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Animal defense strategies and anxiety disorders

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ABSTRACT

Anxiety disorders are classified according to symptoms, time course and therapeutic response. Concurrently, the experimental analysis of defensive behavior has identified three strategies of defense that are shared by different animal species, triggered by situations of potential, distal and proximal predatory threat, respectively. The first one consists of cautious exploration of the environment for risk assessment. The associated emotion is supposed to be anxiety and its pathology, Generalized Anxiety Disorder. The second is manifested by oriented escape or by behavioral inhibition, being related to normal fear and to Specific Phobias, as disorders. The third consists of disorganized flight or complete immobility, associated to dread and Panic Disorder. Among conspecific interactions lies a forth defense strategy, submission, that has been related to normal social anxiety (shyness) and to Social Anxiety Disorder. In turn, Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder do not seem to be directly related to innate defense reactions. Such evolutionary approach offers a reliable theoretical framework for the study of the biological determinants of anxiety disorders, and a sound basis for psychiatric classification.

Key words: defense strategies, basic emotions, anxiety disorders.

INTRODUCTION

Anxiety disorders were once merged within the vague concept of neurosis, but are now divided into distinct nosological classes, characterized by different symptoms, time courses and therapeutic responses (World Health Organization 1992, American Psychiatric Association 1994). This development started in the early 1980s and has allowed, among other advances, the systematic study of pathophysiology.

The most widely used classifications were elaborated by the American Psychiatric Association, called Diagnostic and Statistical Manual of Mental Disorder. The classification of primary anxiety disorders according to its 4th edition (DSM-IV) is shown in Table I.

Panic disorder (PD) is characterized by the occurrence of panic attacks, in which feelings of extreme fear and dread strike unexpectedly and repeatedly, accompanied by marked physiological symptoms. Over time, persistent concerns about having another panic attack or about the consequences of the panic attacks develop. The person becomes afraid of being in situations or places from which escape could be difficult or embarrassing, a condition known as agoraphobia and, in extreme cases, being unable to leave home unless accompanied by someone. Specific phobias (SP) are exaggerated fears of objects (blood), animals (spiders) or situations (closed rooms). Social phobia, recently renamed social anxiety disorder (SAD), refers to abnormal fear of situations in which the person’s behavior can be scrutinized by others. Obsessive-compulsive disorder (OCD) is characterized by intrusive, unwanted, repetitive thoughts (obsessions)
TABLE I

DSM IV classification of primary anxiety disorders.

<table>
<thead>
<tr>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic disorder with agoraphobia</td>
</tr>
<tr>
<td>Panic disorder without agoraphobia</td>
</tr>
<tr>
<td>Agoraphobia without history of panic disorder</td>
</tr>
<tr>
<td>Specific phobia</td>
</tr>
<tr>
<td>Social phobia</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
</tr>
<tr>
<td>Acute stress disorder</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
</tr>
<tr>
<td>Anxiety disorder due to general medical condition</td>
</tr>
<tr>
<td>Substance-induced anxiety disorder</td>
</tr>
<tr>
<td>Unspecified anxiety disorder</td>
</tr>
</tbody>
</table>

and rituals (compulsions) performed out to appease anxiety. Acute stress disorder (ASD) is the development of characteristic anxiety and dissociative symptoms within 4 weeks after an extreme traumatic event and lasts less than 1 month. Posttraumatic stress disorder (PTSD) is the reaction to a terrifying event that keeps returning in the form of frightening, intrusive memories, and brings on hypervigilance and numbing of normal emotions. Generalized anxiety disorder (GAD) is characterized by chronic exaggerated worry and tension over everyday events and decisions.

Whenever the neurochemical or neuroanatomical underpinnings of anxiety disorders are considered, an evolutionary perspective is necessarily (even if unknowingly) adopted, since Darwinian evolution through natural selection is the only epistemological paradigm of present day biological sciences (Kuhn 1996). Although the focus of Charles Darwin’s attention was “on the origin of species” (Darwin 1859), the processes he advocated for – natural selection – explains the conservation of species rather than the beginning of new ones. For new species to arise, other factors, such as environmental change and geographical isolation are also necessary. At first, Darwin suggested that because of adaptive advantage – essentially ability to breed more offspring capable of reaching reproductive age – certain physical characteristics of living organisms are selected and preserved along generations. Later on, he extended this view to behavioral strategies, choosing the expression of emotions in animals, human beings included as an example (Darwin 1872). In this way, the evolutionary perspective was introduced into Psychology.

Along the 20th century, a research program based on evolution was carried out by the discipline called Ethology, aimed at the comparative (in the zoological sense) study of animal behavior. At the beginning, ethological studies have relied on systematic observation of animals in their natural habitat, without any interference. With time, ethological analysis has become increasingly experimental, in order to answer functional questions that have been raised by naturalistic observation (Tinbergen 1972). This development has led to a merge between Ethology and the formerly rival approach, Experimental Analysis of Behavior, which had originated in psychological laboratories dedicated to the study of animal learning. The resulting discipline, Ethoexperimental Analysis of Behavior, provides the empirical data that underpin the theoretical constructs of present day Evolutionary Psychology and Evolutionary Psychiatry.

One of the main contributions of ethoexperimental behavior analysis has been the identification of a basic set of defensive strategies that are common to several species (actually genera) that have been associated to human anxiety and related emotions. Due to the similar environmental constraints prevailing in the planet earth, convergent evolution has taken place, and the same basic defense strategies are displayed by virtually all vertebrate and even non-vertebrate animal species. Nevertheless, for the purpose of relating animal defense strategies to human anxiety in neurobiological terms, only animals that have brains phylogenetically related the human brain are of interest. For this reason, in the present article we review reported studies on defensive strategies displayed by non-human mammals, and discuss the extrapolation of the obtained results to human beings, with a particular emphasis on the neurobiology of anxiety disorders.

REPORTED RESULTS

The concept of levels of defense was originally based on the results of a series of ethoexperimental studies carried out by the research group led by Caroline and Robert Blanchard using wild rats caught in the sugar cane...
farms of Hawaii (Blanchard and Blanchard 1988). The choice of wild animals is due to the fact that laboratory rats have undergone domestication by selective breeding that attenuated defensive aggression along generations, making them easier to handle, but unsuitable for the study of defense (Blanchard et al. 1986).

As a consequence, the results reviewed below are organized according to the proposal by Blanchard and Blanchard (1988) that antipredatory defense is hierarchically organized in levels of defense that go from risk assessment, to escape, tense immobility, defensive threat and, finally, defensive attack. To these strategies we add submission, which occurs only among individuals of the same species.

**RISK ASSESSMENT**

The first level of defense occurs when danger is not present in an environment where the source of danger had previously been met; or when the environment is novel, implicating in potential rewards and threats, generating approach-avoidance conflict. The original experimental condition in which this behavior category has been identified is the so-called 'Visible Burrow System'. This apparatus is a large semi-natural enclosure that allows groups of animals to live, forage, breed, etc. The presence of females provides incentive for males to fight and to establish dominance hierarchies that are very stable across time (Blanchard et al. 2001d). The burrows side-line two borders of a square arena, where food and water are periodically provided. The roof is transparent, allowing observation with red lighting that is invisible to rats. At a given day, a cat is placed in the arena for a certain period, and then removed. In the presence of the cat, the rats emit ultrasonic alarm calls and seek refuge inside the burrows. Long after the cat’s removal, they stay inside the tunnels, not daring to cross the doors that allow entrance into the arena. However, as food and water deprivation increase, the need to explore the arena becomes imperative. As a result, the uppermost male in the colony hierarchy cautiously walks toward one of the doors keeping the belly in touch with the floor (stretched approach) and, in several occasions, pokes the head out of the hole followed by rapid retreat. This behavior pattern has been named ‘risk assessment’, supposedly aimed at the evaluation of the likelihood of danger as opposed to that of reward (Blanchard and Blanchard 1988).

In most species, risk assessment involves specific stimulus processing among the wealth of information that is generally available in natural environments. Because confrontations demand a rapid reaction, existing species are designed by natural selection to rapidly recognize specific features of predators or conspecifics that signal danger through a process called ‘stimulus filtering’ (Alcock 1993). Different perceptual cues that elicit risk assessment have been investigated, among which are odors (Blanchard et al. 2001c, McGregor et al. 2002, Zangrossi and File 1992, 1994), visual cues (Coss and Ramakrishnan 2000) and sounds (Ramakrishnan and Coss 2000). In social species, the predatory risk is also evaluated on the basis of typical vocalizations of conspecifics, as shown by studies using alarm call playback (McCowan et al. 2001).

In response to danger cues, animals express risk assessment in a wide variety of species-typical ways. Among the behavioral topographies studied, there are visual scanning in bonnet monkeys and ground squirrels (Hanson and Coss 1997, Ramakrishnan and Coss 2000, Thorson et al. 1998, Coss and Ramakrishnan 2000), sniffing in mice and rats (Berton et al. 1998, Wallace and Rosen 2000, Benus 2001), stretched approach in rats (Blanchard and Blanchard 1988, McGregor et al. 2002) and contact with odorous objects, also in rats (Zangrossi and File 1994).

Animals often overestimate risk (Thorson et al. 1998), since the cost of spending energy in avoidance and losing valuable resources is relatively small, as compared to that of severe damage or death. On the other hand, assuming a certain level of risk is necessary to obtain living resources.

During risk assessment, non-defensive behaviors, such as locomotion, environmental exploration, self-grooming, feeding and social interaction are inhibited (Blanchard et al. 1998a, Bramley and Wass 2001, Mastripieri et al. 1992), and the degree of suppression of these behaviors may be used as an indirect index of defensiveness or anxiety.

**IMMOBILITY**

The second level of defense in the wild rat has been characterized within an oval runway. After habituation
to the new environment, the experimenter enters the alley at a distance beyond a critical limit from the rat. As the animal perceives the experimenter, the muscles contract in an immobile posture. This tense immobility, often called ‘freezing’ behavior, has thus been conceptualized as a defense strategy against real threat that is at a distance, being thus named ‘distal defense’ (Blanchard and Blanchard 1988). In natural conditions, immobility may be viewed as a primitive camouflage, since it impairs visual or aural detection by the predator (Jedrzejewski et al. 1993).

In the laboratory, freezing is usually characterized by total lack of movement, except those required for breathing. This response has been extensively used as an index of fear in experimental studies, as it occurs in closed environments that do not allow escape in response to stimuli that signal noxious stimuli, most frequently electric foot shock (see, e.g., LeDoux 1996).

Flight

In the above oval runway, if the experimenter approaches the rat beyond a critical distance the animal interrupts immobility and initiates flight. As a consequence, the third level of defense was called ‘proximal defense’ by Blanchard and Blanchard (1988). In addition to flight, defensive threat and fight are also strategies that belong to this level of defense.

Flight occurs when the threat is very close and, of course, an escape route is available (Blanchard et al. 1986, 1998b, Ellard 1993, Hanson and Coss 1997). In natural environments, this strategy is adaptive because it rapidly removes the animal from a threatening situation, bringing it to a safe place such as a burrow or a tree, reducing the probability of capture by the predator (Adams 1979, Ellard 1993). Flight also reduces provocative exchanges between animals, particularly in the case of conspecific agonistic interactions. In economical terms, the animal will flee when the likely benefit of staying and maintaining ongoing activities is significantly smaller than the cost of abandoning the place where he is and the activities he is engaged in.

As pointed out before, the basic defense strategies are conserved across species, determined by their common adaptive function. However, the way each species carries out the same defense strategy varies considerably. This is particularly true in the case of proximal defense. Considering flight, the tactics used by a particular animal take into account the location, the direction of attack, and the predator’s hunting strategy. For instance, in gerbils artificially threatened with a black square metal sheet moved above the animals’ head, two ways of escaping are used. When the trajectory of the threatening stimulus is at an angle, the animal is more likely to run away from the object. However, when the threat comes straight ahead, the gerbil usually runs to the opposite direction, passing under the danger stimulus (Ellard 1993). In natural circumstances, this would require the predator to make a quick turn, which is a difficult maneuver for a flying animal. Bonnet monkeys (Ramahrishnan and Coss 2000) as well as bank voles (Jedrzejewski et al. 1993) respond to the attack of their predators (leopards and weasels, respectively) by rapidly climbing upon trees or similar structures. The voles’ tactic is particularly effective against weasels, which can pursue rodents both on the ground and inside burrows. A burrow, but not a tree, is a safe place when the predator is an owl. Past experience is also important. For instance, Ellard (1993) reported that gerbils choose to run toward familiar places, called home bases, even when more accessible, but yet unknown hiding places are available.

Defensive Threat and Attack

When a barrier is placed in one of the corridors of the oval runway preventing escape, and the experimenter approaches the wild rat very closely, the animal adopts an upright posture and shrieks (defensive threat), before jumping to bite the experimenter (defensive attack). Together with flight, these strategies have been categorized as proximal defense (Blanchard and Blanchard 1988).

The function of defensive threat is to communicate an attacking disposition to the opponent, which is often successful in deferring the attack. Threat is usually expressed by characteristic vocalizations and postures (Blanchard et al. 1998b, Koenig and Rothe 1994); furry animals often raise their body hair, looking bigger and more frightening to the assailing animal (Eibl-Eibesfeldt and Sutterlin 1990). Maternal aggression may be included in this category, although its main function is to protect the offspring rather than the female adult (Benus 2001, Neumann et al. 2001).
Defensive threat is a ‘last-resource’ defense strategy, since it occurs when the predator is about to contact the prey or has already inflicted pain, and an escape route is not available (Blanchard and Blanchard 1988, Blanchard et al. 1998b). Yet, in these extreme circumstances certain species, such as the guinea pig, display tonic immobility or death feigning (Olsen et al. 2002), which is qualitatively different from the behavioral inhibition or freezing discussed above.

Defensive attack differs from offensive attack in both behavioral topography and associated physiological changes (Adams 1979). For instance, in defensive threat the cat displays a characteristic arched-back posture with marked sympathetic manifestations (e.g., pupil dilatation and raised fur), whereas a stretched body posture with pupil constriction and smooth fur precede offensive attack. The latter is displayed by a dominant animal in response to a subordinate, and occurs in disputes about environmental resources, mate or social dominance. In this case, vulnerable body regions of the opponent are usually avoided; the same inhibition is not observed in defensive attack, when vital body areas are targeted (Brain 1981). In rats, for example, offense includes lateral attack, chasing, standing on top of the opponent, and bites targeted at the back of the opponent (Blanchard et al. 2001c). In contrast, defensive attack bites are made at the head and the snout, severely hurting the opponent; this may distract the attacker long enough for the defensive animal to flee away (Blanchard and Blanchard 1988).

**Submission**

This strategy of defense occurs in social species that are hierarchically organized, and ranks among behaviors that are aimed at reconciliation or appeasement, avoiding destructive fights among conspecifics (Marks and Nesse 1994, Gilbert 1998a, b).

Typically, after an agonistic encounter between two males, motivated by dispute over resources, territory, mate or social rank, the defeated opponent displays certain postures that inhibit further attack by the winner. This (re-)establishes the dominance hierarchy, preventing future shocks and maintaining social bonds that are necessary for the group’s stability. For the defeated animal, it not only preserves physical integrity, but also keeps integration with the social group, ensuring food and mating resources as well as protection (De Waal 1986, 2000).

In hierarchically organized species both dominant males and subordinates are constantly evaluating the risks and benefits of their social rank, and therefore the convenience of displaying submissive postures (Gilbert 1998b).

**Human Defense**

In the title of Darwin’s (1872) book, ‘man’ precedes ‘animals’, indicating that his main focus was on human emotions. However, extrapolation from non-human behavior to man has always been a matter of concern, because of the inextricable influence of culture in human conduct. Although rudiments of cultural transmission have been documented in chimpanzees (e.g., Nishimura et al. 2003), only in human beings, cultural productions evolve historically. This emergent phenomenon is based on the brain capacity for symbolic language and for remarkable learning and memory, which was provided by the human biological evolution that took place in the Pleistocene. During millions of years human beings have been hunter-gatherers in the African savannas, and these environmental pressures shaped the species features (Buss and Shackelford 1997). No later environment in which human beings have lived, prevailed long enough to significantly change the basic make up that has been built in that geological era.

In contrast, human culture – the set of information and techniques that is transmitted along generations – has evolved in many directions, following rules that are similar to those of biological natural selection, at least according to some authors (see, e.g., Mesoudi et al. 2004). As a result, human behavior has become extremely variable, since in addition to common biological determinants it is heavily influenced by the individual’s history and the particular cultural background of the social group to which the person belongs.

As a result, the search for biological invariants that cut across cultures becomes a very hard task. Aware of these shortcomings, Darwin himself tried to control cultural influences by looking at emotional expressions in children and mentally ill people, and by studying the recognition of basic emotions in human faces among members of different civilizations (Darwin 1872). In-
Interestingly, the last method is now widely used (Ekman 1993).

To our knowledge, only two empirical studies have been carried out so far to identify in human beings the defense strategies that were originally described in non-human animals. The first was conducted by Blanchard et al. (2001b), in Hawaii, while the second was conducted in Ribeirão Preto, so far reported as a master dissertation (Shuhama 2005). Due to ethical constraints, the experimental analysis of human defense cannot be done by direct behavioral observation. As a consequence, both studies used a fear questionnaire that instructed the participants to choose a primary defensive response to each of twelve scenarios involving a present or potential threatening conspecific. These scenarios were designed to vary features known to influence defensive responding in non-human mammals: magnitude of threat, escapability of the situation, ambiguity of the threat stimulus, distance between the threat and the subject and presence of a hiding place.

The results of the Hawaiian study, performed in 160 undergraduate students of both genders, have shown that male and female responses to the scenarios were highly correlated, except for ‘yell, scream, or call for help’, which was frequent for females, but rare for males. Significant correlations were obtained regarding eight specific hypotheses derived from the animal literature, with some support for two additional hypotheses. While three predicted correlations were not supported in these findings, only a single significant correlation was obtained that had not been predicted on the basis of the animal literature. Overall, these results support the view that the defensive patterning is similar for humans and nonhuman mammals (Blanchard et al. 2001b).

The results of the Brazilian study, performed in 248 undergraduate students (Shuhama 2005), were very similar, except for some differences that are likely to be due to cultural factors. For instance, in one of the scenarios a car was said to approach the rear of the vehicle conducted by the participant very closely. The American subjects of the former study (Blanchard et al. 2001b) have unambiguously interpreted this conduct as highly threatening, in contrast to the Brazilian responders. This difference is probably due to the fact that Brazilian car drivers are less concerned about risk than the American conductors, and often approach the front vehicle in order to ask for permission to overtake it. Another difference was that in general Hawaiian women have evaluated the threats in the different scenarios as more intense than men have done, a gender difference that has not been significant in the Brazilian sample studied. In addition, gender differences that were absent in the first study concerning the evaluation of three dimensions of threat, namely ‘escapability of the situation’, ‘ambiguity of the threat stimulus’ and ‘presence of a hiding place’ appeared in the Brazilian study.

Taken together, the results of these studies indicate that human beings share with non-human mammals the same set of biologically determined defense strategies, the expression of which can be modulated, to a certain extent, by cultural influence. Due to the known shortcomings of the questionnaire methodology, further research on this subject matter is clearly necessary. Reminding that the theoretical constructs of evolutionary Psychology and Psychiatry rely on this assumption, it is remarkable that only few attempts to empirically address the question of the commonality of basic psychobiological processes among non-human mammals and human beings have been made so far.

**IMPLICATIONS FOR PSYCHIATRY**

In human beings, defensive reactions are accompanied by conscious feelings of anxiety, fear, or panic. To what extent these feelings occur in non-human animals is a matter of philosophical argument. Nevertheless, if the evolutionary approach is correct, the brain workings that underpin the defensive strategies discussed above are likely to be conserved along evolution, justifying the use of non-human mammals to investigate the neurobiology of human basic emotions. More complex emotions, such as guilt, pride and jealousy, are heavily determined by psychosocial factors and, therefore, unsuitable for this type of analysis.

The possible relations among basic emotions, their disorders and the above defensive strategies are discussed below.

**ANXIETY versus PANIC**

As soon as they have established the concept of levels of antipredatory defense, Blanchard and Blanchard
(1988) became aware of an overlap between the notion of ‘risk assessment’ and the so-called ‘behavioral inhibition system’, considered as equivalent to anxiety by the late British psychologist Jeffrey Gray (Gray 1982). As a corollary, they have suggested that the same structures implicated by Gray in behavioral inhibition – mainly the septum and the hippocampus – are likely to support risk assessment.

Taking a step forward, Deakin and Graeff (1991) have connected animal defense to normal emotions and psychiatric classes of anxiety disorders. A further elaboration has included the three levels of antipredatory defense discussed above (Graeff 1994). A synthesis of these proposals is summarized in Table II.

According to this proposal, risk assessment (or behavioral inhibition) and freezing are related to anxiety, organized escape to fear, and disorganized flight to panic. These adaptive responses can become excessive or occur in inappropriate conditions, thus becoming pathological. This development is likely to occur in the human species, since the patterns of defense that had been shaped under the selective pressures of the Pleistocene, and remained virtually unchanged may become unfit for the challenges posed by the artificial and rapidly changing environment shaped by cultural evolution (Dixon 1998).

In a similar vein, Nesse (1990) and Marks and Nesse (1994) have argued that the DSM-IV categories of anxiety disorders correspond to exaggerations of normal emotions responding to specific danger situations. In particular, they have connected panic to imminent attack by a predator, agoraphobia to environment in which attack is likely to occur, simple phobias to innate fears, such as that of small dangerous animals, social anxiety to threats to status or group membership, and obsessive cleanness to infectious diseases. These aspects will be addressed to in the following sections.

**Pharmacological analysis**

Pharmacology has been useful to test hypotheses derived from the evolutionary approach, because the same drugs that either improve or aggravate anxiety disorders can be administered to laboratory animals under experimental conditions that attempt to model these pathologies. For instance, if the same neurobiological processes are involved in both GAD and risk assessment, then experimental situations that evoke this defense strategy should be amenable to the effects of drugs that affect GAD. A cardinal feature of these situations is to induce approach-avoidance conflict, which has been deemed essential for generating anxiety (Gray and McNaughton 2000). As expected, animal models of anxiety that generate conflict, such as punishment tests, the light-dark transition box or the inhibitory avoidance task in the elevated T-maze prove to have high predictive value in regard to GAD. That is, anxiety indexes in these models are decreased by drugs, such as the benzodiazepine receptor agonists used as medicine for GAD, and increased by drugs like caffeine and several benzodiazepine receptor antagonists, which have experimentally been shown to aggravate GAD (for a review, see Graeff and Zangrossi Jr 2002).

The second best animal model related to GAD is the so-called ‘conditioned emotional response’ or CER. In this paradigm, the freezing behavior of the rat is measured in an experimental box inside which the same animal had previously received noxious electric footshocks. These shocks may be either signaled by a discrete stimulus – the conditioned stimulus (CS) –, usually a tone or a light; alternatively, no such stimulus exists and the environment becomes a contextual CS. In either case, the amount of freezing is attenuated by anxiolytic drugs (Graeff and Zangrossi Jr 2002). This is a clear model of anticipatory anxiety, like that verified in PD, which arises from the expectation of having further panic attacks. This similar pharmacological profile indicates that GAD and anticipatory anxiety are supported by the same neurobiological processes.

When they were designed, the above models of GAD and anticipatory anxiety were thought to represent anxiety disorders, in general. However these experimental paradigms fail to detect antipanic drugs, supporting the proposal that anxiety and panic are neurobiologically different (Deakin and Graeff 1991). To develop animal models of PD, the evolutionary approach is being explicitly used. The core hypothesis is that panic relates to proximal flight organized in the dorsal periaqueductal gray (PAG) matter of the midbrain (Deakin and Graeff 1991). Three such models deserve mentioning. The first one is the flight response in the ‘mouse defense test bat-
TABLE II
Correlation among defense strategies, anxiety-like emotions and their disorders.

<table>
<thead>
<tr>
<th>Potential source</th>
<th>Defense strategy</th>
<th>Critical brain structures</th>
<th>Emotion</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Conflict)</td>
<td>Risk Assessment (Behavioral inhibition)</td>
<td>Septum-Hippocampus</td>
<td>Anxiety</td>
<td>GAD</td>
</tr>
<tr>
<td>Conditioned stimulus</td>
<td>Freezing behavior</td>
<td>Amygdala</td>
<td>Anxiety</td>
<td>Anticipatory</td>
</tr>
<tr>
<td>Conditioned stimulus</td>
<td>Avoidance</td>
<td>Amygdala</td>
<td>Learned fear</td>
<td>Specific phobias</td>
</tr>
<tr>
<td>Distal</td>
<td>Escape</td>
<td>Medial hypothalamus</td>
<td>Innate fear</td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>Flight / Freeze</td>
<td>Dorsal PAG</td>
<td>Panic</td>
<td>Panic disorder</td>
</tr>
</tbody>
</table>


...tery’ (MDTB) that has been developed by Blanchard et al. (2001a). In this test situation, a mouse is placed inside an oval runway (smaller than that for rats), and a stuffed rat is made to approach the experimental animals. As a function of the distance from the rat, the mouse expresses risk assessment, that is, turns around to look at the predator (differently from rats that only show this strategy when the predator is absent), then freezes (much less than rats), and eventually flees when the threat is very close. If a barrier is placed to shut the runway, defensive threat and attack can also be observed. Pharmacological studies have shown that while risk assessment has predictive value for GAD, proximal flight correlates with panic. More specifically, drug regimens that are clinically effective on PD, mainly chronic administration of imipramine, chlorimipramine or selective serotonin reuptake inhibitors (SSRIs), impair the flight response; conversely, agents that induce panic in PD patients strengthen the same behavior (Blanchard et al. 2001a).

The second panic model, the ‘elevated T-maze’ or ETM (Graeff et al. 1993), has been designed to test Deakin and Graeff’s (1991) proposal. This apparatus consists of two arms unprotected by walls, called the open arms, which are perpendicular to an arm enclosed by walls, except at the extremity that gives access to the intersection with the open arms. The ETM is elevated 50 cm above the floor, the test being based on the natural fear of rats in regard to open and elevated spaces, where they cannot scan the environment with their vibrissae (thigmotaxis). Two tasks are successively performed by the same rat in the ETM, namely inhibitory avoidance and one-way escape. For the first one, the animal is placed by the experimenter at the distal end of the enclosed maze three times, at 30-s intervals; for the second, the same rat is placed, also three times in succession, at the end of one of the open arms. In both tasks, the time taken by the animal to withdraw from the arm with its four paws is measured. Typically, in non-drugged rats the withdrawal latency increases along inhibitory avoidance training, as a result of the punitive consequence of the response – to enter an aversive open arm. In contrast, the escape latency remains unchanged, especially if the rats had been pre-exposed to the open arms for 30 min on the day before the experimental session. Pharmacological results reviewed elsewhere (Graeff et al. 1998, Graeff and Zangrossi Jr 2002, Graeff 2004) have shown that inhibitory avoidance is impaired by drugs that improve GAD, and facilitated by anxiogenic agents, while one-way escape is decreased by anti-panic treatment, and enhanced by the panicogenic agent cholecystokinin 4 (CCK 4).

The third animal model of PD consists of measuring behavioral reactions elicited by electrical stimulation of the dorsal PAG. Schenberg and coworkers have verified that the electrical stimulation of the dorsal PAG of rats observed inside a circular arena elicits a series of responses as the intensity of the electrical current increases, namely freezing, walking, running and jumping. Some of them, particularly running and jumping are attenuated by chronic treatment with chlorimipramine. This and other evidence led to the proposal that electrical stimulation of the dorsal PAG is a model of PD (Schenberg et al. 2001).

It is worth remarking that the three models of PD above are attempts to reach the ideal goal of associating predictive value (mainly of drug response) to theoretical validity, as the same hypothetical constructs have been
made to apply to both the animal model and the modeled disorder, under an encompassing evolutionary perspective.

Specific Phobias

Deakin and Graeff (1991) have suggested that active avoidance and escape strategies are related to learned and unlearned phobias, respectively (Table II). In contrast to the situations that induce anxiety, in active escape or avoidance the source of danger is devoid of rewarding value and, therefore, does not engender approach-avoidance conflict. According to Gray and McNaughton (2000), these responses relate to fear. Testifying to the neurobiological distinction between fear and anxiety, pharmacological evidence shows that escape and avoidance responses are unaffected by anxiolytic drugs, unless heavily sedating doses are used (Graeff and Zangrossi Jr 2002). Similarly, clinical phobias are resistant to pharmacological treatment, being successfully managed by cognitive-behavioral therapy (Leaman 1999).

Therefore, phobias may be viewed as disorders of fear. Marks and Nesse (1994), among others, have remarked that most phobic objects – height (acrophobia), closed environments (claustrophobia), blood (erythrophobia), poisonous insects or animals – are the same, regardless of cultural differences, and no longer represent prevalent dangers in civilized societies. Yet, such dangers were prominent in the Pleistocene, having shaped human evolution. Thus, phobias may be an exaggeration of ancestral fears, which have been ingrained in our brains by natural selection.

Learning mechanisms are also likely to play a role in some phobias, although in most cases the patient is unable to recall any original traumatic event related to the phobia. Even if learning is involved, experimental evidence suggests that it is far easier to make aversive association with certain images, like spiders, than to others, such as flowers (Ohman et al. 1975). This indicates that there are innate fear stimuli that are particular to human beings, as it has been shown in several other species (Marks and Nesse 1994).

So far, the evolutionary paradigm has allowed the association between the three levels of antipredatory defense originally described by Blanchard and Blanchard (1988) with the normal emotions of anxiety, fear and panic, and with the nosological categories of GAD, specific phobias and PD, respectively. Among other consequences, this approach has led to significant advances in the knowledge of the neurobiology of these disorders (for a discussion, see Graeff 2004). Let us now move to further defense categories that occur in circumstances other than predatory threat.

Social Anxiety Disorder

Excepting for specific phobias, SAD is the most prevalent of the anxiety disorders. Nevertheless, its pathogenesis is poorly understood (Furmark et al. 2002).

Within the evolutionary approach, SAD is an exaggeration of social anxiety, a trait acquired along human evolution. Social anxiety signals potential threats and activates coping responses (Stein and Bouwer 1997). Furthermore, making a good impression on others may have survival function, since it elicits important social resources and investments from others and prevents social sanction or exclusion (Gilbert 2001).

The evolutionary function of social anxiety is illustrated by the phenomenon of blushing. Darwin (1872) himself remarked that reddening of the face, neck and ears is associated to “thinking of what others think of us”. In animals that are organized in social ranks, status is signaled by appeasement displays, which indicate acceptance of a submissive status as to a dominant conspecific. In human beings, blushing, together with lowered gaze and nervous grin displayed in anxiety-provoking social situations are reminiscent of animal appeasement displays, and signs of embarrassment mitigate the negative reactions of others. An appeasement “false alarm”, or a dysfunction in otherwise adaptive appeasement signals, may therefore underlie SAD (Stein and Bouwer 1997).

Animal social behavior and SAD appear to be governed by similar neurobiological mechanisms. For instance, drugs that increase serotonergic neurotransmission have been shown to increase social affiliation in monkeys (Raleigh et al. 1991) and to improve SAD (van der Linden et al. 2000). Evolutionary perspectives therefore provide a theoretical framework and inspire animal models that may help to better understand SAD pathogenesis.
POSTTRAUMATIC STRESS DISORDER

The critical feature of PTSD is to have undergone an utterly distressful experience. Therefore, fear learning and memory processes, rather than inborn traits, are fundamental for its pathogenesis (LeDoux 1996). However, only a fraction of those exposed to the same traumatic event develop the disorder, pointing to developmental risk factors.

In this respect, Shore (2002) has suggested that an insecure attachment template may result in infants abused by the parents or caretakers in the first two years of life. This experience would affect the development of the right brain hemisphere, which is dominant for attachment, affect regulation, and stress modulation, thereby, resulting in coping deficits that increase vulnerability to PTSD. This deficit would be expressed as an alternation between intrusive terrifying flashbacks and traumatic images (sympathetic arousal) and dissociation, avoidance, and affective numbing (parasympathetic arousal), which are the main symptoms of PTSD.

Although this conception includes an evolutionary element, represented by Bowlby’s (1988) attachment system, it is not directly related to inborn defense strategies, which are the focus of the present review.

OBSESSIVE-COMPULSIVE DISORDER

Undoubtedly, anxiety is a prominent symptom of OCD, but there is no consensus on whether this condition should be classified as a primary anxiety disorder. Indeed, at variance with the DSM IV (APA 1994), the 10th edition of the International Classification of Disorders (ICD 10; WHO 1992) categorizes OCD independently of anxiety disorders.

Supporting the latter view, neuroimaging studies have implicated in OCD brain structures, such as the caudate nucleus and the thalamus (Saxena et al. 1998), that do not belong to the core systems underlying defensive behaviors. Only in the broadest sense of defense against infectious microorganisms or territorial defense (Nesse 1990, Marks and Nesse 1994) would some frequently occurring OCD symptoms, like compulsive hand washing and checking behavior, be related to the concept of defense. In any case, the evolutionary approach on OCD has been fertile, by relating compulsive symptoms to stereotyped grooming, checking and hoarding routines observed in animals, which are programmed in the striatum, as well as to veterinary pathology, such as paw licking dermatitis in dogs and feather pulling in birds, which favorably respond to SSRIs in the same way as OCD (Rapoport 1991).

CONCLUSIONS

The evidence discussed above supports the view that human beings share with non-human mammals a set of defense strategies that correspond to the basic emotions of anxiety, fear, panic and embarrassment. Dysfunctions of the psychobiological processes that underpin these defense strategies and their related emotions would result in the anxiety disorders classified as GAD, PD, specific phobias and SAD, respectively. PTSD would be mainly due to faulty regulation of learning and memory processes, resulting in an abnormal stress response. At least some symptoms of OCD may be due to overactivity of brain circuits that organize routines of self grooming and territorial checking, which are only remotely related to defense.

According to this evolutionary perspective, anxiety disorders may be viewed as dysfunction of defense mechanisms. This approach may provide a reliable theoretical basis for psychiatric classification, which is nowadays based on phenomenology alone.

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RESUMO

Os transtornos de ansiedade são classificados conforme a sintomatologia, decurso temporal e resposta terapêutica. Paralelamente, a análise experimental dos comportamentos de de-
fesa identificou três estratégias comuns a diferentes espécies de animais, desencadeadas por situações de perigo predatório potencial, distal ou proximal, respectivamente. A primeira consiste na investigação cautelosa do ambiente, avaliando o risco. Supõe-se que a emoção que a acompanha seja a ansiedade e sua patologia, o Transtorno de Ansiedade Generalizada. A segunda é expressa pela fuga orientada ou pela inibição comportamental, sendo a emoção correlata o medo, e a patologia representada pelas Fobias Específicas. Finalmente, a terceira estratégia consiste na fuga desordenada ou na total imobilidade, relacionando-se com o pavoreo. O Transtorno de Ansiedade Obsessivo-Compulsivo não está diretamente relacionado com reações de defesa inatas. Esta abordagem evolucionária oferece um paradigma teórico confiável para o estudo dos determinantes biológicos dos transtornos de ansiedade, que pode melhor fundamentar a classificação psiquiátrica.

**Palavras-chave:** estratégias de defesa, emoções básicas, transtornos de ansiedade.

**REFERENCES**


ANIMAL DEFENSE STRATEGIES AND ANXIETY DISORDERS


