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Anxiety: An Adaptive Emotion

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1. Introduction

Anxiety as an adaptive response is a natural emotion that occurs in response to danger and prepares an organism to cope with the environment, playing a critical role in its survival. Among the components of anxiety, the expression of fear may inform other members of the group about the presence of imminent danger (i.e., an alarm cue). The environment is perceived by a filtering process that involves sensorial receptors. While coping with a stressful situation, an individual may simultaneously emit vocalizations, perform movements to escape, freeze, and deliver to the environment chemicals called alarm pheromones. These cues are recognized by the receptor-individual by specific sensory systems located in the legs and antennae in insects and olfactory sensorial systems in other organisms. In mammals, the sensorial information is integrated by anatomical and functional pathways, with the participation of structures related to emotional memory, namely deep temporal lobe structures. Some stimuli are perceived as relevant when they contain relevant meaning according to previous experience and learning. The participation of ventral striatum and prefrontal cortex connections then leads to the selection of an adequate strategy for survival. The perception of these cues by other individuals in the group establishes intraspecies communication and causes striking behavioral responses in the receptor subject, namely anxiety, but the consequence is likely different. While the emitting subject may be in an emergency situation that is perhaps devoid of a solution, the receptor subject may have the chance to cope with the dangerous situation by employing efficacious strategies, depending on previous experience. The aim of this chapter is to review the participation of such anatomical pathways, their neurotransmission systems, and the resulting behavioral patterns.

2. Expression of fear and anxiety as emotions

Emotions are transient events generated in response to some stimuli that produce arousal reactions and changes in motor behavior, subjective feelings, and subsequent changes in behavior [15]. Thus, emotions are cognitive and somatic reactions, with a short duration, to specific environmental stimuli [7]. In the case of an emergency situation, emotions give way to strategies that allow the survival of the individual and, therefore, the species. Emotional processes are crucial for the control of human behavior [15], and a failure in the management of emotions is a common denominator of a wide range of psychiatric disorders [22].

In broad terms, emotions are considered to have two dimensions. The first dimension is equilibrium, in which emotional states range from positive (i.e., happy or safe) to negative (i.e., fear or anger). The consequent behavioral responses depend on emotional states. For example, in a positive emotional state, there is a tendency to approach the stimuli, whereas negative emotional states are associated with aversion, defense, escape, and avoidance. The second dimension is arousal. Both positive and negative emotional states may vary from a relatively quiet attitude to high levels of restlessness [54; 53]. Examples include freezing in a passive attitude or escaping in more proactive coping patterns [20]. Emotions play a role in the daily lives of individuals, enabling them to cope with everyday situations.

Fear is a part of the anxiety syndrome. It consists of a feeling of agitation caused by the presence of imminent danger and may be considered a protective emotion. From an evolutionary point of view, however, its expression is very similar to anxiety as an adaptive emotion. An exception may be posttraumatic stress, an anxiety disorder in which fear is present even in the absence of the stimulus that elicited the original state of anxiety [100]. Notably, fear can be conditioned by various stimuli, and its study from different methodological perspectives has allowed a better comprehension of the underlying neurobiological processes of anxiety.

3. Is anxiety a disease or an adaptive response?

Anxiety comprises two related concepts. First, it is a disease. Second, it is an adaptive response. As a disease, anxiety is a highly disabling pathological condition, involving cognitive, emotional, and physiological disturbances. Its main symptoms include restlessness, increased alertness, motor tension, and increased autonomic activity [2]. In the long-term, the deleterious effects of anxiety on personal capabilities represents a considerable mental health problem. Generalized anxiety disorder is frequently associated with other pathologies, but it may constitute the only symptom in several manifestations, including panic disorder, posttraumatic stress disorder, and obsessive compulsive disorder [2]. It is one of the most common psychiatric disorders, affecting approximately 28% of the general population [49]. In México, as in other countries, it occurs more often in women than in men [64]. Typically, the symptoms last a long time, even when the stimulus has disappeared [100].

Adaptive anxiety may be considered a useful emotion that leads to survival strategies [4]. In this sense, anxiety is a normal emotion that occurs when an individual copes with a potential-

ly dangerous situation, constituting a mechanism for alertness or alarm [41]. In this case, the symptoms of anxiety, which are identical to the pathological condition, disappear once the stressful stimulus disappears. Meanwhile, in most cases, it leads to coping with the emergency situation. As the best strategy is chosen, the probability of ensuring survival increases.

One of the main differences between the two kinds of anxiety is the contingency of the response to the stimulus. Otherwise, pathological anxiety induces positive feedback, in which anxiety generates more anxiety [75] and, notably, spreads to other individuals in the group [88; 24]. The combination of feedback and the spread of anxiety can lead to a collective panic reaction that involves those individuals who surrounded the first individual who experienced anxiety [89], often with fatal results [74; 62]. One very special case is related to caregivers. Observing a state of anxiety that leads to deteriorated social functioning and health is common in caregivers, with undesirable effects in both the caregiver and patient [94]. Therefore, anxiety may be both a disease and an adaptive response that involves shared processes and in some cases may inclusively consist of a continuum.

4. Anxiety is contagious

In the case of anxiety as an adaptive emotion that leads to survival strategies, the spread of anxiety to other individuals in the group may offer warning signs that allow for the protection of other individuals and consequently the group and ultimately the species [6].

Generally, all stimuli derived from the environment initially undergo a sensorial filtering process in sensorial receptors, beginning with parareceptors [8], reaching synaptic relays, and leading to an integrative process that involves anatomical structures related to emotional memory [43], in which comparisons are made with older elements of memory [92]. As the stimulus inputs reach the striatum and cortical structures [43], a selection of the adequate survival strategy is often reached [34]. In turn, connections with motor areas and motoneurons activates skeletal muscles [43], and a motoric response may be observed. Laboratory animals subjected to a stressful situation (e.g., odors from a predator) will emit only a few responses—attacking, freezing, or escaping—no more and no less.

One important aspect is the meaning of the stimuli. Only a portion of all environmental stimuli is perceived as relevant when it contains a specific meaning according to previous experience. Any of these stimuli may potentially contain relevant environmental information, but its relevance arises when it is properly interpreted. The contrast between the present stimuli and previous experience allows predictions to be made about the real presence or absence of danger and selecting the correct coping response [34; 63]. An intriguing aspect is that most studies of the neural and behavioral framework of these types of motor responses have been performed in laboratory animals (i.e., animals that were completely naive of predators before the test). However, some studies in naturally free animals have found similar results [19; 90]. The interpretation is that a neural framework adapted by natural selection is able to respond in some effective way, even in the absence of any previous experience. Therefore, the neural framework allows an initial response to any dangerous sit-

uation in the environment, yielding necessarily useful strategies for survival. Choosing the best strategy to cope with such situations depends on experience (i.e., learning).

5. Communication and anxiety

During natural selection and evolution, several organisms have developed strategies that allow different but complementary forms of communication between individuals of the same species. Thus, animal communication includes the emission and reception of signals delivered in the environment, usually following some specific code. Moreover, communication also includes behaviors in the receptor-individual. Success in the detection of cues includes a series of processes that consist of emission of the cue, reception by other individuals, encoding, transmission, and decoding [26].

Notably, special situations, such as emergency situations, involve most of the sensorial systems. A primitive form of communication is body language. In this case, environmental information is detected by the visual system. Insects frequently apparently dance while performing stereotyped movements [33] that apparently carry a message whose meaning is not yet fully understood.

The auditory system is involved in the most complex of these forms of communication. A symbolic language that contains a characteristic syntactic structure is apparently peculiar to the human species [79]. In a more primitive form, nonsyntactic and perhaps only symbolic language is observed in other species [6]. In fact, animal vocalizations are devoid of semantic content (i.e., meaning) but possess some semiotic context that contains symbolic value [16]. The signals generated by animals are used for communication and consist of signs that become messages that are capable of influencing the behavior of other individuals who are also able to respond with species-typical signals by distinguishing its semiotic content. For example, most ultrasonic vocalizations of animals, including rats, are true semiotic signs and represent a useful signal within a communication system [63]. Most of these semiotic signals may represent warning cues that seemingly produce some anxiety responses in other individuals of the same species.

Among the signaling systems, chemical cues that consist of pheromones [48] can cause striking behavioral responses, including anxiety [31; 32], when perceived by other individuals of the group. The opposite is also true. Some pheromones consist of cues that indicate the existence of a safe environment [47; 103] by informing other individuals of the same species about the absence of danger or presence of food. In both cases, an emitting-individual releases substances to the environment that are recognized by the receptor-individual by specific sensory systems located, for example, in the legs and antennae in insects [81] or olfactory sensory system in other organisms, including mammals [58]. Figure 1.

6. Neuroanatomical modeling of emotions

Emotional memory allows an individual to recognize signs from the environment and compare them with past experience as an element of judgment to efficaciously respond to the environment by choosing the best coping strategy [14]. During the first half of the 20th century, researchers were interested in the brain mechanisms of emotional behavior [57], and the original concept of the “limbic system” was gradually abandoned. Instead, the very simple, initial anatomical concept (i.e., hippocampus, one thalamic nuclei, mammillary bodies, and cingulum) was enriched by the inclusion of other deep temporal lobe structures, such as the amygdaloid complex [57], so-called mesolimbic structures [73], and prefrontal and orbitofrontal cortices [100]. All of these anatomical regions share similar neurotransmission systems, namely serotonin, norepinephrine, dopamine, and γ -aminobutyric acid (GABA), among others.

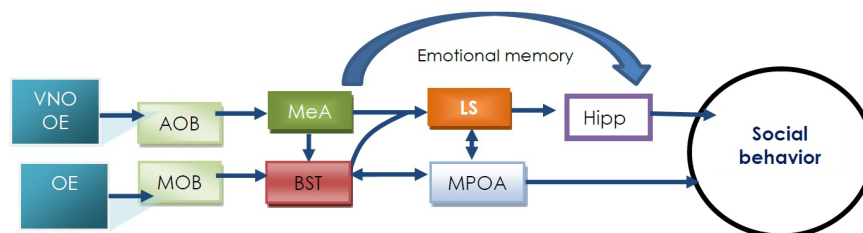


Figure 1. Social recognition and olfactory pathways in rodents. Abbrev. VNO, vomeronasal organ; OE, olfactory epithelium; AOB, accessory olfactory bulb; MOB, main olfactory bulb; MeA, medial amygdala; BST, bed nucleus of the stria terminalis; LS, lateral septal nucleus; MPOA, medial preoptic area; Hipp, hippocampus.

Some alterations in the serotonergic system are associated with psychiatric disorders, such as depression and schizophrenia [87]. Serotonin (5-hydroxytryptamine [5-HT]) is located primarily in the gastrointestinal tract, but it is also detectable in the central nervous system [29] in areas that are functionally related to many behavioral processes. Its main reservoir in the brain is the dorsal raphe nucleus [40; 78], which, among other projections, sends efferent fibers to several structures related to emotional processing, such as the septum, thalamus, amygdaloid complex, nucleus accumbens, hippocampus, and prefrontal cortex [29; 78]. Although a controversial issue [87], an increase of 5-HT in the synaptic cleft exerts anxiolytic effects in animal models of anxiety, such as the social interaction test, light-dark test, Vogel conflict test, Geller-Seifter conflict test, and ultrasonic vocalizations [10, 65], which have been confirmed by many clinical studies [60].

Norepinephrine is related to many functions, such as attention, the regulation of stress, fear, memory, sleep, and wakefulness [27]. It is synthesized in a small group of cells located in the locus coeruleus that sends efferent fibers parallel to those of 5-HT [40; 27]. Norepinephrine is involved in the secretion of corticotrophin-releasing factor, which stimulates the production of adrenocorticotrophic hormone that, in turn, releases corticosterone in the adrenal

glands, which is responsible of the metabolic response to stress [100; 67; i.e. an inseparable component of anxiety]. Anxiety is directly related to increased activity of locus coeruleus neurons. Drugs that increase noradrenergic activity also increase anxiety, and drugs that reduce noradrenergic activity reduce anxiety [40, 27]. Limbic and cortical regions innervated by the locus coeruleus are those that are thought to be involved in the elaboration of adaptive responses to stress, such as the typical scheme seen in fearful behavior in cats [1].

γ -Aminobutyric acid is a neurotransmitter distributed throughout the central nervous system and the quintessential inhibitory neurotransmitter [72]. Modulation of the GABAergic system at its receptors [5] is linked to the neurobiological mechanisms that regulate anxiety [72; 70; 86]. Most drugs with affinity for the GABA_A receptor produce anxiolysis and sedation [96]. These receptors are detectable in the cerebral cortex, amygdala, hippocampus, and striatum [40], providing the physiological basis for the therapeutic action of anxiolytics [72], including gonadal steroids and neurosteroids [25; 12; 61].

Mesolimbic dopamine is found in the ventral tegmental area and involved in the control of cognition and affect [46]. Dopamine innervation of the medial prefrontal cortex appears to be particularly involved in mild and brief stress processing [21]. In turn, the prefrontal cortex plays a role in working memory, in addition to other brain areas, such as the hippocampus. A critical range of dopamine turnover is necessary to keep the working memory system active and ready for optimal cognitive functioning [42], a situation that is impaired in situations of extreme stress [3]. In summary, the dopamine system is important for general emotional responses, selective information processing, hedonic impact, and reward learning. In a broader sense, dopamine is important for reactivity to perturbations in the environment, which is essential for the ability (or failure) to cope with the environment [73; 99].

Multiple neurotransmission systems participate in the processing of anxiety and coping with the environment. Many other neurotransmitters are involved in the regulation of anxiety, including neuropeptides [91], polypeptides [95], and amino acids [104]. Nonetheless, a common denominator is that almost all of these neurotransmitters are located within the anatomical substrate of emotional memory [99], namely the amygdala complex [83].

The amygdala is composed of many functionally heterogeneous nuclei [56]. The lateral and central nuclei of the amygdala mediate the acquisition and expression of reactive defensive behaviors [59; 69], and the basal nucleus plays a key role in fear expression [38]. The basal amygdala nucleus, together with the lateral nucleus and accessory basal nucleus, integrate the basolateral amygdala [84]. As a whole, an increase in the neuronal firing rate of the basolateral amygdala has been related to fear [76], anxiety [101], emotional learning [17], and Pavlovian conditioning [28]. The basal amygdala nucleus appears to mediate fear-motivated reactions [55] but not conditioned auditory fear responses, such as freezing [69]. The central nucleus of the amygdala projects to various brain structures via the stria terminalis and ventral amygdalofugal pathway. The anatomical circuit responsible for the startle reflex begins in auditory pathways and reaches the central amygdala nucleus [18]. Pathways from the amygdala to lateral hypothalamus are related to peripheral sympathetic responses to stress [45]. Early findings reported that electrical stimulation of the amygdala in cats produced peripheral signs of autonomic hyperactivity and fear-related behavior, commonly seen when

the animal attacks or is being attacked [39]. Electrical stimulation of the amygdala in human subjects also produces signs and symptoms of fear and anxiety, namely increased heart rate, blood pressure, and muscle tension, accompanied by subjective sensations of fear and anxiety [9] and an increase in plasma catecholamines [30]. Important reciprocal connections also exist between cortical association areas, the thalamus, and the amygdala, which may account for fear responses [82]. These findings demonstrate that the amygdala plays an important role in conditioned fear and the modulation of peripheral stress responses.

7. Fear and anxiety as a consequence of natural selection

The relationship between mother and child is essential for the survival and normal development of infants [71; 85]. Maternal odors attract and guide neonates to the maternal breast [98]. The role of mothers is to provide a source of nutrition for their offspring, but also to protect them from predators [80; 71]. Maternal odors produce signs of calm. Kittens, pups, and human babies exhibit increased agitation and vocalizations when placed in an unfamiliar environment, but when they return to their nest or stay in close proximity to their mother, they calm down [66; 85]. Amniotic fluid olfaction reduces crying in human babies when they are separated from their mothers [97]. Recently, we analyzed human amniotic fluid, colostrum, and breast milk. Eight fatty acids were consistently found in measurable amounts in these three biological fluids. Both amniotic fluid and a mixture of its fatty acids acted as feeding cues, leading to appetitive behavior [11]. Moreover, both amniotic fluid and a mixture of its fatty acids exerted anxiolytic effects in animal models of anxiety [13]. These findings indicate that a system of protection against anxiety is present during intrauterine life, at least in mammals, suggesting a process of natural selection in which an individual is protected from extreme anxiety, even before birth.

With regard to the opposite process, alarm cues (i.e., pheromones) are released by an animal in threatening situations, informing members of the same species about the presence of danger (e.g., the proximity of a predator; 36). The responses of conspecifics to alarm pheromones include fear, autonomic responses, and freezing [51], increased awareness [35], defensive behavior [52], and an increase in anxiety-like behavior (32; 44; i.e., some behaviors mediated by deep temporal lobe structures). A single exposure to predator odors (i.e., 2,3,5-trimethyl-3-tiazoline) contained in fox feces and cats increased *c-fos* expression in the lateral septal nucleus and central amygdala [19; 90], among other structures. An arterial spin labeling-based functional magnetic resonance imaging study found that neuronal activity increased in the dorsal periaqueductal gray, superior colliculus, and medial thalamus during alarm pheromone exposure [50]. Exposure to odors from potential predators also elicited fast waves in the dentate gyrus [37] and enhanced long-term potentiation in the dentate gyrus [23]. Both the main and accessory olfactory systems are responsive to 2-heptanone [102]. The medial amygdala nucleus receives indirect inputs from the main olfactory system from the piriform cortex, periamygdaloid cortex, and cortical amygdala nucleus and direct inputs from the accessory olfactory system [92]. The hippocampus also receives odor information from both olfactory systems through entorhinal cortex connections [77]. Herein, neurons

from medial and cortical amygdala nuclei are activated in the presence of alarm pheromones [52], and the medial amygdala is involved in the neuronal circuitry associated with memory formation related to odors derived from predators, further leading to the expression of unconditioned and conditioned fear behavior [68; 93]. Figure 2.

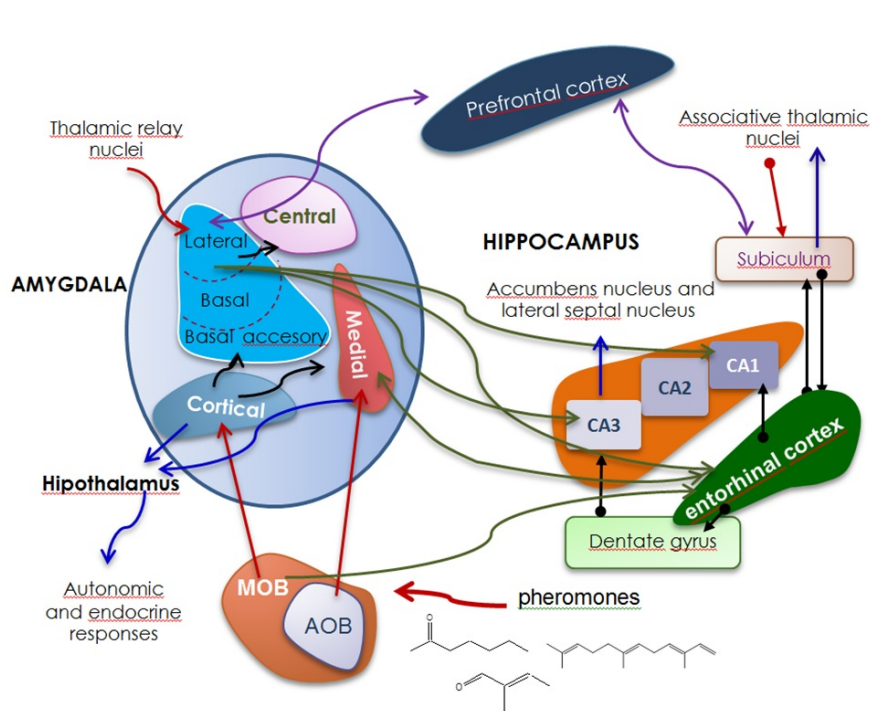


Figure 2. Anatomical representation of emotional memory circuit. Connections between amygdala and hippocampus, modulate the use of memories related to sensorial stimuli. Abbrev.: AOB, accessory olfactory bulb, MOB, main olfactory bulb.

8. Conclusions

Most of the known responses to alarm cues have come from studies in laboratory animals that reproduce and feed under relatively comfortable conditions. They live inside very well controlled facilities, distant from predators and dangerous situations. One may reconsider the concept of the rhinencephalon, an almost forgotten anatomical entity that involves brain structures (Figure 3) related to emotional memory and is present in mammals, reptiles, and birds. The rhinencephalon, at least as a concept, contains one of the primitive sources of capturing information from the environment—the olfactory system. The concept is completed by connections of this sensorial system with deep temporal lobe structures (i.e., emotional memory-related structures). Therefore, the existence of the rhinencephalon in many species suggests that the integration of anxiety responses is a broad, essential characteristic determined by natural selection. In such a case, anxiety as an adaptive response is common to species with a centralized nervous system. Anxiety as an adaptive response is also naturally

contained in the brain, and it is expressed even before the organism learns the most efficacious behavioral response.

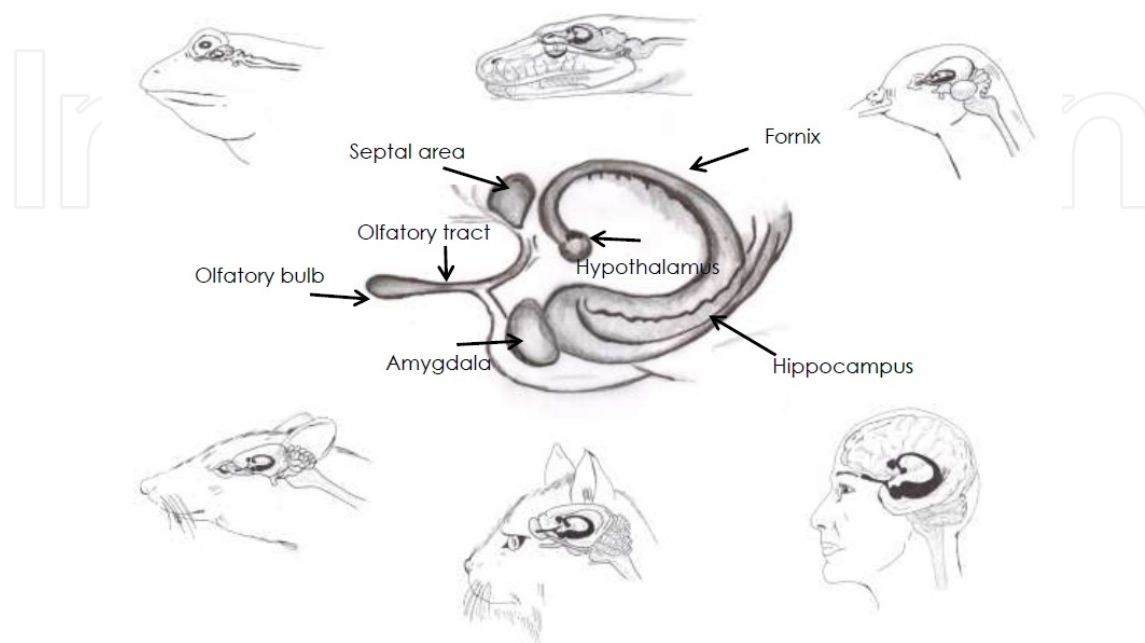


Figure 3. Schematic representation of rhinencephalon in several species. Since on evolution point of view (shaded area), rhinencephalon represents as integrative and primitive framework present in the central nervous system, integrating emotions essential for survival, such as fear and anxiety.

Nature protects the mother and fetus during intrauterine development, in which the development of the fetus occurs in an environment that protects it from anxiety. Especially in mammals, early learning acquired through maternal-infant interactions during the first phase of life and subsequent learning acquired through interactions with dominant members of a given group allow the individual to learn to select the most effective survival strategy, with the participation of prefrontal brain structures.

Consequently, two processes occur. One process depends on the neural framework that will respond even in the absence of any previous experience. The other process is a consequence of learning. Working together, the outcome is the utility of anxiety as an adaptive reaction that contributes to the survival of the species.

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