

Jacek Debiec and Joseph LeDoux

Fear and the Brain

FEAR IS A NATURAL PART OF LIFE. IT OCCURS WHENEVER WE ARE THREATENED. Threats come in many forms. A snake on the ground in front of you is a biologically prepared threat, and so is being face-to-face with an angry human. Evolution has put this kind of information into our brains as a way of dealing with recurring and common themes. When we encounter them we have the familiar fight/flight response. But not all threats are genetically programmed. Most of the things that make us afraid are things we have learned about in our lives.

Biological research over the past two decades has made considerable progress in understanding how the brain learns about danger. Most of this work has been conducted in animals. For some people, words like "biological," "brain," and "animals" imply genetic predetermination. But this is not true. First of all, *biological* does not mean genetic. Nurture is just as much a part of biology as nature. The research we will describe in this paper in fact is all about how we learn to be afraid through experience. Second, it is important to realize that the *brain* is a rich source of information about human nature. By studying psychology through the brain, we can discover things about the mind that we cannot learn by studying the mind alone. Third, much of the progress in understanding the brain basis of psychological functions has come from studies of *animals*. This is certainly true of fear. While animals are not people, the brain and body of animals, like rats, respond similarly to the human brain and body when threatened. Muscles tense. Blood pressure rises. Stress hormones are released. This is all part of the physiological solu-

tion of how to rapidly deal with a threat. These responses, however, can also occur in anticipation of something that might happen—in which case we tend to call it anxiety rather than fear.

What does the tension of muscles or the rise of blood pressure in a rat have to do with fearful feelings in humans? Actually, quite a lot. Every animal has to have the ability to detect and respond to threats. Otherwise, it could not make it through the day. This is the job of the brain's defense system. However, a subjective feeling of fear can only occur in animals that have the capacity to be aware of their own brain's activities. Fear, in other words, is the feeling that results when the defense system is active in a brain that has the capacity for self-awareness. This undoubtedly occurs in humans. Whether it occurs in other creatures is not known, and may be unknowable. But if activation of the defense system is a key component of the neural basis of fearful feelings, and the defense system works similarly in rats and people, then studies of the defense system in rats tells us about an important system underlying human feelings of fear.

Even without this theoretical link to fearful feelings, studies of fear behavior in rats are still important. This work, as we will see, has identified a brain region called the amygdala that is essential for fear learning in rats. This same region is known to be altered in fear disorders in humans, including post-traumatic stress disorder (PTSD), panic disorder, and phobia, as well as other conditions, including depression, autism, and schizophrenia. We will summarize in this paper some of what has been discovered about the defense system through studies of fear learning in rats.

HOW IS FEAR LEARNING STUDIED IN RATS?

Much work on fear has involved fear conditioning, a variant on the conditioning procedures developed by Pavlov (1927). In fear conditioning a relatively neutral event (a conditioned stimulus, CS), such as tone or light, is paired with an aversive event (an unconditioned stimulus, US), such as electric shock. After pairing with the US, the CS acquires an ability to elicit behavioral, autonomic, and endocrine responses. These

responses are expressed automatically in the presence of danger. Fear conditioning occurs in a variety of species, ranging from flies, worms, and snails to fish, reptiles, and birds to mammals, including people.

Several aspects of learned fear are important to keep in mind as we explore the neural basis of this form of learning. First, fear conditioning occurs quickly. Quite often, a single CS-US pairing is sufficient to establish a memory. In the wild, rapid identification of a threat followed by efficient behaviors boosts chances of survival. Second, once acquired, fear learning remains accessible throughout the life of an animal. Survival is also enhanced if danger, once learned about, does not have to be relearned. Third, defensive responses to stimuli previously associated with physical harm sometimes weaken through experiences that show that the stimulus is no longer harmful. However, the original learning can often be recovered either spontaneously or as a result of stressful events months or years after they have been weakened. Fourth, fear motivates other kinds of behaviors, such as avoidance and approach. Once these behaviors get ingrained, they become part of their own reality, determining the behavioral patterns of an individual.

HOW DOES FEAR CONDITIONING WORK IN THE BRAIN?

The anatomical pathways underlying the acquisition of conditioned fear have been extensively studied in recent years. Much of the evidence comes from studies involving the auditory modality (auditory fear conditioning) in rats, which we will focus on here. Information about the conditioned stimulus is transmitted through the sensory pathways to the thalamus and cortex, and from each of these brain regions to the amygdala. These two independent sensory inputs into the amygdala are differentially involved in fear processing (LeDoux, 1996). The “low road” or thalamic pathway provides the amygdala with a rapid but imprecise representation of the sensory input, while the cortical path or “high road” conveys a more complex representation based on cortical computations.

The amygdala (the Latin word for almond) was named after its almond-shape by the anatomist Burdach in 1819. It is located deep

inside the temporal lobe and consists of several distinct groups of cells organized in nuclei. Numerous studies have led to the conclusion that damage to the amygdala interferes with the acquisition and expression of conditioned fear. It does not matter what kind of stimulus you use to turn the amygdala on, it does not matter what kind of response you measure as fear response, and it does not matter what kind of animal you do the experiment on, as long as that animal has an amygdala, the amygdala is involved in fear processing. The regions of most relevance to fear conditioning are the lateral (LA), basal (B), accessory basal (AB), and central (CE) nuclei of the amygdala.

The LA is responsible for linking the information about the neutral tone with that of the US (usually a mild shock to animal's feet), which is conveyed through the nociceptive or pain pathways. The LA, in turn, sends fibers to the CE, which projects to a variety of structures in the brain controlling fear behaviors and accompanying autonomic and endocrine responses. The CE also receives efferents from the basal and accessory basal nuclei, which in turn receive inputs from LA. But in addition to providing an additional link between LA and CE, these receive inputs from higher cortical areas. For example, connections from the hippocampus to B and AB may convey information about the spatial context in which the CS and US occur.

A key aspect of memory formation during fear conditioning involves the convergence of information about the auditory CS and the nociceptive US in the LA. Through this pairing, the tone gains access to the emotional response circuits controlled by CE.

Recent studies also provide some insight into the cellular and molecular mechanisms underlying fear conditioning (for a summary see LeDoux, 2002; Blair et al., 2001; Schafe et al., 2001; Maren, 2001). When individual cells that process the CS are simultaneously activated by the strong US, the processing of the CS in LA is modified in such a way that it more effectively drives the output cells that control fear responses. This plasticity of CS processing is triggered by the entry of calcium into synapses on the distal dendrites of LA cells through two sources: the NMDA class of glutamate receptors and voltage-gated

calcium channels. The resulting elevation in calcium, in turn, leads to the activation of certain protein kinases (especially calcium/calmodulin kinase, mitogen activated kinase, and protein kinase A). These then move into the cell nucleus and lead to gene expression and protein synthesis. The proteins are then shipped back to the recently active synapses, where they lead to a strengthening of the ability of the CS inputs to activate those synapses. This process of memory formation is commonly referred to as memory consolidation (McGaugh, 2000).

The traditional view of memory consolidation is based on the idea of protein synthesis. In this model of learning, we store information and then, each time we retrieve information, we are retrieving what we initially learned. However, a new perspective of memory has emerged from recent studies. According to these developments, whenever the memory is retrieved it renders protein synthesis dependent again and undergoes *re*-consolidation (Nader, Schafe, and LeDoux, 2000; Debiec, LeDoux, and Nader, 2002). In this view, we learn, we store, we retrieve, and when we retrieve the next time, we are not retrieving the original experience—we are retrieving our last retrieval. In other words, upon retrieval a new memory is formed. It has been proposed that the major role of reconsolidation is to strengthen or to update the memory (Sara, 2000; Dudai, 2004). The discovery of these dynamic processes may help to explain why the memory is vulnerable to the experience we have in the meantime. Furthermore, it paves the way for selective memory manipulation in patients suffering from debilitating, intrusive memories of trauma.

WHAT ARE THE IMPLICATIONS OF FEAR LEARNING IN THE RAT BRAIN FOR NORMAL AND PATHOLOGICAL HUMAN FEAR?

A growing number of studies have also suggested an important role of the amygdala in human fear. Damage to areas of temporal lobe including the amygdala (LaBar et al., 1995) or to the amygdala alone (Bechara et al., 1995) impairs fear conditioning in humans. Brain imaging studies of the human brain demonstrate increased func-

tional activity of the amygdala during fear conditioning (LaBar et al., 1998; Morris, Buchel, and Dolan, 2001). Recent work suggests that this augmented firing correlates with activity in the thalamus but not the cortex (Morris and Dolan, 2004; Pasley, Mayes, and Schultz, 2004). The thalamic input into the amygdala thus appears to play an essential role in fear processing in humans, as it does in animals. It has important implications for our understanding of fear. While the “high” cortical route is generally believed to be necessary for conscious identification of the stimuli, the “low road” conveys rough information sufficient and critical to trigger fear responses beyond the grasp of conscious awareness. Imaging studies also reveal that subliminal presentations of dreadful stimuli lead to stronger activations in the amygdala than do explicit threads (Whalen et al., 1998).

While the amygdala is implied in fear learning and the storage of implicit fear memory, the hippocampus is thought to be a part of the system, which is responsible for the acquisition of declarative memory in the human brain (Phelps, 2004). Thus, a person with selective damage to the amygdala and with an intact hippocampus fails to acquire conditioned responses to fearful stimuli, but does learn the facts about conditioning, while damage to the hippocampus alone impairs explicit learning, but not implicit fear acquisition (Bechara et al., 1995). Distinct systems in the human brain are involved in learning and storage of declarative and implicit knowledge about dangerous events. Furthermore, the underlying brain structures, the amygdala, and the hippocampus differently respond to stress. Chronic exposure to stress leads to the atrophy of hippocampal neurons (McEwen, 1999) and to the hypertrophy of the amygdala (Vyas et al., 2002). These findings may account for several behavioral manifestations. Individuals who suffered from severe traumatic experiences can sometimes develop amnesia for the event but at the same time they may have enhanced emotional responsiveness to the trauma-related stimuli.

Clinical studies reveal the importance of the amygdala in emotional life. Specifically, the amygdala has been implicated in several fear disorders in humans, including PTSD, specific and social phobia,

and panic disorder, as well as in major depression and schizophrenia (Gorman et al., 2000; Pitman, Shin, and Rauch, 2001; Kent and Rauch, 2003). Therefore, it has been proposed that the neural circuits of normal fear are dysfunctional in fear disorders, and that similar malfunctions may account for the overlapping symptoms and frequent comorbidity of psychopathological conditions (Stahl, 2003).

However, the amygdala is not the only region involved in fear regulation. Experiments in rats have implicated the medial prefrontal cortex in extinguishing fear conditioning responses (Morgan, Romanski, and LeDoux, 1993; Milad and Quirk, 2002). Based on animal models, PTSD, a condition characterized by persistent, intrusive re-experiencing of past traumatic events, has been considered to be a result of a failure of cortical inhibition over the hyperactive amygdala (Shin et al., 2004). Indeed, recent brain-imaging studies of PTSD subjects demonstrate hyperactivity of the amygdala and hypoactivity of the medial prefrontal regions in response to fearful stimuli (Shin et al., 2004; Gilboa et al. 2004). Stress-induced alterations in medial prefrontal cortex might predispose certain individuals to learn fear in a way that is later difficult to extinguish (LeDoux, 2000).

CAN WE LEARN ABOUT THE POLITICAL USES OF FEAR FROM STUDIES OF FEAR LEARNING IN THE BRAIN?

Politics involves social relations, authority, power, and decision making. There is no question that fear can contribute to these phenomena. Fear has been traditionally recognized as one of the fundamental forces that shape human life. According to Thomas Hobbes, fear as a shared emotion was even a grounding point for public life (Hobbes, 1996). Hobbes believed that having control over human fears meant holding power in the society. Although Hobbesian philosophy has been critically revised (Blits, 1989), the intersections of fear and politics still remain a significant field of interest (Robin, 2004).

How then can brain studies contribute to our understanding of the political uses of fear? Although the humanities and natural sciences, using different theoretical backgrounds and methodologies, analyze