Title
Fear: A Blessing and Curse

Journal
Berkeley Scientific Journal, 19(1)

ISSN
1097-0967

Author
Koti, Shruti

Publication Date
2014

DOI
10.5070/BS3191025158

Undergraduate

Fear: a Blessing and Curse

Shruti Koti

Imagine a lone adventurer standing at the edge of a cliff, miles away from civilization. He looks down at the unknown below and, taking a deep breath, jumps, attached to nothing but a single bungee cord. He feels the wind in his face, his clothes billowing up above him, and something else: a hollow pit in his stomach and the terrifying feeling that he may die at any moment. It sounds extreme, but what he is feeling is something we have all experienced, and it is completely natural: fear. To jump, the bungee jumper had to overcome his fear of heights, a fairly common fear as far as phobias go. However, grappling with fear is not always this easy.

The reason we feel fear is not a mystery – evolutionarily, it puts you on guard and reduces your likelihood of getting attacked. Bats have evolved echolocation to detect and catch their prey; moths in turn have evolved echolocation and evasive flight maneuvers. Noctuid moths, which are eaten by bats, respond to bat echolocation in three ways: a startle response, sonar jamming, and acoustic aposematism (Yager, 2012).This is a prime example of how in a predator-prey relationship, there is an evolutionary arms race in which prey is usually better adapted for exaggerated caution. This basic fear response forms the biological foundation for human anxiety disorders.

Early learning theory hypothesized that stimuli that became associated with fears were equipotent, i.e. every stimulus had an equal chance of becoming a feared stimulus (Carey, 1990). However, in practice, the limited range of common fears – heights, enclosed spaces, and certain types of animals (snakes, spiders) – led theorists to favor the concept of prepotency or preparedness, which states that we are biologically predisposed to certain fears, or "primed" to automatically select certain evolutionary stimuli.

Fear is a complicated term because it can refer to both an emotion and a physical response to a stimulus. A stimulus is an object or event that promotes a fear response (increased heartbeat, freezing, etc.). Then fear conditioning is the behavioral process that leads organisms to predict and react to adverse events or stimuli – this refers to the natural fear acquisition process, too, not just processes occurring in laboratories. Conditioning occurs if the probability of the unconditioned stimulus (US) in the presence of the conditioned stimulus (CS) is different than it its absence. One of the most famous examples of classical (Pavlovian) conditioning was an experiment in which a little boy was conditioned to fear white rats. Initially, he showed no fear of a white rat, the neutral stimulus. Then the rat was continuously presented along with loud, unpleasant sounds – here the sounds were the unconditioned stimulus. By repeatedly pairing the rat with the unconditioned stimulus, the white rat (now the conditioned stimulus) came to evoke a fear response (the conditioned response) in the child (Jones, 1924).

In general, a selective associative model shows four basic characteristics shaped by evolution: selectivity with regard to input, or threatening stimuli; automaticity, the triggering of a response in the absence of conscious awareness; encapsulation, the resistance to conscious cognitive influences; and specialized neural circuitry, the module controlled by a specific neural circuit that has been shaped by evolution (Hofmann, 2008).

"...we are biologically predisposed to certain fears, or "primed" to automatically select certain evolutionary stimuli."

In expressing fear, exposure to acute stress triggers the "fight or flight" response, stimulating activity in the hypothalamic-pituitary-adrenal (HPA) axis, the locus coreruleus, noradrenergic systems, and the neurocircuitry of the fear system. The fear circuitry includes the amygdala and its subnuclei, the nucleus accumbens, the hippocampus, ventro-medial hypothalamus, periaqueductal gray, several brain stem nuclei, thalamic nuclei, insular cortex, and some prefrontal regions. Some regions, however, play a more prominent role in fear circuitry.

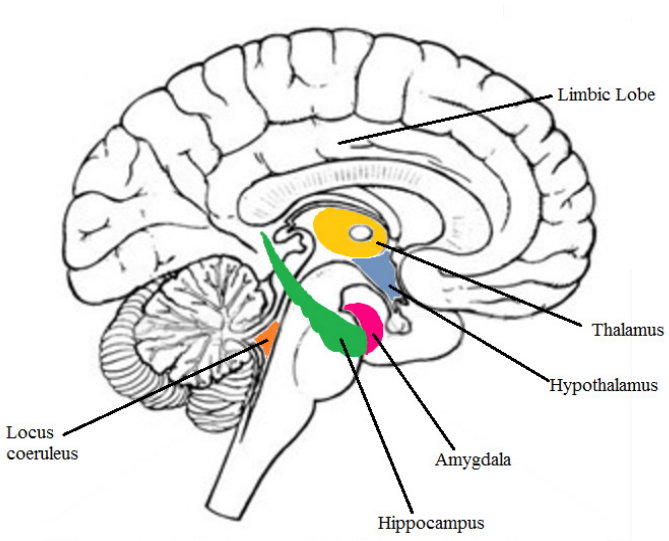
The forebrain structures that have expanded the most in evolution are the prefrontal cortex and the amygdala. It has been shown that damage to the right and left amygdala disrupts fear conditioning: the right correlates with expression of learning, and the left hemisphere is involved in tasks that require cognitive interpretation of stimuli (Delgado et al, 2008). There are extensive connections between the amygdala and the visual system, consistent with behavioral, lesion, and neuroimaging data which show that the amygdala tunes visual brain areas for effective perception of fear-related stimuli (Öhman, 2009). Sensory information reaches the amygdala by two pathways. The first involves classical sensory

nerve bundles connected from peripheral sensors to sensory thalamic nuclei, then onto specific sensory cortices, eventually activating the amygdala. The second, the low road pathway, details a direct link to the amygdala from the thalamus without cortical processing.

The amygdala is arguable the most important component of the expression and processing of fear in fear circuitry, and as such is supported by the activity of other regions. The rodent analogue to the medial prefrontal cortex in humans, the infralimbic prefrontal cortex, shows enhanced activity following learning of an extinguished CS, and it also inhibits a fear response (Jovanovic and Ressler, 2010). The hippocampus is involved in contextual processing. Additionally, the fear or anxiety neurocircuitry overlaps with the neurocircuitry that brings about a stress response. The stress system leads to the activation of the limbic-hypothalamopituitary-adrenal axis (LHPA), and the secretion of several stress hormones. However, the activation of fear does not necessarily activate a LHPA stress response, and, inversely, the activation LHPA axis is not necessarily experienced as fear or anxiety – it is also activated with waking up, food intake, and nausea. In general, while fear itself may only involve subcortical areas of the brain located primarily in the limbic circuitry (including the amygdala, thalamic nuclei, and hippocampus), associated processes also involve cortical, cognitive components.

Over time, the conditioned response to a CS may decrease, and the process by which a CS previously predicted a US no longer occurs. This is process is called extinction, and is caused by changes in expectancies and contingency beliefs that are stored in long term memory – specifically, a reduction in the strength of the CS-US expectancy. While fear conditioning involves new learning in the amygdala, extinction learning occurs in the medial prefrontal cortex, regulating amygdala activity. Gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, is altered differently in fear acquisition and extinction, which illustrates that the two processes act in opposing ways. Gephyrin, a scaffolding protein involved in inserting GABA into the surface membrane of a cell, decreases at the protein and mRNA level in the amygdala following fear learning, but increases with extinction learning (Jovanovic and Ressler, 2010). Extinction was initially assumed to be an automatic, unconscious process, but these molecular pathways show that it is actually a new form of learning (not forgetting) that changes the CS-US relationship, so that the CS no longer elicits a fear response. Experimentally induced fear responses can be eliminated by telling subjects that the US will no longer follow the CS, or by adding a stimulus that acts as a "safety signal."

We all have the same basic structures in our nervous systems, but we are not all afraid of the same things. What, then, causes differences in why our fear responses are expressed? Certain experiments have provided evidence to suggest that fear is genetically influenced. In a basic twin model, with phenotype differences from 4 sources,



monozygotic (MZ) and dizygotic (DZ) twin pairs were studied for additive genes (A),[2] genetic dominance (D),[3] common/familial environmental factors (C), and individual specific environmental factors (E). The best fit model showed that there were 2 additive genetic influences, and no familial environmental sources of variance, though individual factors did play a role (Hettema et al, 2003). This study helped show that fear conditioning is moderately heritable in humans, though it may differ in evolutionary stimuli and neutral stimuli. It is important to keep in mind, however, that fears and phobias are not inherited in the same way as blood type, for example; only the propensity is transmitted, which can be expressed in different ways.

There is other evidence related directly to fear acquisition that shows that fear pathways are not low level processes. Surprisingly, fear can be learned without directly experiencing the CS and US, as in observing events. For example, young Rhesus monkeys learn to fear snakes by observing other monkeys express fear towards snakes (Hofmann, 2008). This directly supports social learning theory, and can be applied to humans, as well. A child could acquire a fear of spiders just by observing a family member respond fearfully to spiders. All of this suggests a higher order cognitive process. Cognitive processes refer to US expectancies and the perception of controllability and predictability of future events. Therefore contemporary theories include considerations of additional variables such as anxiety sensitivity and cognitive processing.

Most of the testing of fear acquisition has been in understanding fear conditioning artificially in a lab setting. There are two physiological responses that have typically been used as behavioral measures for fear conditioning: acoustic startle response and skin conductance response (SCR). The acoustic startle response is characterized by a reflex contraction of skeletal muscles in response to a strong stimulus. This provides a good model to study emotional processing since the amygdala is directly connected to the startle circuit. The other response, the fear conductance response, is an index of sympathetic nervous system activity which is frequently used

in measuring fear acquisition with the aid of brain imaging studies.

Fear is a "basic emotion": it occurs in all humans across cultures, and fulfills the evolutionary adaptive function by mobilizing quick and adaptive reactions in response to threatening situations. Exaggerated fear responses form the basis for anxiety disorders. Anxiety, is more complicated than fear – it is a cognitive association that connects basic emotions to events, meanings, and responses. These associations are less "hardwired" than basic emotions, so they depend a lot on the individual. Anxiety disorders are actually fairly common in the general population – the lifetime prevalence of an anxiety disorder is about 28.8% (Shin and Liberzon, 2009). The major difference between human anxiety disorders and fear conditioning models in animals is the absence of a clear US in anxiety disorders, and the role of avoidance and cognitive components in humans. Exaggerated fear in patients with anxiety disorders could occur because emotional responses fail to extinguish, or that extinction learning is no longer recalled. Panic attacks, for example, are discrete episodes of fear or discomfort that occur without the presence of real danger. Social phobia is the persistent fear of social or performance situations involving possible scrutiny by others, and thus a fear of embarrassment leads to avoidance of social situations. While the details are different across the spectrum, all anxiety disorders share a lack of perceived control over negative emotional and bodily reactions. One anxiety disorder in particular, posttraumatic stress disorder, causes biochemical changes in the body that differ from other psychiatric disorders.

Epidemiological studies show that the majority of individuals have been exposed to at least one potentially traumatic event (PTE), but only a minority of PTE-exposed individuals develop PTSD (Amstadter, Nugent, and Koenen, 2009). A potentially traumatic event is a powerful incident which are life threatening, or pose a threat to an individual's physical or mental well being. Examples include death of a friend or family member, physical injury or illness, separation or abandonment, and war. However, exposure trauma is not sufficient to develop PTSD. Prior experiences with uncontrollable events, intensity of arousal following trauma, and individual characteristics such as intelligence all determine whether a PTE will lead to PTSD in a given person.

Symptoms of PTSD include intrusive memories of the traumatic event, avoidance of triggers, negative changes in thinking and mood, and changes in emotional reactions. Sufferers of PTSD often have trouble sleeping, are easily startled, and may show difficulty maintaining close relationships. Surprisingly, many anxiety disorders are comorbid with mood disorders, meaning there may be certain neurocircuitry abnormalities in common. Major depression is comorbid with anxiety disorders like PTSD, panic disorders, and social phobias. So if much of the neurocircuitry is similar among anxiety disorders, and even with depression, what causes PTSD specifically?

"A child could acquire a fear of spiders just by observing a family member respond fearfully to spiders."

PTSD is the only anxiety disorder that includes a direct conditioning effect in its diagnosis. In general, the amygdala is activated in response to trauma-related imagery, combat-related sounds or smells, fear conditioning, and fearful facial expressions. A hypersensitive amygdala could account for the exaggerated fear response and persistence of traumatic memories following a PTE; amygdala activation is thus positively correlated with PTSD symptom severity. The mechanism of PTSD involves, among other things, elevations in catecholamines (a class of monoamines, including adrenaline, noradrenaline, and dopamine) during and immediately following exposure to a potentially traumatic event (PTE) – this can over-consolidate memories, resulting in intrusive recollections and re-experiencing symptoms. Increased catecholamines during traumatic stress without regulatory influences can lead either to over salient or fragmented memory acquisition (Amstadter, Nugent, and Koenen, 2009). Other regions of the nervous system are also implicated, and when combined, these hypersensitive areas lead to deficits in extinction, emotion regulation, and contextual processing. For example, abnormal hippocampal function could contribute to deficits in contextual processing, and impairments in memory; a twin study suggests that diminished hippocampal volumes could be a familial risk factor, implying that risk of PTSD is at least partly heritable (Shin and Liberzon, 2009).

Genetic studies, have made several important contributions to the study of PTSD. Trauma-exposed adult children of Holocaust survivors that had PTSD were more likely to develop PTSD following trauma exposure than were adult children of survivors without PTSD. This was also supported by a similar study of children of Cambodian refugees (Amstadter, Nugent, and Koenen, 2009). Clearly,

data indicate a degree of distinctness of genetic influences on PTSD and some degree of overlap in genetic contributions to other mental disorders. However, the majority of genes that affect risk for PTSD also influence risk for other psychiatric disorders, which raises the question: how much is genetic and how much is environmental? In one study, combat exposed veterans with PTSD did not show impaired extinction learning, but they did show less extinction retention the day after acquisition, when compared to exposed veterans without PTSD (Jovanovic and Ressler, 2010). Thus it seems that impaired retention of extinction specifically seems to be an acquired trait.

Just as PTSD vulnerability can be inherited, there are also examples of specific gene alleles that may impart resilience to PTSD and anxiety disorders. A recent study shows that polymorphisms in the gene FKPB5 (which is important in the pathway of regulating glucose metabolism) may moderate PTSD, given exposure to childhood sexual abuse (Amstadter, Nugent, and Koenen, 2009).

Though it may seem that the eventuality of developing PTSD is somehow preordained, there are ways to reverse its effects. The most effective strategies for treating anxiety disorders include exposure therapy with or without cognitive strategies, and pharmacotherapy (for example, selective serotonin reuptake inhibitors). Exposure therapy involves a patient being repeatedly exposed to a feared object or situation for prolonged periods with a supported therapist. The idea is that the lack of aversive consequences will stimulate extinction training. There are two conditions necessary for emotional processing to occur: the activation of fear memory, and the incorporation of corrective information.

Behavioral treatment for anxiety disorders is based on the processes of habituation and extinction. Habituation allows individuals to ignore harmless events by producing a decline in response to the repeated presentation of a neutral stimulus via non-associative learning. Verbal instructions can modify the extinction processes by changing the contingency, which explains the mechanism of exposure therapy. However, cognitive therapy is not limited to cognitive modification; emotional and behavioral responses are equally important. Some even distinguish between intellectual (learning to identify misconceptions, testing the validity of thoughts, and substituting them with more appropriate ideas), experiential (exposing themselves to experiences to change misconceptions), and behavioral approaches (encouraging the development of specific forms of behavior). Thus far, environmental factors that promote resiliency have been the focus of PTSD treatment, and prolonged exposure protocol has been effective in treating women with PTSD following physical and sexual assault, as compared to other control conditions. The problem arises from the fact that once the fear memory is formed, it can still be modified by methods that interfere with memory consolidation; at this point it is still possible to intervene and modify memory by associating it with safety, not danger cues. However, PTSD is rarely caught at this early point.

Perhaps the solution lies in medication or pharmacological solutions. Medication can normalize amygdala responses, which could reduce the severity of PTSD symptoms. Propranolol, administered immediately after trauma, can prevent fear consolidation – studies with animal models show that it interferes with formation of emotional memories. Orally administered D-cycloserine may lead to inhibited amygdala activity during repeated presentation of faces. Other preclinical trials include the GABA circuit modulation, and enhancement of extinction through HPA axis modulation of the cortisol (Jovanovic and Ressler, 2010).

The identification of modifiable environmental factors, for example, social support, that buffer the effects of environmental pathogens and genetic vulnerability to stress will have important clinical implications. D-cycloserine (DCS), a partial N-methyl-d-aspartate (NMDA) agonist, enhances extinction in rats depending on the dose. DCS can still facilitate extinction when given up to 3 hours after extinction training which suggests that DCS allows memory consolidation of extinction. In one study, exposure therapy followed by DCS doses resulted in larger reductions of acrophobia symptoms at 1 week and 3 months after treatment by showing greater decreases in post-treatment SCR fluctuations than in the control group that received a placebo (Hofmann, 2008). This was also true in treating social anxiety. Therefore seems that a combination of medication and exposure therapy could be the best approach going forward

> "PTSD is the only anxiety disorder that includes a direct conditioning effect in its diagnosis."

Over the past century, our understanding of fear and anxiety disorders has advanced miles, but we still have a long way to go. For example, genetic research thus far has been guided by a "main effects" model that examines the effects of either genotype or environment on the manifestation of psychiatric phenotypes. However, another model, which proposes that the effects of environmental stressors on psychiatric disorder phenotypes are moderated by genotype, may be better suited to PTSD research, as a key feature of the disorder is exposure to environmental stresses. As we continue to make advances in the fields of genetics and neurobiology, our understanding of fear will only grow, until perhaps one day, we will find a way to overcome it altogether.

References

Shin, L. M., & Liberzon, I. (2009). The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology, 35(1), 169-191.

Öhman, A. (2009). Of snakes and faces: An evolutionary perspective on the psychology of fear. Scandinavian journal of psychology, 50(6), 543-552.

Hettema, J. M., Annas, P., Neale, M. C., Kendler, K. S., & Fredrikson, M. (2003). A twin study of the genetics of fear conditioning. Archives of general psychiatry, 60(7), 702-708.

Amstadter, A. B., Nugent, N. R., & Koenen, K. C. (2009). Genetics of PTSD: fear conditioning as a model for future research. Psychiatric annals, 39(6), 358.

Hofmann, S. G. (2008). Cognitive processes during fear acquisition and extinction in animals and humans: Implications for exposure therapy of anxiety disorders. Clinical psychology review, 28(2), 199-210

Carey, G. (1990). Genes, fears, phobias, and phobic disorders. Journal of Counseling & Development, 68(6), 628-632.

Jovanovic, T., & Ressler, K. J. (2010). How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. American Journal of Psychiatry, 167(6), 648-662

Delgado, M. R., Nearing, K. I., LeDoux, J. E., & Phelps, E. A. (2008). Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron, 59(5), 829-838.

Yager, D. D. (2012) Predator detection and evasion by flying insects. Current opinion in neurobiology, 22(2), 201-207.

Jones, M. C. (1924) A Laboratory Study of Fear: The Case of Peter. Pedagogical Seminary, 31, 308-315

Hofmann, S. G. (2008). Cognitive processes during fear acquisition and extinction in animals and humans: Implications for exposure therapy of anxiety disorders. Clinical psychology review, 28(2), 199-210

---

[1] Sonar jamming occurs when non-target sounds interfere with echolocation. Aposematism is a similar evolved response which affects the bat's ability to effectively locate prey through echolocation.

[2] The additive genetic effect is an estimate of the change in a trait that is associated with changing one allele (one of a number of alternative forms of the same gene) with another allele within a population.

[3] The relationship between alleles of one gene, in which the expression (phenotype, or physical characteristic) of one allele is masked by the dominant expression of another allele.

Image Sources

http://www.scn.ucla.edu/images/spider468x286.jpg

https://farm3.staticflickr.com/2524/3681765412_ab52df8a83_m.jpg

Layout by Abigail Landers