

The biology of fear and anxiety

The emotions are the important part to show the way of human daily life although it is amazing to see how an emotion works? However there has been lack of adequate research to understand the nature of emotion. Apart from different emotions “Fear” and “anxiety” can be a good representative of emotions to shed light to understand the fundamental processing of emotion in the brain. Fear conditioning is the well-defined experimental procedure to elicit and measure fear in humans as well as in non-humans experimental animals (Le Douarin, 1995). Anxiety disorders constitute the largest group of mental diseases in European countries (Andin-sobocki et al., 2005). Regulation of fear and anxiety are the heart of many psychopathological disorders and a significant problem for the community. During the past two decades NPY system has also recognized as a key component for the recovery of psychiatric states. In spite of currently available therapeutics, a considerable portion of patients requires long-term treatment throughout the whole life or does not respond at all. For the coping with these limitations, focusing on a better understanding of these diseases and improved treatment is urgently needed. The fundamental mechanisms of fear and anxiety are highly conserved across species making it possible to study human emotions in animal model.

The Biology of fear and anxiety

Fear Vs Anxiety

“Fear- Behavioural manifestation associated with clearly identified imminent threat.

Anxiety- Generalized fear without object, an apprehensive anticipation of future potential threats”

The main function of fear and anxiety is to act as a signal of danger, threat, or motivational conflict, and to trigger appropriate adaptive responses. For some authors, fear and anxiety are undistinguishable, whereas others believe that they are distinct phenomena. Ethologists define fear as a motivational state aroused by specific stimuli that give rise to defensive behavior or escape. Animals may learn to fear situations in which they have previously been exposed to pain or stress, and subsequently show avoidance behavior when they re-encounter that situation. Young animals may show an innate fear reaction to sudden noise or disturbances in the environment, but rapidly become habituated to them. When they are used to a familiar environment, then a fear of novelty may develop. Ethologists have also made the important observation that fear is often mixed up with other aspects of motivation. Thus, conflict between fear and approach behavior may result in displacement activities (e.g., self-grooming in rats and mice). Such displacement activities may be the behavioral expression of an anxious state, but anxiety is a concept that is apparently not used by ethologists, perhaps because their definition of fear does in fact include all the more biological aspects of

anxiety. Many authors, however, have argued that differences in their etiologies, response patterns, time courses, and intensities seem to justify a clear distinction between anxiety and fear. Although both are alerting signals, they appear to prepare the body for different actions.

Anxiety is a generalized response to an unknown threat or internal conflict, whereas fear is focused on known external danger. It has been suggested, "anxiety can only be understood by taking into account some of its cognitive aspects, particularly because a basic aspect of anxiety appears to be uncertainty. Also, it is reasonable to conclude that anxiety can be distinguished from fear in that the object of fear is 'real' or 'external' or 'known' or 'objective.' The origins of anxiety are unclear or uncertain. Other authors pointed out that "situations lacking in clear indications of situational contingencies or likely outcomes are associated with considerable stress. The uncertainty regarding these situations highlights a lack of control that contributes to feelings of anxiety and makes coping more difficult. Barlow has described anxiety as a unique and coherent cognitive-affective structure within our defensive and motivational system. At the heart of this structure is a sense of uncontrollability focused largely on possible future threats, danger, or other upcoming potentially negative events, in contrast to fear, where the danger is present and imminent. The fact that anxiety and fear are probably distinct emotional states does not exclude some overlap in underlying brain and behavioral mechanisms. In fact, anxiety may just be a more elaborate form of fear, which provides the individual with an increased capacity to adapt and plan for the future. If this is the case, we can expect that part of the fear-mediating mechanisms elaborated during evolution to protect the individual from an immediate danger have been somehow "recycled" to develop the sophisticated systems required to protect us from more distant or virtual threats.

Defense and coping strategies

Fear or anxiety, result in the expression of a range of adaptive or defensive behaviors, which are aimed to escape from the source of danger or motivational conflict. These behaviors depend on the context and the repertoire of the species. There are two fear coping strategies-

Active coping strategies

Passive coping strategies

Active coping strategies are used when escape from threat is possible, and the autonomic changes associated with these active strategies are mediated predominantly by sympathetic activation (hypertension, tachycardia), the fight-or-flight. "Fight or flight," was coined exactly 75 years ago, in 1929, Walter Cannon originally formulated this term for the human response to threat, Fear and anxiety. The phrase "fight or flight" has influenced the understanding and expectations of both clinicians and patients; however, both the order and the completeness of Cannon's famous phrase are suspect. "Fight or

flight" mischaracterizes the ordered sequence of responses that mammals exhibit as a threat escalates or approaches. In recent years, ethologists working with nonhuman primates have clearly established four distinct fear responses that proceed sequentially in response to increasing threat. The order of these responses may have important implications for understanding and treating acute stress in humans. The sequence, originally described by Jeffrey A. Gray, begins with what ethologists call "the freeze response" or "freezing," terms corresponding to what clinicians typically refer to as hypervigilance (being on guard, watchful, or hyper-alert). This initial freeze response is the "stop, look, and listen" response associated with fear. The survival advantage of this response is obvious. Specifically, ethological research has demonstrated that prey that remain "frozen" during a threat are more likely to avoid detection because the visual cortex and the retina of mammalian carnivores primarily detect moving objects rather than color.

Passive coping strategies, such as immobilization or freezing, are usually elicited when threat is inescapable, and are usually characterized by autonomic inhibition (hypotension, bradychardia), and a more pronounced increase in the neuroendocrine response activation of the hypothalamopituitary-adrenal axis and increased glucocorticoid secretion.

This type of passive response was originally described by Engel & Schmale as a conservation-withdrawal strategy. The concept of alternative (active/passive) strategies itself owes much to the work of Henry and coworkers. Specific brain circuits appear to mediate distinct coping reactions to different types of stressors.

Psychopathological fear/anxiety

Although fear act as a signal of danger, threat, or motivational conflict, it can become pathological and interfere with the ability to survive with various challenges and stressful events and even alter normal body conditions can develop specific anxiety disorders, i.e., social phobia, obsessive-compulsive and panic disorders, and specific phobias. Anxiety disorders are marked by excessive fear (and avoidance), often in response to specific objects or situations and in the absence of true danger, and they are extremely common in the general population. According to a recent epidemiological study, the lifetime prevalence of any anxiety disorder is 28.8% (Kessler et al, 2005).

Increased anxiety in animal models, as a trait, can be attributed to at least two sets of factors: (i) a genetic predisposition, essentially linked to the expression of genes that are involved in the various neurochemical mechanisms underlying fear and anxiety; and (ii) the influence of environmental factors. These environmental factors can interact with the expression of the relevant genes during early development and determine the functional properties of the neural and biochemical systems involved in coping with stressful events. They can also modulate the learning processes that occur at a later stage, when the individual is confronted with various life events, and determine the capacity to cope successfully with aversive or threatening situations in adulthood.

These predisposing factors, either innate or acquired, determine individual “affective styles” or coping strategies, which are thought to play an important role in vulnerability to psychopathology.

Animal model

However, most animal models of fear/anxiety are based on the use of mammalian species, particularly rats and mice. These models fall into two broad categories. In the first one, animals are confronted with situations that generate an anxious state (state anxiety models). This state of anxiety can be either conditioned (e.g., conditioned fear, avoidance, and punishment-induced conflict tests) or unconditioned (e.g., aversive and ethological conflict tests). In the second category, the models are concerned with trait or “pathological” anxiety genetic manipulations (transgenic or “knockout” animals) or selective breeding creates lines of rats or mice that permanently express an increased or decreased level of fear/anxiety.

To study of the cellular and molecular bases of fear requires a model system in laboratory animals. The most popular model is classical (alias pavlovian) ‘fear conditioning’. To understand how this works, it helps to recall how Pavlov trained his dogs in his St Petersburg lab a century ago. In a typical experiment, a dog was presented with a sound, and immediately afterwards with meat, which evoked salivation. In the language of psychology, the sound is the conditioned stimulus, the meat the unconditioned stimulus, and salivation in response to meat is the unconditioned response. With time, the dog learned that the sound predicted food, and salivated when presented with the sound alone (the conditioned response). Now, let's substitute the dog with a mouse (or rat), keep the sound, but replace the food with an electric shock to the foot. The result is that the mouse learns to fear the sound. Fear has many manifestations, one of which — freezing of movement — is commonly used as the conditioned response in lab animals

We used genetically modified mice for Neuropeptide Y (NPY), for the characterization the role of NPY and its receptors in fear and anxiety.

Neuroanatomy (functional circuitry) for fear/anxiety

Excessive fear is a key component of anxiety disorders, it is not surprising that the search for the neurocircuitry of anxiety disorders has its roots in and has been closely intertwined with studies of fear circuits in animal models. A large volume of experimental work has examined the neurocircuitry associated with fear responses, mainly in rodents, using primarily fear conditioning, inhibitory avoidance, and fear-potentiated startle models. Key components of fear circuitry including the amygdala (and its subnuclei), nucleus accumbens (including bed nucleus of striaterminalis BNST), hippocampus, ventromedial hypothalamus, periaqueductal gray, a number of brain stem nuclei, thalamic nuclei, insular cortex, and some prefrontal regions (mainly infralimbic cortex)

have been identified in recent studies (for recent reviews see Davis, 2006; Maren, 2008; Quirk and Mueller, 2008). These regions have their respective roles in the various components of fear processing such as the perception of threat or of unconditioned stimuli, the pairing of an unconditioned stimulus and conditioned response (learning/conditioning), the execution of efferent components of fear response, and the modulation of fear responses through potentiation, contextual modulation, or extinction. These basic components of fear circuitry are well preserved across species and likely support similar functions in humans. Animal work using in vivo electrophysiological recording, tracing and lesions/reversible inactivation techniques was indispensable in acquiring this knowledge. Some recent work had even suggested that there might be separate fear and anxiety systems orchestrated through the central nucleus of the amygdala and the BNST, respectively (Davis, 2006). These types of findings are particularly exciting as they might allow for a better focus on the neurocircuits involved in pathological anxiety.

Involvement of Amgdala in fear conditioning

Part of the neuronal circuitry that subserves fear conditioning is found in the amygdala, a collection of neural structures in the temporal lobe of the brain that controls many aspects of emotional and social behaviour. According to a generally accepted model, information about the conditioned and unconditioned stimuli becomes associated in the lateral nucleus of the amygdala, and output from the amygdala controls the expression of fear. Although its exact role is still uncertain, the amygdala is known to be essential for the formation of memory of fearful experiences. Furthermore, in keeping with the conceptual framework that underlies contemporary neurobiology, it is believed that 'fear' in the amygdala to previously innocent stimuli is caused by experience-induced changes in its synapses (the connections between nerve cells).

Blanchard DC, Hynd AL, Minke KA, Monemoto T, Blanchard RJ. Human defensive behaviors to threat scenarios show parallels to fear- and anxiety-related defense patterns of non-human mammals. *NeurosciBiobehav Rev.* 2001;25:761-770.

Goldsmith HH, Lemery KS. Linking temperamental fearfulness and anxiety symptoms: a behavior–genetic perspective. *Biol Psychiatry.* 2000;48:1199-1209.

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