upon them (there are currently no diagnostic brain scans or blood tests).

1. **Intrusive symptoms**, which frequently include recurrent memories or bad dreams about the event. The memories and dreams may be so vivid that the person with PTSD actually feels as though they are reexperiencing the event in the present moment. These memories may be triggered by sights, sounds, smells, or anything else that is associated with the traumatic event (e.g., if a rape survivor smells the same cologne as the rapist wore or a combat veteran hears fireworks that sound like gunfire). When a person with PTSD is reminded of their traumatic experience, it can be very distressing, and they may have strong and long-lasting physiological responses such as increased heart rate, heavy breathing, or increased sweat. In some cases, they may have a dissociative “flashback” and actually feel as though the traumatic experience is happening all over again.

2. **Avoidance of trauma reminders**. People with PTSD may spend great effort to avoid anything that reminds them of their traumatic event and even spend effort to avoid thinking about it. For example, this may involve not leaving the house to avoid reminders of being assaulted in one’s neighborhood, or it may involve drinking alcohol or using drugs to try and numb thoughts and feelings. Avoidance can also be a barrier to therapy because people with PTSD frequently do not want to talk about their traumatic experience with a therapist.
3. **Negative changes in mood and cognition**, which can involve distorted thoughts and emotions. A person with PTSD may believe that they are bad or that they deserved whatever happened to them. They may have trouble remembering parts of the traumatic event or may have disorganized or inaccurate memories, for example, incorrectly remembering that it was their own fault when it actually was not. They may feel as if their future will be cut short. They may have strong feelings of guilt, fear, shame, sadness, or anger and may no longer enjoy doing things that once brought them pleasure. People with PTSD may feel isolated and unable to connect with others and may have difficulty experiencing positive emotions like joy and love.

4. **Hyperarousal symptoms.** People with PTSD may feel “on alert” and have an exaggerated startle response. For example, if someone with PTSD hears a door slam, they may jump out of their seat. They frequently have difficulty sleeping and difficulty concentrating. They may become irritable or have angry outbursts over very small problems. They may engage in reckless and dangerous behavior like starting fights or driving too fast. People with PTSD also may feel constantly anxious and vigilant and may spend effort looking and preparing for danger even when they are safe.

These symptoms are relatively common in the immediate aftermath of a traumatic experience, but for most people, they will fade away within a few weeks (Nemeroff et al. 2006). In approximately 10–30% of people who have experienced or witnessed a traumatic event, the symptoms do not fade (Keane et al. 2006). Therefore, PTSD is often conceived of as a failure of fear extinction (discussed below). Symptoms are not considered PTSD unless they continue to cause significant distress for longer than one month after the trauma. For some individuals, PTSD may be with them for the rest of their lives, even decades after the event that triggered it. The symptoms of PTSD can be severe and debilitating. PTSD is associated with many negative consequences such as increased family, legal, social, physical health, and employment problems (Keane et al. 2006). It is also important to note that PTSD does not look the same in all people, for example, one person with PTSD may appear highly anxious and emotional, while another may appear blunted and almost emotionless. PTSD is associated with increased risk of suicide. Some people may not exhibit all of the four diagnostic symptoms and therefore do not technically “qualify” as having PTSD, but this does not mean they are not suffering or that they do not deserve treatment. PTSD also has a high level of comorbidity, meaning that other forms of mental illness such as depression or substance addiction very frequently accompany PTSD. With certain types of traumatic events like combat or assault, PTSD is also often comorbid with brain injury, and a history of brain injury is a vulnerability factor for PTSD. There appears to be a genetic component to PTSD risk, but a history of previous traumatic experiences such as childhood abuse is also a profound risk factor (discussed below). In traumatized children, PTSD presentation may vary greatly depending on current age, age of trauma, type of trauma, and the interaction among those three factors.
Modern neuroscience techniques have enabled us to gain insight into the brain basis of PTSD symptoms. Here, we will review fear-learning research, as it relates to PTSD (see previous chapters for a more thorough discussion of fear learning).

The Fear Conditioning Model of PTSD

Some History of Fear Conditioning and Extinction Studies

In the early 1900s, Russian scientist Ivan Pavlov famously trained dogs to salivate to the sound of a bell. He did this by pairing the bell (conditioned stimulus) with the presentation of meat powder (unconditioned stimulus), so the dogs learned that the bell predicted the food (Pavlov 1927). After several such pairings, the dogs would salivate (conditioned response) to the sound of the bell even when no food was presented. In other words, the dogs had been conditioned to salivate to a bell. Pavlov also demonstrated that if he continued to ring the bell repeatedly without ever reinforcing it with more food, the dog would eventually learn that the bell no longer predicted food and would no longer salivate to the bell. In other words, the conditioned response would be extinguished or become extinct. This entire process is known as classical conditioning and extinction. Obviously, it is evolutionarily important for organisms to have the ability to learn which cues predict positive things like food or sex, but equally important is the ability to learn about negative things like poisons or danger and to learn about environmental cues that predict threat. Pavlov also reported studies of unpleasant stimuli – like sour-tasting weak acid or a bitter-tasting tonic on the tongue – to condition dogs. After repeatedly paring the sound of a clock ticking (conditioned stimulus) with placing a drop of acid or tonic on the tongue (unconditioned stimulus), the dogs eventually began to gag (conditioned response) at the mere sound of the clock. This type of experiment is the precursor of a specific kind of classical conditioning called fear conditioning (Rudy 2008). Just like with the extinction of classical conditioning, if the clock continued to repeatedly tick without anything unpleasant being placed on the dog’s tongue, the dog would eventually learn that the clock no longer predicted a bad taste and would stop gagging to the ticking sound. This is an early example of fear extinction (Milad and Quirk 2012; VanElzakker et al. 2014).

Another famous precursor of fear conditioning occurred in the 1920s, in what became known as the “Little Albert” experiment (Harris 2011). Scientists Watson and Rayner conditioned an 11-month-old child to be afraid of a white rat by making a loud, frightening noise while he was approaching the animal. After seven sessions of such conditioning, the child cried and showed apprehension when again presented with the rat, even in the absence of a loud noise. The concept of fear conditioning generalization was said to be demonstrated when Little Albert reacted with fear or hesitation to similar objects such as cotton, a mask with a white beard, a brown rabbit, and a black fur coat. Historians still debate who the real “Little Albert” was.
However, despite the fear conditioning sessions and despite what many psychology textbooks have incorrectly claimed, it is very unlikely that he grew up to be terrified of white furry animals and similar objects. For one thing, while a loud noise might be startling for a child, it is not the kind of horrifying or life-threatening traumatic experience that triggers lifelong psychiatric problems. One would suspect that the next several times he saw a white rat without anyone scaring him by making a loud frightening noise, Little Albert would have formed a new memory associating the rat with a lack of loud noises. In other words, his fear would have been extinguished by fear extinction. Importantly, once Little Albert learned that white rats no longer predicted loud noises, he should have been able to remember that fact even if he saw a white rat years later or in a different place. This is called fear extinction recall.

Fear conditioning is an important model for PTSD because it explains why reminders of a trauma could trigger a fear response as intensely as the original trauma (VanElzakker et al. 2014, 2016; Pitman et al. 2012; Jovanovic and Ressler 2010; Maren et al. 2013; Milad and Quirk 2012). Just like a clock should not normally cause a dog to gag and cotton should not normally make a child feel nervous, the smell of cologne or the sound of fireworks should not normally cause intense fear in people. But in some cases, otherwise-neutral cues can trigger a fear response long after the actual danger has passed: if cologne reminds a rape survivor with PTSD or fireworks remind a combat veteran with PTSD of their ordeal, they may have an intense fear reaction as though they were facing the danger all over again. Individuals with PTSD who undergo fear conditioning under experimental conditions have shown increased fear conditioning as well as deficits in fear extinction and fear extinction recall (e.g., VanElzakker et al. 2014, 2016). In other words, people with PTSD are better at learning fear, worse at learning safety, and worse at remembering any safety that they did learn.

**Fear Conditioning Behavior in Rodents**

Much of what is known about the neuroscience of fear conditioning and extinction come from studies of rodents, especially rats, due to the ability to utilize invasive techniques such as brain structure lesioning or direct neuronal recording during conditioned fear learning, expression, and extinction (LeDoux 2012; Rudy 2008). In rat studies, the most commonly measured conditioned response is called freezing behavior, in which rats hold completely still so that predators will not notice them. Therefore, when a tone or colored light (conditioned stimulus) repeatedly predicts a small electrical shock (unconditioned stimulus) delivered to a rat’s paws through a metal cage floor, even if the tone or colored light is subsequently presented without a shock, the rat will freeze (conditioned response). A related phenomenon called contextual fear conditioning occurs when a rat experiences a shock in a certain context (like a specific cage), and later reexposure to that context leads to freezing behavior (Rudy 2008; Maren et al. 2013). When a rat hears a sudden loud noise, it will startle before freezing. If that loud tone occurs in a conditioned context, or while a conditioned stimulus is being presented, the startle reflex will be larger. This is
known as **fear-potentiated startle** and is another commonly measured conditioned response. Unlike freezing, fear-potentiated startle also occurs in humans and is therefore especially useful when comparing rodent research to human research (Jovanovic and Ressler 2010). Fear extinction works the same way in rodents as it does in dogs and humans: if a conditioned stimulus is repeatedly presented without being reinforced by the unconditioned stimulus, the conditioned response will gradually extinguish. It is important to note that rodent behavioral responses such as freezing and fear-potentiated startle that are referred to as “fear expression” are actually just instinctual defensive behaviors – it is impossible to know whether a rat or mouse actually feels fear or anxiety in a way that compares to human emotions (LeDoux 2012). Nevertheless, a large literature uses the term “fear” to describe these conditioned responses, and so this chapter will as well, despite the imprecise nature of the term.

**Fear Conditioning and Extinction Neurocircuitry in Rodents**

During fear conditioning, there must be a way in which neurocircuitry binds together sensory information from the neutral conditioned stimulus with the fear-inducing unconditioned stimulus (shock) in order to respond with fear to an otherwise-neutral conditioned stimulus like a tone or colored light. And during fear extinction learning, there must be a way to stop that same fear response from taking place – either through “unlearning” the fear association or from learning a new “safety” association that competes with the existing “fear” association. Rodent research has allowed scientists to understand the neurocircuitry of fear conditioning and extinction with great detail (see Fig. 1).

The **amygdala** is an important structure for learning about danger (LeDoux 2012). The central nucleus of the amygdala is the “output” of the fear-response system and triggers behavioral responses such as freezing and fear-potentiated startle, as well as autonomic sympathetic nervous system responses. Lesions of the central nucleus of the amygdala prevent freezing to a fear-conditioned tone. So how do sensory experiences (like tones, colored lights, and shocks) that enter the ears, eyes, and skin lead to these fear responses? Like other sensory experiences, the conditioned and unconditioned stimuli are processed in the thalamus and somatosensory cortex. Because a crucial function of the brain is to quickly recognize danger and mobilize a response that will keep an organism alive, the brain has evolved a “strategy” for maximizing reaction time during potential danger, which is the utilization of two distinct pathways from the senses to action. You may have experienced this distinction if you have ever looked at the ground and jumped when you saw a snake, but then upon closer inspection realized that it was actually just a rope. At first glance, the rope was similar enough to a snake that your brain defaulted to a fast (and potentially lifesaving) fear reaction, at the expense of detailed sensory processing. This distinction is built into the neurocircuitry of fear conditioning and extinction that has been uncovered by rodent research. The “cortical pathway” relays more detailed sensory information through the hippocampus and
neocortex before integration and evaluation in the lateral amygdala. This slower cortical pathway allows the hippocampus to compare incoming sensory information to past experiences, detecting novelty or familiarity. This comparison function of the hippocampus would also facilitate Little Albert noticing the difference between a white rat and a bundle of cotton. The cortical pathway also allows the neocortex to provide the organism with a detailed and nuanced sensory experience. In contrast, a faster “subcortical pathway” sends a very basic sensory representation directly from the thalamus to the central and lateral nuclei of the amygdala, for immediate responses (e.g., Arnsten 2009; Rudy 2008). The binding together of the conditioned and unconditioned stimuli is supported by the lateral nucleus of the amygdala. The lateral amygdala projects directly and indirectly to the central amygdala, which as stated above triggers responses. The central amygdala’s output is inhibitory; therefore, the default response is the fear response, and this response must be “overridden” by safety information. In rodents, the dorsal medial prefrontal cortex is called the prelimbic cortex, and the ventral medial prefrontal cortex is called the infralimbic cortex. Activation of the prelimbic cortex is associated with the

Fig. 1 A simplified schematic of fear conditioning and extinction neurocircuitry, showing functional homology of rat and human brain regions. PL in rat and dACC in human are homologues, both project to the lateral nucleus of the amygdala. IL in rat and vmPFC in human are homologues, both project to the basal nucleus and intercalated cells of the amygdala. The circuitry within the amygdala is shared among species. Arrowheads represent excitatory projections and bar endings represent inhibitory projections. Within the amygdala, green shapes represent glutamate (excitatory) cells, and red shapes represent GABA (inhibitory) cells. Projections from lateral nucleus to CeL, from basal nucleus to CeM, and some other connections are not shown. CeL centrolateral subdivision, CeM centromedial subdivision, dACC dorsal anterior cingulate cortex, H hippocampus, IL infralimbic cortex, Itc intercalated neurons, PL prelimbic cortex, SC somatosensory cortex, T thalamus, vmPFC ventromedial prefrontal cortex (Adapted from VanElzakker et al. 2014)
expression of conditioned fear, while activation of the infralimbic cortex is associated with the lack of fear expression. In other words, the prelimbic cortex acts as an “accelerator” during conditioning, and the infralimbic cortex acts as “brakes” during extinction. The infralimbic cortex is necessary for contextual fear conditioning responses, probably because it is connected to the amygdala and hippocampus. The hippocampus is a key structure in determining whether contextual cues are associated with danger or with safety (Rudy 2008; Maren et al. 2013).

**Fear Extinction Is New Learning, Not Unlearning**

A question raised above asked whether fear extinction is established through “unlearning” the conditioned fear association or through learning a new “safety” association that competes with the existing conditioned fear association. There is good evidence that fear extinction learning involves the learning of a new and competing “safety” association and not the unlearning of the “fear” association. This is demonstrated by the three phenomena of renewal, spontaneous recovery, and reinstatement. **Renewal** is related to contextual fear conditioning, but is relevant even if the conditioned stimulus is a discrete cue such as a tone or colored light. When conditioning occurs in one context and extinction occurs in another context, a change from the extinction context either back to the conditioning context or into a third context can cause the conditioned response to renew. **Spontaneous recovery** refers to the fact that after much time has passed since extinction learning, presenting the conditioned stimulus again can cause the conditioned response. **Reinstatement** happens when, after fear extinction, the unconditioned stimulus is simply presented again. Even if the unconditioned stimulus is presented in isolation, a fear response to the formerly extinguished conditioned stimulus can be reinstated. For example, if a rat is conditioned to expect a foot shock when a blue light is presented, that response can be extinguished by repeatedly presenting the blue light without any shock. However, if at some later time the rat simply experiences another foot shock even without seeing a blue light, the conditioned response can be reinstated, and subsequent presentations of the blue light will cause freezing. Renewal, spontaneous recovery, and reinstatement are all evidence that extinction does not make the fear memory simply disappear because each of them can cause a conditioned response to return rapidly, without needing to repeat the conditioning process. The fact that extinction does not involve unlearning is important for PTSD, as will be shown later.

If the fear memory does not simply go away during extinction, then extinction must involve the learning of new information. New extinction learning competes with what was learned during conditioning. If fear conditioning involved learning “blue lights predict a shock,” then extinction learning involves a competing “blue lights no longer predict a shock.” So how does the extinction memory “win” that competition and dictate the response? Research in rodents suggests that the infralimbic cortex is a key structure in this process. Blocking the N-methyl-D-aspartate (NMDA) receptor for the excitatory neurotransmitter glutamate impairs extinction learning because the infralimbic cortex has direct excitatory projections to
the intercalated neurons of the amygdala (Milad and Quirk 2012). The intercalated neurons produce the inhibitory neurotransmitter GABA, and they hold inhibitory influence over amygdala output. Fear extinction can be caused artificially by using direct electrical stimulation of the infralimbic cortex while a rat is in a fear-conditioned context or is experiencing a fear-conditioned stimulus. The infralimbic cortex is also a key structure in fear extinction recall. PTSD-related rodent research often involves testing drugs or other interventions that can improve fear extinction learning or its recall. The neurocircuitry of fear conditioning, fear extinction, and fear extinction recall shows a remarkable level of evolutionary preservation across species, including human beings.

**Psychophysiological Studies of Fear Conditioning and Extinction in Healthy Humans Have Replicated Rodent Studies**

Modern fear conditioning and extinction experiments on humans often use a small electric shock to a finger or a puff of air to the eye or throat as the “fear”-inducing unconditioned stimulus and pair it with a tone or colored light as the conditioned stimulus. More complex paradigms present images on a computer screen, using images of differently colored lights in different rooms, allowing the pictures of different rooms to serve as “contexts.” A common measure of conditioned response is a psychophysiological response such as skin conductance response on the palm of the hand because activation of the autonomic sympathetic nervous system causes sweaty palms: when two small recording electrodes are placed near each other on the palm, the electrical conductance between them will increase as the amount of sweat increases. Measures of fear-potentiated startle response in humans include electromyographic response, which records electrical activity in muscles that control the eyelid or forehead, as well as heart rate response. Fear conditioning and extinction studies that have measured those psychophysiological responses in healthy humans have found very similar results to studies of freezing and fear-potentiated startle in rodents: robust responses to a conditioned stimulus that decreases after extinction learning. For the purposes of this chapter, however, studies of fear conditioning and extinction in humans were able to begin addressing the underlying neurocircuitry with the advent of functional neuroimaging. This is especially important for the neuroscience of PTSD because the structures involved in fear conditioning and extinction are the same structures that are dysfunctional in the brains of people with PTSD.

**Functional Neuroimaging Can Be Used During Human Fear Conditioning and Extinction**

Historically, most of what was known about the brain came from observing people with brain injuries. If a patient started having an observable deficit after some particular structure was damaged, an inference was made about the injured brain
structure’s normal function. While some important advances were made by these inferences, with the development of noninvasive technology, the understanding gained in just the last few decades dwarfs the cumulative understanding gained through all human history. Modern brain imaging techniques allow unprecedented study of the function and structure of living humans (reviewed in more detail in an earlier chapter). Brain imaging is generally divided into structural and functional techniques. Structural techniques are like a photograph in that they create an image of the size and shape of the brain. Structural images do not change moment to moment depending on what the person being scanned is thinking or experiencing. Functional techniques are more like a movie in that they show the brain in action. Functional images do change depending on what the person being scanned is thinking or experiencing. Therefore, functional imaging is particularly interesting in conditions such as PTSD, in which the symptoms are psychological. Functional brain imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are able to record specific biological activity in the brains of living, awake, responsive research volunteers. Studies of fear conditioning and extinction can present shocks to a finger and images on a screen to individuals while their brains are being scanned. It is fairly common to also record skin conductance during scanning sessions, although it is less common to conduct fear-potentiated startle paradigms during scanning because any head movement interferes with brain imaging.

The Neurocircuitry of Fear Conditioning and Extinction Is Similar in Humans and Rodents

The human brain is obviously much larger and more complex than a rat brain, but the fundamental fear circuitry is preserved across evolution. Just like in rats, in humans the amygdala (Latin for “almond”) and hippocampus (Greek for “sea horse”) are bilateral structures meaning there are two of each – one in the left hemisphere and one in the right hemisphere. In humans, a large band of cortex called the cingulate (Greek for “belt”) cortex wraps the limbic system structures in the center of the brain. The cingulate cortex is often divided into several parts, with the anterior cingulate cortex (ACC) considered to be part of the prefrontal cortex (PFC). What is called the prelimbic cortex in rat (the “accelerator” during fear conditioning) is called the dorsal anterior cingulate cortex (dACC) in humans. The rostral anterior cingulate cortex (rACC), subgenual anterior cingulate cortex (sgACC), and medial frontal gyrus together comprise the ventromedial prefrontal cortex (vmPFC). What is called the infralimbic cortex in rats (the “brakes” during fear extinction) is the vmPFC in humans (see Fig. 2 for a structural MRI of the human brain structures being discussed).

Some Caveats About Functional Neuroimaging Studies

It should be noted that these are all complex structures composed of different cell types. For example, just like the rat amygdala, the human amygdala is composed of
several interacting nuclei, some of which are excitatory and some of which are inhibitory. Our understanding of these nuclei is mostly from animal models and postmortem dissection because they are too small to be separately visualized by live human functional brain imaging. Therefore, when studies report “amygdala activation,” this necessarily comes with the caveat that we cannot know which specific nuclei are active. And perhaps importantly, functional brain imaging does not directly measure neuron activity but rather measures biological processes such as the use of oxygen or glucose (see the chapter on fMRI or PET for a review). Therefore, noninvasive functional brain imaging like fMRI and PET cannot

Fig. 2 Structural magnetic resonance image (MRI) showing the human brain structures of interest in this chapter: (a) a sagittal MRI slice showing the dorsal anterior cingulate gyrus (dACC) and structures comprising the ventral medial prefrontal cortex (vmPFC) including the rostral anterior cingulate cortex (rACC), medial frontal gyrus, and subgenual ACC; (b) a sagittal slice showing the amygdala and hippocampus; and (c) a horizontal slice showing bilateral insula (also called the insular cortex) (Reproduced from VanElzakker et al. 2016)
differentiate between excitatory or inhibitory processes because they both require oxygen and glucose. However, rodent and human amygdala nuclei are assumed to work the same basic way (see Fig. 1).

The Functional Neurocircuitry of PTSD Reflects Increased Fear Conditioning and Decreased Fear Extinction

The neurocircuitry of PTSD is exactly what one would expect from a condition that renders people better at learning fear, worse at learning safety, and worse at remembering any safety that they did learn. In PTSD, the brain’s fear “accelerators” are too responsive, and the fear “brakes” are not responsive enough. In healthy human studies of fear conditioning that recorded simultaneous skin conductance during functional neuroimaging, amygdala and dACC activation correlate with skin conductance response, demonstrating that their activation is the brain proxy for the conditioned response. During fear conditioning, those structures that are normally active in healthy controls (amygdala, dACC) are more active in people with PTSD. This is evidence that fear conditioning is stronger in PTSD. Even when presented with a simple unconditioned stimulus (finger shock), the amygdala and insula of people with PTSD activate more than they do in healthy people (Linnman et al. 2011). The insula, or insular cortex, is an association cortex that processes pain and emotion, monitors internal bodily state, and responds during sustained fear paradigms. The amount of insula activation during finger shock correlated with PTSD symptom severity and may be a brain proxy for anxiety. During fear extinction learning in healthy people, the amygdala and dACC gradually stop activating, but in people with PTSD, they continue to activate. This is evidence that extinction of the fear response is weaker in PTSD. The vmPFC and hippocampus activate in healthy people during fear extinction learning and recall, but in PTSD, those structures fail to activate, or they even deactivate. This is evidence that the new extinction “safety” memory fails to inhibit the conditioned fear memory in PTSD. And in fear extinction recall, the amygdala and dACC stay “turned off” in healthy people, but in PTSD they activate. This is evidence that the conditioned fear memory “wins” the competition with the extinction memory and dictates the response. Interestingly, the hippocampus and vmPFC also appear to be involved in fear conditioning generalization, as studies in healthy people have found that hippocampus and vmPFC activation increase with the presentation of stimuli that are similar but not the same as a conditioned stimulus. Given the general functional neuroimaging pattern of underactivation of the hippocampus and vmPFC in people with PTSD, this may be a mechanism that explains conditioned fear generalization in PTSD. Furthermore, several structural neuroimaging studies have found that the hippocampus and vmPFC are smaller in people with PTSD compared to controls.

Perhaps the most interesting thing about the functional neurocircuitry of PTSD is the fact that the pattern just described is seen not only in studies of fear conditioning and extinction in PTSD but also in virtually every other kind of neuroimaging study. While scientific literatures are almost never completely consistent and the specifics
of experimental tasks can lead to different results, scores of studies have found the same general pattern. Specifically, the amygdala and dACC (and to a lesser extent the insula) are generally more responsive in PTSD, while structures of the vmPFC (such as the rACC, sgACC, and medial frontal gyrus) are generally less responsive. Studies of the hippocampus are somewhat less consistent, and in some study designs, the hippocampus is less activated in PTSD than in healthy control individuals, while in other studies it is more activated in PTSD. This may largely depend on the type of experimental task being used, among other factors. As briefly mentioned above, one of the more consistent structural brain imaging findings in PTSD is that individuals with PTSD have a smaller hippocampus than comparison controls (discussed more below).

The same general pattern of hyperresponsiveness in the amygdala and dACC and hyporesponsiveness in the vmPFC has been shown in many different kinds of experiments. This includes fear conditioning and extinction paradigms, symptom provocation paradigms, emotional paradigms, nonemotional paradigms, and resting-state paradigms (e.g., VanElzakker et al. 2016). Fear conditioning and extinction studies were discussed above. Symptom provocation studies are intended to understand the brain basis of symptoms and include scanning the brain while participants hear, view, or even smell personalized reminders of their traumatic experience (in other words, conditioned stimuli). Emotional paradigms use general emotional stimuli like violent pictures or pictures of faces with different emotions. For example, Fig. 3 shows data from a study in which fMRI brain scanning was conducted while photographs of fearful facial expressions were shown to 13 men with PTSD and 13 men who had experienced trauma but did not have PTSD (Shin et al. 2005). The right amygdala of the men with PTSD activated more than the right amygdala of the men without PTSD. In the PTSD group, amygdala activation was also negatively correlated with vmPFC activation, and vmPFC activation was negatively correlated with PTSD symptom severity.

The same general pattern of hyperresponsiveness in the amygdala and dACC and hyporesponsiveness in the vmPFC has also been shown in studies that use emotionally neutral stimuli, such as attention tasks that use simple shapes like circles and squares or simple sounds like tones. The pattern we have been discussing has even been shown while people with PTSD are at rest, sitting quietly without being presented with any stimuli at all. Again, not all studies have shown this same pattern, but most have. The fact that these functional brain problems can be detected in PTSD patients even without reminding them of trauma poses an interesting question because PTSD is caused by a traumatic event. Therefore, it is tempting to assume that its symptoms must all be trauma related. However, there are three possibilities for any biological abnormality in PTSD:

1. The abnormality is an emergent property of PTSD symptoms.
2. The abnormality is a consequence of trauma exposure and occurs in all people after trauma, regardless of whether or not they have PTSD.
3. The abnormality has existed since birth or childhood or otherwise predated the trauma, and it occurs in people with PTSD because it is part of what made them vulnerable to PTSD.
Fig. 3 The functional magnetic resonance image (fMRI) in Fig. 3 displays activation to fearful versus happy facial expressions in the right amygdala that was greater in a PTSD group versus trauma-exposed control group. The bar graph shows BOLD (blood oxygen level-dependent) signal change in the amygdala in each condition (relative to the baseline of looking at a fixation cross “+” on a blank screen) for each group. Error bars represent standard error of the mean. Images of fMRI BOLD response always depict a contrast between groups and/or conditions. A typical functional image such as Fig. 3 illustrates a “difference in differences.” The arrow indicates activation in the right amygdala, where the BOLD response detected by the fMRI scanner during one experimental condition (looking at fearful faces) compared to another condition (looking at happy faces) differs between PTSD and control groups. The data analysis steps that yield such an image are as follows: First, within each individual subject, we statistically compare brain responses in one condition to those of another condition (e.g., amygdala responses to fearful versus happy faces). This comparison yields a statistical image for each subject that shows the brain areas that are activated significantly more (or less) in one condition versus another. Second, these “difference images” per subject are combined depending on group, such that the combined difference images of the PTSD group are statistically compared to the combined difference images of the control group. The result is an image like Fig. 3 that can show brain regions that are significantly more (or less) activated in one group than another. The same process can be completed using difference images that compare the BOLD response during fearful faces to the BOLD response during fixation cross. (Figure adapted from Shin et al. 2005)
Most studies of PTSD use case–control experimental designs in which a group of individuals with PTSD are compared to a control group without PTSD. This type of study can be quite valuable as long as the control group is carefully selected by paying attention to their trauma history. However, if the control group is not carefully selected, any abnormality found in individuals with PTSD will be difficult to explain: the abnormality could be related to PTSD itself or could occur in all people after trauma. This is why many studies of PTSD include three groups: trauma-exposed people with PTSD, trauma-exposed people without PTSD, and trauma-unexposed people. If an abnormality occurs in the PTSD group but not in the trauma-exposed-but-healthy group nor in the trauma-unexposed group, the abnormality must be related to PTSD itself. Yet that design is still unable to inform whether the abnormality existed in those people with PTSD even before their trauma or symptoms. The best study design for such a question would be a prospective design: measure a trait in a large number of people before subjecting them to trauma, to determine whether the trait predicts PTSD. For obvious ethical reasons, we cannot deliberately subject people to traumatic experiences during research. However, some studies have utilized a similar design by studying individuals who are highly likely to experience traumatic events, for example, studying soldiers before and after they go off to war. These studies are difficult, expensive, and fairly rare, but they are able to inform questions about the origin of abnormalities discussed above. Another way to answer questions about the origin of biological abnormalities in PTSD is by studying identical twins (as discussed below).

The same question of origin arises with structural abnormalities, or differences in the size and shape of different brain structures in people with PTSD, such as the finding of a smaller hippocampus in PTSD. Some scientists thought that the experience of trauma might shrink the hippocampus, possibly because of the stress hormone cortisol causing damage. However, a psychiatrist named Dr. Roger Pitman designed an ingenious study that argued against this explanation. He studied Vietnam combat veterans who had an identical twin that did not fight in Vietnam (reviewed in Pitman et al. 2012). His research group discovered that the combat-unexposed twins of combat veterans with PTSD had a smaller hippocampus than the combat-unexposed twins of combat veterans without PTSD and that the size of the hippocampus of the combat-unexposed twin correlated with the PTSD severity of the combat-exposed twin (Gilbertson et al. 2002). This was evidence that a small hippocampus is actually a vulnerability factor for PTSD, as opposed to being caused by PTSD or trauma. This is not to dismiss the possibility that trauma exposure or PTSD status could influence hippocampal volume – indeed, some studies have shown that hippocampal volume increases in PTSD patients during successful treatment, which is evidence that hippocampal volume is related to PTSD symptoms. However, the twin design provided good evidence that a small hippocampus is, at least partially, a pre-trauma vulnerability for PTSD.

Other studies of the same twin population have provided evidence that there are many brain, endocrine, and cognitive vulnerabilities for PTSD that exist before trauma. For example, in 2009, Dr. Lisa Shin, Dr. Roger Pitman, and others conducted
PET scans of the brains of Vietnam combat veterans and their combat-unexposed identical twins (Shin et al. 2009). The results are illustrated in Fig. 4. In this technique, a safe and small amount of radioactively tagged glucose is injected into an arm vein while subjects sit quietly with their eyes closed. The radiation breaks down quickly in the body, and the scanner can measure exactly where in the brain it is breaking down. More active cells will use more glucose, and the PET scanner will detect this. As discussed above, the dACC is more active in the brains of people with PTSD during fear conditioning, extinction, and extinction recall and during trauma-related paradigms, emotional paradigms, and nonemotional paradigms. Shin et al. (2009) demonstrated that the dACC of people with PTSD also uses more glucose even when they are at rest. However, this study also discovered that the combat-unexposed, healthy identical twins of people with PTSD also had the same pattern. This is evidence that a hyperactive dACC is a vulnerability factor for PTSD, as opposed to a result of trauma or PTSD (Fig. 5).

Several Genes that Cause Increased Fear Conditioning and Decreased Fear Extinction Also Confer Risk to PTSD

It may be tempting to assume that because identical twins share identical inherited genes, any vulnerability to PTSD revealed by twin studies must be genetic. However, these identical twins were also raised together, leading to the possibility that shared childhood environment could be the true explanatory factor. In reality, both the shared genes and the shared environment probably play a role. However, several studies have explicitly examined the contribution of certain genes to PTSD. Interestingly, some of those genes have also been found to explain variance in measures of fear conditioning and extinction. PTSD-associated genes that are also implicated in increased fear conditioning or decreased fear extinction include the serotonin transporter gene (5-HTLPR); dopamine-related genes such as DAT1, DRD2, and COMT; and neuroplasticity-related genes such as BDNF. A review of the genetics of PTSD is beyond the scope of this chapter, but the reader is referred to some of the review articles listed below for more information (Amstadter et al. 2009; Jovanovic and Ressler 2010; Pitman et al. 2012; VanElzakker et al. 2014). A discussion of the stress hormone-related gene FKBP5 is at the end of the chapter.

Exposure Therapy Utilizes the Concept of Fear Extinction

Exposure-based talk therapy is arguably the treatment for PTSD that enjoys the most empirical support, and it is based on the concept of extinction of conditioned fear (Nemeroff et al. 2006). In a safe and supportive environment, an individual with PTSD talks to their therapist about the traumatic event(s), repeatedly and in greater
Increased resting metabolic activity in the dorsal anterior cingulate cortex (dACC) is a vulnerability factor for PTSD. Figure 4 displays information about the nature of resting-state brain activity in PTSD, as measured by positron emission tomography (PET) scanning. All participants were injected with a small amount of weakly radioactive glucose and asked to sit quietly with their eyes closed. The PET scanner is therefore able to detect the areas of the brain that are using energy, referred to as regional cerebral metabolic rate for glucose (rCMRglu). The participants in this study were combat veterans who had identical twins that were not exposed to combat. In about half the twin pairs, the combat-exposed twin had PTSD (“PTSD twin pairs”). In the other half of twin pairs, the combat-exposed twin did not have PTSD (“non-PTSD twin pairs”). Like Fig. 3, the functional image portrays comparative statistical information as opposed to directly portraying biological information. In this case, the image shows the comparison of glucose use in PTSD twin pairs, compared to non-PTSD twin pairs. The arrow denotes an area in the dACC in which the rCMRglu is greater in PTSD twin pairs, compared with non-PTSD twin pairs. The data are superimposed on a template image of many combined structural brain scans. The bar graph shows the average amount of rCMRglu in each of the four groups. Error bars represent standard error of the mean. Unlike fMRI BOLD signal which is only meaningful as a contrast between groups or conditions, PET rCMRglu is meaningful as an independent value (Figure adapted from Shin et al. 2009)
and greater detail. The therapy therefore repeatedly exposes the patient to progressively stronger trauma-related memories and stimuli. This is analogous to Pavlov repeatedly ringing the bell without providing meat powder. Without being reinforced by additional trauma, the conditioned fear responses of the patient should gradually

**Fig. 5** (a) Cortisol travels through the bloodstream and passes through the cell membrane. Glucocorticoid receptors (GR) and mineralocorticoid receptors (MR, not shown here) sit in the cytoplasm and are usually connected to chaperone proteins, including FKBP5. When GR or MR is connected to an FKBP5 protein, it is more difficult for cortisol to bind to the GR or MR. (b) When cortisol binds to GR or MR, FKBP5 detaches. If there is a large amount of FKBP5 protein in the cytoplasm, the GR or MR may become reconnected to FKBP5. Two cortisol-bound GR or MR complexes will connect together. (c) If two GR-cortisol complexes connect, this is called a GR homodimer. If two MR-cortisol complexes connect, this is called an MR homodimer. If one GR-cortisol complex and one MR-cortisol complex connect, this is called a heterodimer. The homodimer or heterodimer will translocate into the nucleus. If an FKBP5 protein from the cytoplasm connects to the homodimer or heterodimer, it is difficult to translocate into the nucleus. Therefore, if there is a large amount of FKBP5 protein in the cytoplasm, translocation is less likely. (d) The homodimer or heterodimer connects to the glucocorticoid response element on the DNA inside of the nucleus. This causes FKBP5 mRNA to be transcribed and then translated into FKBP5 protein. The FKBP5 proteins will sit in the cytoplasm. More FKBP5 protein means that cortisol has more difficulty connecting to GR and MR and that the homodimers and heterodimers will have more difficulty translocating into the nucleus. GR homodimers, MR homodimers, and GR-MR heterodimers all have different effects on DNA and will cause different amounts and types of mRNA and protein to be produced. The proteins affected by homodimer and heterodimer differences include FKBP5, GR, and MR. If the glucocorticoid response element is methylated, certain types of mRNA (and therefore certain types of protein) may not be produced at all.
extinguish. Of course, key deficits in PTSD are the failure of fear extinction learning and its recall, and therefore, this process is difficult and does not always work. Most studies report an average effectiveness of approximately 40–70 % symptom reduction (Nemeroff et al. 2006), but some PTSD patients do not respond to exposure therapy at all, often because they drop out. There are several features of fear extinction learning that also explain why PTSD is such a difficult clinical problem. Specifically, the three extinction phenomena discussed above – renewal, spontaneous recovery, and reinstatement – each relate to relatively common clinical phenomena in PTSD patients.

An individual may spend hours, weeks, and even years in a therapist’s office, talking about their traumatic experience in great detail, effectively extinguishing conditioned fear association for any cues that remind him of the trauma. But the phenomenon of renewal tells us that such extinction is context dependent (Maren et al. 2013). In other words, the extinction will only be effective in the therapist’s office. Everywhere else, the fear association “wins” and the safety association “loses.” Practically speaking, this is not strictly true, and the positive effects of exposure-based therapy can generalize to other contexts. Nevertheless, the extinction association will always be strongest in the context in which it was learned. For this reason, therapists have tried strategies such as conducting therapy in multiple contexts including home visits, computer-based virtual reality, or visits to the site of the traumatic experience. The fact that the therapeutic context must be safe to be effective explains why PTSD is such a severe problem in places marred by ongoing violence, military occupation, or recurrent natural disasters. Spontaneous recovery manifests in that minority of individuals (less than 25 % of people with PTSD) with “delayed-onset PTSD,” in which symptoms do not emerge until 6 months or more after the traumatic event (APA 2013). The phenomenon of reinstatement can be seen if individuals who have recovered from PTSD experience another highly stressful event, even if it is unrelated to their original trauma. One published article reported a case of a WW2 veteran who had experienced nightmares and flashbacks for one year after the war, at which point the symptoms stopped (Pitman 2011). After being symptom-free for 30 years, the veteran went to a doctor for unrelated back pain, and that checkup revealed a fatal cancer diagnosis. The night after the cancer diagnosis, the patient again experienced nightmares – not of cancer but again of his WW2 combat experiences. This is a powerful demonstration of the fact that his traumatic memories were not ever erased, but had rather gone into a fragile latency and could be reinstated by stress.

Reconsolidation Provides Hope for Weakening Traumatic Memories During Their Recall

Renewal, spontaneous recovery, and reinstatement are each extinction learning-related phenomena demonstrating that the reduction in fear responses occurring after extinction involves new learning of a competing safety association, as opposed to a weakening of the fear memory. However, there is an extinction recall-related phenomenon called reconsolidation that has shown some promise as a mechanism by which the weakening of a fear memory actually can be induced (Nader and Hardt
Rodent research has revealed that when a memory is recalled, it enters a temporarily labile state and must be “reconsolidated” back into long-term memory. An implication for PTSD symptom maintenance is that each time a PTSD patient recalls their traumatic experience, that memory is open to alteration, which could be part of why memory for the traumatic event is often skewed and inaccurate in PTSD, for example, incorrectly remembering that it was their own fault when it actually was not. However, a treatment implication of reconsolidation is that when a PTSD patient describes their traumatic experience during exposure therapy, the memory is temporarily vulnerable to disruption and weakening with targeted drugs. Pharmacological disruption of conditioned fear during its recall is an active area of preclinical PTSD research, especially in rodent models. Research has included attempts to activate NMDA receptors (described above) or block beta-adrenergic receptors during fear memory reconsolidation. The next generation of neuroscientists may discover a way to exploit reconsolidation to ease the intensity of traumatic memories for millions of people suffering from PTSD.

Beyond the Fear Conditioning Model of PTSD

The Fear Conditioning Model of PTSD Is Helpful but Incomplete

The neurocircuitry of PTSD, as described above, clearly supports the fear conditioning model of PTSD. As one might expect from the symptoms, individuals with PTSD have dysfunction in brain structures involved in fear learning, fear expression, emotional and cognitive control, and memory. However, two important caveats must be described. First, it is almost certainly the case that other structures are also important in the development and maintenance of PTSD. Abnormalities in other structures such as the thalamus, brain stem, and cerebellum have been reported but are understudied in PTSD for a number of reasons including limitations of neuroimaging methods. Second and perhaps most importantly, the fear conditioning model of PTSD does not explain all psychological symptoms or biological observations in PTSD. For example, the fact that the insular cortex is consistently more responsive in PTSD is evidence that the fear conditioning model is incomplete, because the insular cortex is considered to be an important structure in monitoring internal states such as ongoing anxiety, but is not considered central to fear conditioning or extinction. Intrusive reexperiencing symptoms are perhaps the defining characteristic of PTSD and can be explained by the fear conditioning model. However, individuals with PTSD continue to experience hyperarousal and anxiety symptoms even in the absence of trauma reminders, and these symptoms may be better explained by a general sensitization of the nervous system than by associative fear conditioning (Pitman et al. 2012; Zoladz and Diamond 2013). Evidence for such sensitization includes increased autonomic arousal (skin conductance, heart rate, startle response, etc.) in PTSD. The development of PTSD may also be associated with a shift from the cortical pathway to the subcortical pathway (discussed earlier, see Fig. 1). This shift could explain why sensory reminders of trauma like cologne or
fireworks could immediately trigger a fear response in individuals with PTSD: the detailed and nuanced sensory processing of the cortical pathway is skipped in favor of fast fear-response reactions.

Other evidence for nervous system sensitization in PTSD include endocrine abnormalities that suggest an overly responsive sympathetic nervous system (Pitman et al. 2012; Zoladz and Diamond 2013). This includes increased norepinephrine responses to stress, which may be related to lower levels of neuropeptide-Y, which inhibits norepinephrine. Allopregnanolone is a steroid hormone that induces the inhibitory neurotransmitter GABA and also inhibits the stress hormone system. Some studies have found that the levels of allopregnanolone are reduced in people with PTSD.

People with PTSD Are More Sensitive to Stress Hormones

While it may seem intuitive that individuals with PTSD have more of the stress hormone cortisol in their blood, this is not the case—in fact, early studies seemed to support the hypothesis that PTSD was associated with reduced circulating cortisol. Subsequent studies have failed to consistently support these early findings, and it is probably the case that circulating cortisol levels in PTSD are affected by age at trauma, time since trauma, type of trauma, comorbidity of depression or head injury, and other factors. However, there is consistent evidence that individuals with PTSD are more sensitive to the effects of the stress hormone cortisol (Yehuda 2009). This evidence comes from studies of the dexamethasone suppression test. For background information on the stress hormone system and the dexamethasone suppression test.

When an individual experiences a subjectively stressful event, the brain initiates the neuroendocrine stress response of the HPA axis (hypothalamic–pituitary–adrenal axis). First, neurons of the paraventricular nucleus (PVN) of the hypothalamus produce and release corticotrophin-releasing hormone (CRH, sometimes called CRF for corticotrophin-releasing factor) into the bloodstream that supplies the anterior pituitary. When CRH reaches the anterior pituitary, it induces the release of adrenocorticotrophin hormone (ACTH) into the body’s general blood circulation. When ACTH reaches the cortex of the adrenal glands that sit on top of the kidneys, it triggers the production and subsequent release of the steroid hormone cortisol. The HPA axis has a built-in “off switch” in the form of a negative feedback loop: cortisol from the adrenal glands circulates through blood back to the brain and pituitary gland, where it shuts off CRH and ACTH, respectively. This is referred to as glucocorticoid negative feedback because cortisol is a type of glucocorticoid steroid hormone. To test the function of this system, a doctor or scientist can inject a patient with a synthetic form of cortisol called dexamethasone. If the negative feedback system is working, the dexamethasone injection should cause the levels of ACTH and cortisol in the blood to decrease (injection of cortisol would have the
same effect, but dexamethasone is used instead so that cortisol can be measured). This is the dexamethasone suppression test. Several studies have found that compared to control groups, individuals with PTSD show greater dexamethasone suppression of ACTH and cortisol (Yehuda 2009). Because dexamethasone mimics cortisol, this is evidence that individuals with PTSD are more sensitive to the effects of cortisol.

The fact that people with PTSD are more sensitive to cortisol has interesting implications for PTSD. Released during a stressful experience (and also naturally in a daily rhythm, peaking in the morning), cortisol passes easily through cell membranes and has effects on many body systems, including preparation for energy use to help the body cope with the sympathetic arousal experienced during stress and suppressing the immune system to save energy. Importantly for PTSD, it also passes through the blood–brain barrier and has direct effects on the brain, including interacting with the stress-related neurotransmitter norepinephrine (including via beta-adrenergic receptors, mentioned earlier) to enhance fear memory consolidation in the amygdala (McGaugh 2004). It makes sense that part of the body’s response to danger should be to enhance memory, so that danger can be avoided in the future. The interaction in the amygdala between norepinephrine and cortisol may be an important part of why individuals with PTSD show enhanced fear conditioning. As with other hormones and neurotransmitters, cortisol has its effects because cells contain receptors for it.

**Glucocorticoid Receptor Function Is a Possible Mechanism for Increased Sensitivity to Cortisol in PTSD**

The vmPFC and hippocampus are brain structures with high levels of receptor for the stress hormone cortisol. The most common receptor for cortisol is the glucocorticoid receptor (GR), which is in most cells of the body, but within the brain is particularly concentrated in the vmPFC. The second most common receptor for cortisol is the mineralocorticoid receptor (MR), which is most concentrated in the kidneys and in the hippocampus. In the hippocampus, both GR and MR often appear together in the same cell. Recall that the vmPFC and hippocampus act as the “brakes” on fear responses during fear extinction, interacting to form a context-dependent “safety” association that competes with the fear association. The vmPFC and hippocampus are also the two brain structures most likely to be smaller in PTSD. Together with the evidence of cortisol–norepinephrine interactions in the amygdala described above, these findings point to an abnormal response to cortisol as a potentially important part of enhanced fear conditioning and decreased fear extinction capacity in PTSD.

There is evidence of GR alterations in PTSD. GR has been studied much more than MR, and it is still unknown whether MR is altered in PTSD. Researchers have taken advantage of the fact that GR is in most cells of the body by extracting white
blood cells from the blood of people with PTSD, in order to study GR function within those cells. The function of GR within white blood cells is assumed to be largely similar to their function in brain cells. Such studies have provided evidence that alterations in GR explain the enhanced sensitivity to cortisol in PTSD (van Zuiden et al. 2013). For example, a prospective study took blood samples from soldiers before they left for combat. After combat, the soldiers were assessed for PTSD symptoms. The amount of GR in white blood cells before combat predicted PTSD symptoms after combat. This study provides the intriguing possibility of a blood test for PTSD vulnerability. Interestingly, low expression of a gene called \textit{FKBP5} in the white blood cells taken before combat also predicted PTSD symptoms after combat. The function of the FKBP5 protein, which is the product of the \textit{FKBP5} gene (genes are italicized, proteins are not), may explain why individuals with PTSD are sensitive to cortisol. Again, some background information is necessary first.

Within cells, the GR and MR proteins sit in the cytoplasm (there is some controversy over whether they also sit on the cell membrane surface but that will not be addressed here). Cortisol is lipophilic and passes easily through membranes into the cytoplasm, where it contacts GR or MR. But while sitting in the cytoplasm before coming in contact with cortisol, GR and MR are normally connected to several chaperone proteins, including the FKBP5 protein. When GR or MR binds with cortisol, the receptor protein detaches from the chaperone proteins and translocates into the cell’s nucleus. In the nucleus, the cortisol–receptor complex attaches to DNA, at locations called glucocorticoid response elements. There, GR and MR act as transcription factors, with the ability to turn on or off a host of genes, producing their messenger RNA (mRNA) which then can produce their protein products. This is how cortisol has its effects: its receptors are hormone-dependent transcription factors that affect other genes.

The effects of the FKBP5 protein on GR may explain differences in sensitivity to cortisol. When FKBP5 is connected to GR, it reduces the affinity with which GR is bound by cortisol and also makes it more difficult for the GR–cortisol complex to translocate to the nucleus. In other words, FKBP5 inhibits the ability of cortisol to function via GR (and, we assume, also MR). A larger amount of FKBP5 protein in the cytoplasm means that GR function is more likely to be inhibited. One of the genes induced by the GR–cortisol transcription factor is \textit{FKBP5} itself. The increased FKBP5 protein inhibits GR function, functioning as an intracellular negative feedback loop. If a particular person produces less FKBP5 protein, they may be more sensitive than usual to the effects of cortisol because their GR would not be inhibited from binding with cortisol or from translocating into the nucleus. As described earlier, soldiers with lower \textit{FKBP5} mRNA expression in their white blood cells before combat had more severe PTSD symptoms after combat. This is evidence that less FKBP5 protein was being produced, and therefore, GR was uninhibited — leading to increased sensitivity to cortisol. The specific reason that increased cortisol sensitivity leads to PTSD symptoms is not yet understood, but as described above, it may be at least partially due to cortisol’s effects on the amygdala, vmPFC, and hippocampus.
Epigenetic Changes to DNA May Be the Reason that Previous Trauma Is a Vulnerability Factor for PTSD

Many of the functional changes to neurocircuitry and the HPA axis that make a person vulnerable to PTSD probably exist from the moment of birth. As described earlier, inherited genes are part of vulnerability to PTSD. But perhaps the most profound risk factor for PTSD is a history of previous traumatic experiences such as childhood abuse. Even independently of inherited genes, childhood adversity predicts PTSD following an adult traumatic experience. How could this be? How could childhood experiences lead to the kind of long-lasting biological changes that affect a person’s response to traumatic stress years later? For example, how could the reduced FKBP5 gene expression (and therefore reduced production of the FKBP5 protein) that leads to disinhibition of GR function be the result of experience? The answer may lie in the field of epigenetics, the study of external (as opposed to inherited) effects on genes. Epigenetics is the study of changes to chromosomes that occur without changing DNA sequence.

Methylation and chromatin remodeling are two types of epigenetic changes that happen directly to the DNA molecule as the result of life experiences. Methylation is the attachment of a methyl group (one carbon and three hydrogen atoms) to DNA. Methylation of the promoter (“on switch”) of a gene is a relatively common epigenetic mechanism that silences that gene. In contrast, demethylation un-silences genes. Rat research has demonstrated that early life experiences can alter DNA methylation states, leading to permanent changes in behavior and HPA axis function. Methylation often works in concert with chromatin remodeling, a process that physically alters DNA architecture, changing its function by exposing or hiding genes. These long-lasting changes can be due to environmental experiences, making epigenetics a compelling candidate to explain the mechanisms of how previous traumatic experiences such as childhood abuse could interact with inherited risk to increase vulnerability to PTSD. Such a vulnerability then interacts with adult traumatic experience, and PTSD emerges.

Several studies have found PTSD vulnerability explained by an interaction between FKBP5 and childhood adversity (Mehta and Binder 2012). For example, out of four different inherited forms of FKBP5, one particular form of FKBP5 moderated the risk of PTSD associated with a history of childhood abuse in African-Americans. Interestingly, when African-Americans with a particular form of this allele had no history of childhood adversity, they had the lowest risk of PTSD, but allele carriers with a history of childhood adversity had the highest risk for PTSD (Xie et al. 2010). Other studies have also reported on FKBP5 alleles that did not themselves predict PTSD, but rather interacted with childhood trauma to predict vulnerability to PTSD (Mehta and Binder 2012). Interestingly, the epigenetic modifications to DNA caused by childhood stress occur near glucocorticoid response elements, the section of DNA where the cortisol–GR complex attaches after it translocates to a cell’s nucleus. Because the FKBP5 gene is itself transcribed by the cortisol–GR transcription factor, the methylation of glucocorticoid response elements could be the reason for decreased FKBP5 gene expression. Fascinatingly, some epigenetic changes due to trauma may persist across generations.
Outlook

There is no cure for trauma, and no therapy or medicine can make life simple and free of adversity. All of our minds contain painful memories from the past, and we do our best to learn our lessons and grow. But in some people, the memory of trauma is a source of unrelenting and continuous suffering, even decades later. Easing the suffering of people with PTSD is the ultimate goal of research into the neuroscience of PTSD. Impressive advances have been made toward this goal.

This chapter mentioned exposure therapy, but other types of therapy have also been studied and found to be effective (Nemeroff et al. 2006). Most forms of talk therapy for PTSD still have fear extinction as the root mechanism. There are also several drugs that are used to treat PTSD. For example, serotonin reuptake inhibitors (SRIs) and drugs that block alpha-1 or stimulate alpha-2a adrenoreceptors have been found to ease PTSD symptoms in some people. In general, combining drug therapy with exposure-based talk therapy works better than drugs alone. One area of research is to discover other options for drugs that can help people with PTSD when they are taken every day. Another major goal of PTSD research is to discover adjunct or supportive interventions that would work to enhance extinction learning or weaken conditioned fear (via reconsolidation) during exposure therapy. Such treatments would be paired with sessions of extinction therapy as opposed to being used every day. Drugs that block beta-adrenergic receptors and drugs that enhance NMDA receptor action are being studied in PTSD because they were found in rodent models to enhance fear extinction learning or disrupt fear memory reconsolidation. Other interventions such as vagus nerve stimulation, transcutaneous magnetic stimulation, biofeedback, cannabinoids (medical marijuana), oxytocin, or glucocorticoid therapy have shown some promise in enhancing fear extinction learning in healthy humans or rodent models and may be used in the future for enhancing exposure therapy in PTSD. While the human family should work toward making therapeutic medical devices and drugs available to everyone who needs them, the reality is that those things are expensive and that some of the most traumatized human beings are also some of the poorest. Therefore, an important area of research will be to create a better understanding of whether cost-free interventions such as mindfulness meditation, concentration exercises, and even diet can help mitigate PTSD symptoms. A related goal is PTSD education after natural disasters or political violence.

There are already many treatments for PTSD, but not all are effective for all people. Often, a person with PTSD will try some particular form of therapy for several months before it becomes clear that the therapy is not working. This has great costs in terms of medical resources and human suffering. Therefore, an important area of ongoing research is in treatment prediction. There has been some progress in using pretreatment functional and structural neuroimaging to predict talk therapy and drug therapy treatment response in PTSD and other anxiety disorders (e.g., Shin et al. 2013). However, functional brain imaging is expensive and labor intensive, and structural brain imaging is only slightly less so. In the future, clinicians may be able to use inexpensive blood tests, behavioral tests, or psychophysiological tests to determine which type of therapy will work best for a particular person with PTSD.
Many of the abnormalities seen in PTSD are not necessarily specific to PTSD and are shared by other anxiety disorders (e.g., Shin and Liberzon 2010) or other forms of mental illness. Childhood trauma is a vulnerability factor for PTSD, but is also a vulnerability factor for depression. Epigenetic effects on the \(FKBP5\) gene due to childhood trauma are associated with risk for both PTSD and depression. PTSD and depression very frequently occur together. However, interestingly, the function of cortisol seems to be opposite in PTSD and depression with glucocorticoid sensitivity in PTSD as opposed to glucocorticoid resistance in depression. This complex paradox is filled with unanswered questions for future researchers and argues against treating different forms of mental illness as separate categories.

Perhaps no form of psychopathology has undergone such a rapid growth in understanding as PTSD. After millennia of renaming, misunderstanding, and mistreating PTSD, less than 40 years of research into the neuroscience of PTSD has resulted in it being one of the better-understood forms of mental illness. In this short chapter, I have only discussed a fraction of the neuroscience and biology of PTSD. PTSD is a complex condition with effects on the brain, endocrine, immune system, cognitive, sleep, and other systems. For more information, the reader is directed to some of the excellent review articles referenced below.

**References**


