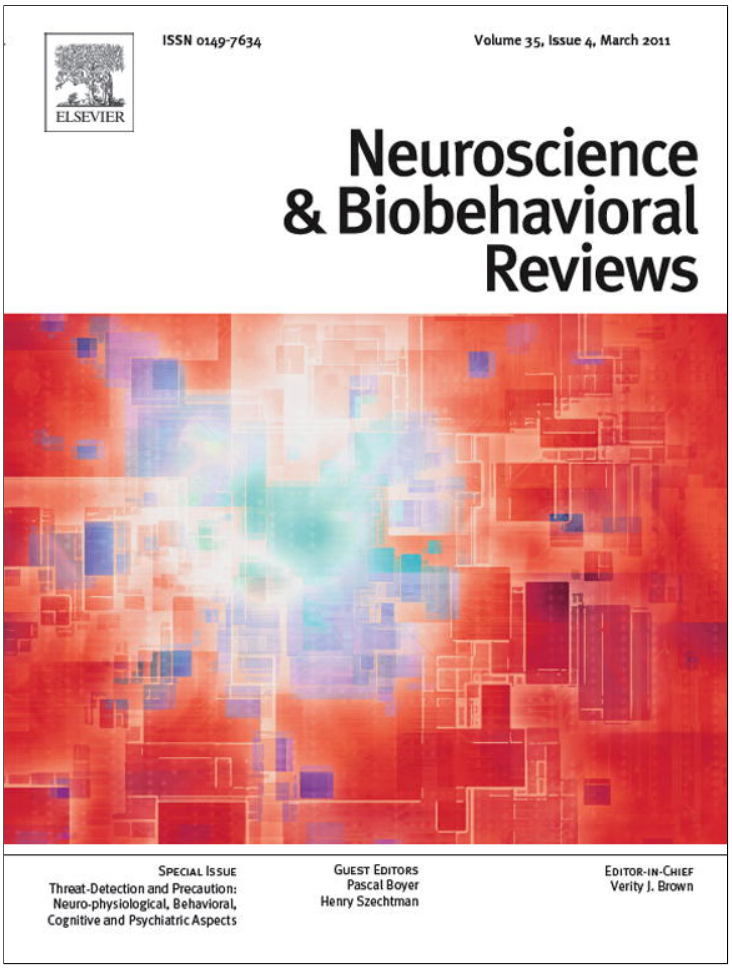

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Review

Risk assessment as an evolved threat detection and analysis process☆

D. Caroline Blanchard[a,*], Guy Griebel[b], Roger Pobbe[c], Robert J. Blanchard[c]

[a] Pacific Biosciences Research Center and Department of Genetics and Molecular Biology, John A. Burns School of Medicine, University of Hawaii, United States
[b] Sanofi-Synthelabo, Paris, France
[c] Department of Psychology and Pacific Biosciences Research Center, University of Hawaii, United States

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ABSTRACT

Risk assessment is a pattern of activities involved in detection and analysis of threat stimuli and the situations in which the threat is encountered. It is a core process in the choice of specific defenses, such as flight, freezing, defensive threat and defensive attack, that counter the threat and minimize the danger it poses. This highly adaptive process takes into account important characteristics, such as type and location (including distance from the subject) of the threat, as well as those (e.g. presence of an escape route or hiding place) of the situation, combining them to predict which specific defense is optimal with that particular combination of threat and situation. Risk assessment is particularly associated with ambiguity either of the threat stimulus or of the outcome of available defensive behaviors. It is also crucial in determining that threat is no longer present, permitting a return to normal, nondefensive behavior. Although risk assessment has been described in detail in rodents, it is also a feature of human defensive behavior, particularly in association with ambiguity. Rumination may be a specifically human form of risk assessment, more often expressed by women, and highly associated with anxiety.

Risk assessment behaviors respond to drugs effective against generalized anxiety disorder; however, flight, a dominant specific defense in many common situations, shows a pharmacological response profile closer to that of panic disorder. Risk assessment and flight also appear to show some consistent differences in terms of brain regional activation patterns, suggesting a potential biological differentiation of anxiety and fear/panic systems. An especially intriguing possibility is that mirror neurons may respond to some of the same types of situational differences that are analyzed during risk assessment, suggesting an additional functional role for these neurons.

Contents

The topic of this special issue: 'Threat-DetectionProcesses: Neuro-physiological, Behavioral, Cultural and Psychiatric Aspects' reflects a great deal of recent research and attention to an important phenomenon that was virtually untouched until about 20 years ago. This particular contribution will focus on behavioral aspects of threat detection processes, mainly but not exclusively on an infrahuman level where they, or some of their components, are variously labeled 'vigilance' (in field studies) or 'risk assessment' (in laboratory work). We will attempt to describe these processes in rodents as part of an evolved pattern of defensive behaviors to threat, noting also an intriguing empirical link to human defenses. As risk assessment and other defensive behaviors have come to be utilized as models for investigation of anxiety and panic in laboratory rodents, a literature on the effects of drugs modulating anxiety and panic will also be described. Finally, some brief attention will

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* Corresponding author. Tel.: +1 808 956 8067; fax: +1 808 956 9612.
E-mail address: blanchar@hawaii.edu (D.C. Blanchard).

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be given to potential neural systems underlying risk assessment, as opposed to other more specific defensive behaviors. In total, these topics provide substantial evidence for an evolutionary conservation of risk assessment and other defenses across mammalian species, and provide evidence in support of a view that these behavior patterns may be linked to anxiety disorders in people.

1. Defensive behaviors

Defensive behaviors have evolved because they improve an animal's chance of survival in confrontations with threat; in particular, threat from predators and attacking conspecifics (Blanchard, 1997). As predators make their living by consuming prey, while attacking conspecifics enjoy substantial rewards as the result of successful attack, both have evolved a number of behavioral (and sometimes structural) adaptations that make such attack likely to succeed. This analysis suggests that successful defense against such an array of adaptations requires behaviors that are sensitive to those features of both the attacker and the environment that are likely to enable particular actions to be useful in thwarting the attack. A first, crucial, step in defense is to detect and determine relevant features of both the threat stimulus and the situation in which it is encountered, in order to mount the optimal response to this particular threat.

This first 'detection and analysis' component of the defense pattern is typically labeled "vigilance" in the context of field studies, or "risk assessment" in laboratory work. While these terms cover much the same material there are subtle but important differences in the phenomena to which they are typically applied. Vigilance, often measured by a cessation of ongoing behaviors and sensory scanning of the environment, largely reflects behaviors involved in detection of threat stimuli, or increased watchfulness after such stimuli are detected. Risk assessment has been more extensively studied in situations manipulated to provide or withhold features such as an escape route, in order to tap the analysis component of this activity; an analytic function being inferred from the clear differences in subsequent defensive behaviors seen in response to these relevant situational differences (Blanchard, 1997). Because the individual behaviors that constitute both initial and consequent components of the defense pattern have been somewhat more precisely described in laboratory work, and because the term "risk assessment" or "RA" is a more comprehensive one, including post-detection cognitive analyses as well as detection-related activities, this is the term that will be used here.

In RA, animals confronted by danger signals or potential dangers abruptly cease their ongoing behaviors and orient toward the threat, utilizing all relevant senses to investigate the stimulus. This action can clearly be seen when overhead cameras record rats confronted with novel or innately threatening stimuli such as the odor of a cat: They orient toward the stimulus with ears forward, to catch slight sounds, and heads moving slowly from side to side so as to facilitate both visual and olfactory detection (Blanchard and Blanchard, 1989). Under some circumstances, the animal may even approach the potential threat, utilizing a low-back or stretched-approach pattern, interspersed with periods of immobility that reduce the likelihood of itself being detected as it attempts to approach and investigate the potential danger (Blanchard et al., 1990).

This RA pattern is prominent when the threat stimulus is ambiguous, either as to its threat potential, OR in terms of aspects that influence the adaptiveness of the specific defensive behaviors that might be utilized in thwarting or escaping it, such as its size, type, and location. Taking the last of these as an example, an as yet unlocalized threat source is a particular danger because efforts to avoid or evade it might actually be counterproductive, for example running into, rather than away from, the unlocalized threat. Moreover, in any violent confrontation an unlocalized animate threat has the advantage of surprise. Thus animals under threat must be aware not only of the presence and location of the threat source, but also of their own location with reference to escape routes or hiding places (Ellard and Eller, 2009; Ydenberg and Dill, 1986). RA-based information may shape the direction of a defensive response such as flight: Ellard and Eller (2009), reviewing the computation of optimal escape routes from threat in gerbils, report that these animals can compute the shortest escape route to a known target even when this is invisible due to the interposition of barriers. In addition, the escape route taken when there is a looming threat stimulus may be a complex function of distance to both the threat and the escape target (Ellard and Goodale, 1988). RA-based information can also determine the choice of one specific defense over another; for example hiding over flight or freezing, when RA indicates that a suitable hiding/protective option is available.

As a brief summary of a complex process, RA enables the animal to predict, with much greater precision than would otherwise be the case, the likelihood of success of each specific defense that it might make with reference to a particular threat. This is not to imply that nonhuman animals (or indeed humans) engage in a conscious process of evaluating each possible behavior in terms of relevant threat and environment conditions. However, the precision with which specific defenses are associated with different circumstances, in both lab rats and humans (see below) make it clear that some type of neural mechanism that provides such evaluative/analytic function is present across mammalian, and likely many nonmammalian, orders (Blanchard et al., 2001a,b).

These specific behaviors, most strongly seen in response to an unambiguously threatening stimulus, include flight if an escape route is available; hiding if there is a place of concealment or protection; freezing (cessation of movement) if there is neither a flight route or a hiding place; defensive threats that increase in probability and intensity as the threat stimulus approaches; defensive attack as contact with the threat stimulus becomes imminent; and, especially in highly social species, alarm cries or other behaviors that may inform other conspecifics of the presence of the threat (Litvin et al., 2007). Within a particular species, the choice of these behaviors may be highly predictable, on the basis of features of the threat stimulus and the situation in which it is encountered (Blanchard, 1997). Thus for wild rats (*Rattus norvegicus*), confronted by a human threat stimulus in an inescapable situation, the distance between the subject and the threat is a rather precise determinant of freezing (distances greater than 1 m), with defensive threat occurring at about 1 m distance, and defensive attack at about .5 m. In a situation that is identical except for the presence of an escape route, the animal flees rather than freezing, but may stop running and turn to attack its pursuer if the distance between the two is reduced to near zero. In other studies, the presence of a burrow or hide box elicits hiding rather than either flight or freezing (Blanchard and Blanchard, 1989; Dielenberg and McGregor, 1999). Other specific behaviors such as an explosive startle reaction or defensive burying may be related to or comprise components of one or more of these general tactics. The latter, for example, involves throwing things—dirt or other substrate—at potentially dangerous objects. If the object responds by movement when hit or covered, then it reveals itself as an animate rather than an inanimate object, thereby contributing to its potential as a threat, and providing information that may be crucial in the choice of an appropriate defensive response (Coss and Owings, 1978).

As these examples suggest, the threat itself, plus expediting or enabling features that make particular behaviors successful in terms of dealing with the threat stimulus, must all be detected and to some degree analyzed in order to be useful. These are core functions of risk assessment. Although—absent some method for selectively reducing risk assessment in a particular situation—this

relationship has not been explored experimentally, risk assessment behaviors have also been reported to be associated with learning about the threat (Pinel and Mana, 1989) and suggested to be a crucial component of context conditioning to threat (McGregor et al., 2002). Thus, even for less encephalized mammals such as rodents, RA appears to be a highly sophisticated behavior that is pivotal in the choice of other, more specific, defenses and in optimizing aspects of their execution, e.g. orientation, and trajectory of movement. It is likely present to some degree in any situation involving threat, but is more protracted, and perhaps more likely to fail, in terms of optimization of response, in situations of great ambiguity or complexity.

Notably, in virtually all such studies utilizing an animal predator (cat, for rat or mouse studies; rat for mouse studies) the subjects were naïve to this type of predator, prior to testing. While it can be argued that flight, freezing or other defenses might have been learned previously in the context of conspecific attack, the fact that some such defenses occur in preweanling animals (Hubbard et al., 2004; Takahashi, 1992) to never-before-encountered predators, argues strongly against a pure learning explanation of their occurrence.

An additional, and potentially equally important, role for RA is in the reduction of defensiveness when threat is not, or is no longer, present. This process involves the same detection activities as does determination of the presence of threat, but it is much more conservative. In contrast to a virtually immediate assumption of defensiveness when threat or cues to threat are detected, determination that a potential danger is not actually dangerous, or that an actual threat is no longer present, may be a very drawn-out business. In one study (Blanchard and Blanchard, 1989), rats living in a visible burrow system and confronted in an open surface area by a cat (which was quickly removed), fled to the burrows and declined to emerge on the surface for at least 5 h: Some had not emerged 20 or so hours later. This "return to normal" function is very adaptive from an evolutionary perspective, in that it permits other behaviors, more useful than defense when no threat is present, to occur. It is obvious that impairment of this mechanism would result in a prolongation of defensiveness and delay or omission of a return to normal, nondefensive behavior, such as may be seen in chronic anxiety or depression (Blanchard et al., 1991). On the other hand, resumption of normal activity after inadequate assessment that the threat is no longer present, could be catastrophic, which accounts for the conservative nature of this aspect of RA.

Both aspects of risk assessment—facilitation/optimization of defense and return to nondefensiveness, may be important components of the adaptiveness of a social or colonial lifestyle, especially in vertebrates. Many social species utilize "sentinels" that, during their service in this role, refrain from normal appetitive behaviors in order to keep watch for danger. Conversely, when a danger is no longer present, such groups may return to normal behaviors more rapidly than do individuals of the same species. Both features reduce time devoted to the threat-detection aspects of risk assessment, and may also improve the accuracy of detection of threatening and nonthreatening conditions (Bell et al., 2009).

2. Some theoretical treatments of defensive behaviors and psychopathology

The association of defensive behaviors with threat, and some apparent behavioral and functional similarities between, particularly, RA and symptoms of anxiety disorders suggested a biological relationship between the two types of behavioral phenomena. This view, at a relatively low and empirical level, was a component of analyses of RA almost from the point where the pattern was conceptualized (Blanchard et al., 1991). Attempts to evaluate such relationships by analysis of effects of drugs effective against anxiety, on specific defenses, resulted in the development of the Mouse Defense Test Battery (MDTB) (Griebel et al., 1995) and later the Rat Exposure Test (RET) (Yang et al., 2004). The MDTB has measures of particular defenses in the context of an (anesthetized) rat approaching the mouse subject in a runway that offers no concealment. In this context RA is measured, first, through a peculiarity of mice being chased by a predator, that they may stop abruptly and sometimes turn to face the pursuing predator, even approaching it on some occasions; and, second, by approaches/withdrawals to a stationary predator. The RET measures mouse responsivity to a rat when the mouse is capable of hiding in a chamber connected via a tunnel to the enclosure in which the (noncontacting) rat is located, and RA is measured by stretch attend and stretch approach behaviors, which can be evaluated in the different locales; chamber, tunnel, rat area.

Coming from a very different angle, behavioral analyses of panic disorder (PD) patients, the English psychiatrist Bill Deakin and the Brazilian neurobiologist Frederico Graeff made a parallel suggestion, that the basic motivation during a panic attack was to flee from wherever the attack was taking place. This hypothesis has resulted in a great deal of attention, particularly in combination with the view that the dorsal columns of the midbrain periaqueductal gray are a pivotal component of the flight system, and a potential substrate for hyperactivity that may be involved in panic attacks. These concepts were important in the development of the elevated T maze (ETM) in which a rodent, after thorough familiarization with both the open (crosspiece) and the closed (stem) component of this elevated maze, is placed on the end of an open arm and allowed to move to (flight) the preferred closed (stem) area. Manipulations that alter the flight component of behavior on this maze can then be compared to those affecting an inhibitory avoidance behavior that is seen when the familiarized rodent is placed in the closed, stem section and its latency to emerge onto the open arms is measured. Flight/escape from the open arms is treated as the primary measure of the ETM, interpreted in terms of a relationship to panic, while inhibitory avoidance may be viewed as more related to anxiety.

Although risk assessment has primarily been considered in the context of anxiety (Blanchard et al., 1991), it is interesting that rumination, an apparently similar process directed more generally at problems in the individual's life, is as prominent a component of depression, as of anxiety (APA, 2000). Notably, "depressed people believe that their ruminations give them insight into their problems" while other aspects of depression such as anhedonia and reduced activity may be seen as allowing more attention to analysis of problems that may have contributed to triggering the depression (Andrews and Thomson, 2009). The more traditional assessment that rumination involves maladaptive cognitions (e.g. Beck, 1967; Seligman, 1975) reflects that, in both anxiety and depression, the clinical condition is associated with failure of detection/analysis mechanisms to arrive at a successful resolution of the problem. Moreover, rumination may mediate the relationship between some genetic factors implicated in depression (here, the BDNF Val66Met polymorphism) and the clinical condition (Hilt et al., 2007).

These general analyses provide some of the background for a more theoretical treatment of the biology of anxiety, in which flight represents action or movement away from a threat stimulus, whereas anxiety involves movement toward threat (McNaughton and Corr, 2004). It is notable that while approach to a threat stimulus provides a very clear criterion for anxiety, and may reflect both the approach sometimes seen in RA as well as the defensive attack associated with extreme proximity/contact with the threat source, the definition of anxiety as approach has lost most of the core concepts and functions of either RA (e.g. that this is a detection/analytic process that responds to ambiguity about the threat stimulus or about the chance of success of specific responses to that stimulus

and in that situation) or defensive attack (that it reflects proximity of threat and involves an element of irritability or agonistic reaction to potential threat stimuli).

3. Drugs differentiate RA and flight

The suggestions that RA may be involved in generalized anxiety disorder (GAD) (Blanchard et al., 1991) and that flight may be associated with PD (Deakin and Graeff, 1991; Griebel et al., 1995) have led to an extensive literature on the effects of psychoactive agents in both the MDTB, and the ETM. Reviews of results obtained with the MDTB (Blanchard et al., 2001a, 2003) provide support for an association of RA with anxiety: Many drugs effective against GAD (a range of benzodiazepines; chronic administration of tricyclics and selective serotonin reuptake inhibitors) consistently reduced RA behaviors. The ability of drugs effective against GAD to reduce risk assessment supports a view that risk assessment is a focal feature of GAD. It is also notable that excessive rumination—potentially a specifically human form of RA— is more associated with women than men, and that females are overrepresented in GAD by about 2–1 (Aldao et al., 2010).

While RA did respond consistently to antiGAD drugs, it is notable that some other defensive behaviors did, as well. In particular, defensive threat/attack was also reduced, a phenomenon that may reflect that GAD is a somewhat mixed category with "irritability" or "hyperreactivity" related symptoms as part of its set of criterion measures, in addition to those reflecting "vigilance and scanning" (APA, 1980). In fact, one drug that is clinically effective against GAD, buspirone, has no significant effect on RA: It does, however, strikingly reduce defensive aggression to a predator, and also contextual anxiety to the situation in which the predator has just been encountered (Griebel et al., 1998). This pattern is also true, although with less polarization, of selective serotonin reuptake inhibitors such as fluoxetine. This reduces defensive aggression and contextual anxiety as well as RA, but with a greater impact on the first two of these (Griebel et al., 1995). "Irritability" and "hyperreactivity" appear to correspond rather well to the specific behaviors that make up defensive (as opposed to offensive) aggression in rodents, and the responsivity of these behavioral traits to drugs such as buspirone, and fluoxetine may be an important mechanism in the effectiveness of these drugs in reducing GAD.

Flight in the MDTB is strongly reduced by drugs effective against PD (high-potency benzodiazepines such as alprazolam; chronic administration of SSRIs, tricyclics and MAO inhibitors) (Blanchard et al., 2003). Moreover, SSRIs, and tricyclics tended to enhance flight when given on an acute basis, providing the first example of an animal model showing this particular bimodal response, which is common in clinical studies (Griebel et al., 1995). Notably, buspirone does not alter flight in the MDTB (Blanchard et al., 2003), and has no effect on PD (Zamorski and Albucher, 2002)

In the ETM, escape/flight reductions were verified after systemic and chronic, but not acute administration of 5-HT reuptake inhibitors which are clinically used to treat PD, such as imipramine, fluoxetine and escitalopram (Teixeira et al., 2000; Poltronieri et al., 2003; Pinheiro et al., 2008). This fits well with findings that the therapeutic effects of such compounds on PD only appear following chronic administration (Johnson et al., 1995). On the other hand, systemic and acute administration of drugs that are clinically effective against GAD (e.g., diazepam, buspirone, and ritanserin) impairs the other behavioral task measured in the ETM, inhibitory avoidance, while leaving the escape/flight response unchanged (Graeff et al., 1998). Such pharmacological results suggest that flight and avoidance tasks measured in the ETM model two different subtypes of anxiety disorders, PD and GAD, respectively. However, this literature does not necessarily support a view that inhibitory avoidance is equivalent to RA. Buspirone reduced inhibitory avoidance in both mice and rats (Carvalho-Netto and Nunes-de-Souza, 2004), but had no effect on RA in the MDTB (Griebel et al., 1998).

4. Functional homologies of defensive behaviors between rodents and humans

These attempts to relate rodent defensive behaviors to human anxiety disorders quickly ran into an information gap: Are there systematic parallels between normal rodent and human behavioral responses to threat? How do these relate to threat-linked psychopathologies? In an attempt to provide some information on the first of these questions, Blanchard et al. (2001b) devised a set of scenarios precisely aimed at determining what people thought that they would do in response to combinations of threatening stimuli and situations previously shown to modulate the form of defensive responses in rodents. This involved creating a set of 12 threat scenarios modeled tightly on the rodent defense data, each setting up a threat stimulus and situation, and asking the respondent to choose their first response to the situation, from a list of 10. The list contained 6 choices based on those made by rodents (flee, hide, scream, attack, check it out, and freeze) as well as 4 more that seemed more likely to be selected by people, such as "ask for an explanation" or "negotiate." However, instructions explicitly invited the respondent to write in their first choice response if this were not on the list.

The scenarios themselves were designed to vary relevant features of the threat or the threat situation such as ambiguity of the threat stimulus, presence of a way out (escape route) or place of hiding/concealment. The major departure from the analysis made in rodent studies was the nature of the threat. In animal studies this was either a predator (MDTB) or some threatening aspect of the situation (ETM). Attacking predators are far from being a common aspect of life in the 21st century, in Hawaii, so we elected to use attacking conspecifics, to reduce the probability that respondents would find these scenarios strange or ridiculous. A group of graduate students in Psychology, with no knowledge of the study or its goals, were asked to rate the purposefully manipulated factors (e.g. threat ambiguity, presence of an escape route or hiding place, defensive distance) for each scenario, assigning a numerical rating for each characteristic, in each scenario. Thus while the authors constructed the scenarios, the numerical ratings for expediting and threat stimulus characteristics resulting from their manipulations were based on evaluations by an independent, blinded, panel.

These scenarios were read and responded to, by a group of 160 undergraduates, evenly divided as to gender, at a community college. Subjects were asked to choose their first response to each such situation, and the first response chosen in each such scenario was analyzed in terms of the same range of factors (threat stimulus and situational characteristics) that strongly determine the form of attack in laboratory animal studies. The similarities in these relationships were striking. Over three quarters of the "first response choices" were similar to those identified in animal research, with the remainder reflecting human abilities presumably not available to nonhuman animals, such as "negotiate". Given 12 scenarios and 2 genders, there were 24 gender/scenario first choices. Of these, 23 were from the "rodent" list. These choices provided some suggestion of a specific gender difference in terms of anticipated first responses, in that while females selected "scream" far more often than men, whereas the latter chose "attack" for many of the same scenarios. This potential gender difference may, however, be exaggerated because of two factors. First, while attackers, even when discrete and present, were not specified as to their sex, interviews with subjects after the test indicated that an overwhelming majority view was that the attackers were male. As adult human

Table 1
Comparison of correlations obtained in two studies, between particular threat and stimulus conditions, and first choice behaviors of human subjects from Perkins and Corr (2004).

	Blanchard et al. (2001a,b) (Hawaii)	Perkins and Corr (2004) (Wales)
1. Risk assessment/ambiguity of threat	**+.89/+.86**	**+.89/+.85**
2. Flight/ambiguity of threat stimuli	−.50/−.63*	−.56/−.59*
3. Defensive attack/ambiguity of threat	−.53/−.29	−.54/−.44
4. Flight/escapability of threat	+10/+.04	+.12/+.10
5. Defensive attack/escapability of threat	*−.76/−.65*	**−.87/−.89**
6. Defensive attack/distance of threat	*−.59/−.64*	*−.62/−.69*
7. Hiding/availability of a hiding place	*+.59/+.63*	+.33/+.30

* $p < .05$.
** $p < .01$.

females are generally smaller than males, an attack choice may have been less desirable for them. A second factor was that men who had actually experienced a conspecific threat situation similar to that described in a specific scenario were more inclined to choose "scream" than if they had not. For all other responses than the "scream–attack" duo, male and female choices were similar, i.e. highly correlated across the 12 scenarios.

The core findings of this study were comparisons between the relationships between threat/expediting stimuli described for rodents, and those found between ratings of the same threat/expediting stimuli and responses in the scenarios. Significant and sometimes extremely high correlations were found between stimulus/situational characteristics and the defensive behaviors with which they were associated. Eight significant correlations ($r = .58$ or greater, in the predicted direction) were obtained; Particularly relevant in the present context was a nearly +.90 correlations between defensive attack and either threat escapability, or defensive distance.

These findings have been replicated in settings that make it difficult to believe that they are dependent on a common cultural orientation. In Brazil, Shuhama et al. (2008) reported that 22 of the 24 gender/scenario choices were of "rodent" defensive behaviors, with agreement (including ties) between these choices and those made in Hawaii in 17 of the 24 cases. Further examination of gender/scenario cases where there were differences suggest that some of these may have been systematic, with the Brazilians choosing "check it out" (RA) or "apologize" where the Hawaii respondents tended to select specific defenses such as "flee" or "look for a weapon." While this may indeed reflect a cultural difference, it is notable that the difference may be socioeconomic or educational rather than nationalistic in origin: The Honolulu sample was from a blue-collar community college while the respondents in Brazil were medical students. In addition, one specific discrepancy may reflect differences in what respondents regard as threatening: In contrast to the Hawaii sample, Brazilians were minimally defensive to a scenario that described being tailgated in a car ("Brazilians always drive like that!" personal communication: Frederico Graeff).

In Wales, Perkins and Corr (2003) repeated the scenario study with results indicating striking agreement with those of Blanchard et al. (2001b) relating to threat ambiguity and RA: Both studies reported positive correlations of .85–.89 between these events for male and female respondents (Table 1). Other specific findings, although in good agreement with the Hawaii study, suggested several ways that defenses again a human threat may indeed be different or more complex than those of rodents confronted with a predator. In particular, the lack of an effect of an escape route on flight may reflect utilization of some of the more "human" responses such as "negotiate" or "apologize". Both might be useful against a human attacker, but not against a predator. Such relatively minor or potentially easily explained differences aside, the data presented by Perkins and Corr (2003) and Shuhama et al. (2008) strongly suggest that the relationships described by Blanchard et al. (2001b) between threat/expediting stimuli and defensive behaviors have a considerable degree of cross-species (as well as cross-cultural) generality, with not only individual human defensive behaviors, but the patterns of their responsivity to important antecedent and surrounding situations showing important similarities to those of nonhuman mammals. This appears to be specifically and particularly true for the relationship between threat ambiguity and RA, enhancing the value of this area of research to conceptualization of psychiatric conditions that may involve processes involved in the detection and assessment of risk.

A recent article by Perkins, Corr, and their colleagues (Perkins et al., 2009) attempted to evaluate some of these relationships in terms of drug effects on actual behaviors. Using a translation of an active avoidance task for human subjects, and with the theoretical perspective (McNaughton and Corr, 2004) that anxiety can be defined in terms of approach to threat while fear involves departure from threat, they investigated the effects of lorazepam and citalopram on joystick approach and avoidance responses of a green dot, to a red dot threat stimulus associated with a loud burst of white noise. They reported that the antianxiety drug lorazepam (Martin et al., 2007), but not the antipanic citalopram (Bezchlibnyk-Butler et al., 2000) significantly reduced risk assessment-like approaches in subjects showing low social fear on the Fear Survey Schedule (Wolpe and Lang, 1974), consonant with a view that RA is related to anxiety.

4.1. Neural systems in RA

As the above studies suggest, there is some foundation for a view that in mammals there is cross-species conservation, not only of individual defensive behaviors, but also for the patterning of defensive behaviors in response to relevant combinations of threat and expediting stimuli. In parallel to this behavioral analysis, there appears to be emerging evidence that some of the brain systems underlying these patterns show similarities from nonhuman mammals to humans. Some of the most beautifully detailed studies of regional brain activation in rats and mice confronting predators have come from the laboratory of Newton Canteras (2002), who has shown consistent evidence of the involvement of a hypothalamic "medial defense zone" (MDZ) particularly involving interconnections of three hypothalamic structures; the anterior, ventromedial, and dorsal premammillary nuclei, with input from the medial, the basolateral and lateral nuclei of the amygdala and bed nucleus of the stria terminalis, and from the hippocampus and lateral septum; and with output through the dorsal columns of the periaqueductal gray. Some of these amygdala nuclei have also been implicated in studies of responsivity to painful stimuli such as shock and in conditioning of both contextual and specific stimuli to painful events (LeDoux, 2007) When the fur/skin odor of a cat, which is known to elicit a strong immediate response and a robust contextual con-

ditioned response following a single exposure, was presented to rats, c-FOS activation appeared in the same MDZ structures and from the medial amygdala and hippocampus/lateral septum, but with less activation in some other amygdala nuclei that appear to respond to other aspects of cat exposure (Dielenberg et al., 2001). Dielenberg et al. (2001) study also found activation in prefrontal cortex, an area that had not been examined in the original Canteras studies.

This view of the neural systems involved in responsivity to a predator has recently been expanded by Cezario et al. (2008) to reinforce the separation of structures like the hippocampus and lateral nucleus of the septum as largely providing information on the context in which the predator is encountered, as opposed to the amygdala sites involved in detection of the threat itself. This article and others (e.g. Carvalho-Netto et al., 2010) note also a projection from the MDZ to thalamic nuclei that appear to be involved in both unconditioned and conditioned aspects of responsivity to a predator, potentially providing a link to cortical areas linked to the production of specific defenses. Notably, virtually all of these studies involved exposure to cat odor or to a cat separated from the rat subject by a barrier. Thus while detection of the predator was clearly involved, specific defenses such as flight and defensive attack were not only unnecessary but generally impossible. While it is not possible to assert that no specific defenses were attempted, the neural systems showing c-Fos activation in these studies may provisionally be considered as more associated with RA and freezing (which frequently occur together) than with specific defenses.

Martinez et al. (2008) reported a similar analysis of c-Fos for mice exposed to a cat under conditions similar to those used in the rat studies from the Canteras lab. They found extremely similar activation patterns to those in rats, providing strong evidence of cross-species generality of this pattern. In addition, they measured the behaviors of their mice, finding high levels of RA and freezing but virtually no flight; providing support for a view that the areas activated in these cat-exposure studies involving barriers between the subject rodent and the threat are more representative of systems involved in RA, than in flight or other specific, active defensive responses.

In the ETM, c-Fos has been evaluated following escape/flight behaviors, and, after a period of inhibitory avoidance (Silveira et al., 2001). Areas activated in association with inhibitory avoidance included the medial amygdala, the anterior hypothalamic nucleus—both prominent components of the system out lined by Canteras and his associates—and the median raphe. In contrast, escape/flight responses were associated with activity in the basolateral amygdala and the dorsal PAG. As the basolateral amygdala is activated in response to a clear and discrete threat (a cat) but not when only a cat odor is encountered (compare Canteras, 2002; Dielenberg and McGregor, 1999), a MeA – BLA difference is consonant with a distinction between RA and specific responses to discrete, present, threat stimuli. Both behaviors were associated with activity in the dorsomedial hypothalamic nucleus, a site in which manipulations may effect cardiovascular changes (DiMicco et al., 2002) and in the paraventricular nucleus of the thalamus, one of several thalamic areas that are potentially involved in an interface between subcortical and cortical mechanisms related to defense (Carvalho-Netto et al., 2010; Hsu and Price, 2007, 2009).

A recent report by Mobbs et al. (2009) used functional magnetic resonance imaging (fMRI) to investigate neural systems active while human subjects were involved in navigation through a two-dimensional maze containing a "predator" symbol that under high "capture" conditions delivered a shock on 7 of 8 contacts with the subject's blue triangle. In a "post-encounter" condition, in which the threat stimulus was present but not attempting to "capture" the blue triangle, i.e. that involved the detection of a threat but no specific responses to it, fMRI indicated activity in a variety of forebrain structures, including the ventromedial prefrontal cortex, hypothalamus, hippocampus and amygdala, an array that is strikingly similar to the regions shown by the McGregor (Dielenberg et al., 2001) and Canteras (e.g. 2002) groups to be associated with rats' responsivity to cat odor or to a cat from which it is separated by a barrier.

In contrast, during a "circa-strike" condition involving active avoidance of the "chasing" predator stimulus, enhanced activity was found in the midbrain (also replicating Mobbs et al., 2007) as well as in several forebrain structures (e.g. mediodorsal thalamus, right striatum and insula, and dorsal anterior cingulate gyrus). All of these have some involvement with motor functioning, and the striatum has been linked to OCD (Fineberg et al., 2010), consonant with a view that they may be particularly associated with specific behavioral aspects of defense.

The parallels between human imaging data and c-Fos data in animals should include caveats due to the very different techniques involved. As one example, c-Fos studies can provide much finer-grained resolution of specific active sites than can current imaging techniques. Also, these studies of regional brain activation to threat in animals have provided an actual unconditioned predator, typically in situations where no specific defensive response was useful, whereas the Mobbs et al. (2007, 2009) studies involved learning, both with regard to the threatening nature of the stimulus, and the active responses by which it might be avoided. However, even with these substantial differences between the paradigms, the similarities between cat and cat odor exposure situations, and fMRI findings during "post-encounter" situations are consonant with a view of parallels in the patterns of brain system activation during detection/analysis of threat stimuli, for rats and people.

4.2. Another set of parallels: mirror neurons and the prediction of behavior outcomes

Mirror neurons are neurons that fire not only when a subject is moving its own body (hand or mouth) but also when observing another individual performing the same action. These neurons have been detected and investigated in monkeys and in humans (Rizzolatti et al., 1996, 1999) and there are some indications that similar neurons may exist in rats (Marini et al., 2008) as well. Much of the excitement concerning mirror neurons relates to their potential role in development and to the possibility that deficiencies in the mirror neuron system may be involved in some of the sociality and social cognition problems in autism spectrum disorders (Hadjikhani et al., 2006). However, mirror neurons may have a number of functional roles, some of which may be only indirectly related to the ability to imitate others, or to understand the social and emotional implications of observed gestures and actions.

A recent study by Caggiano et al. (2009) identified a subset of mirror neurons in rhesus monkeys that encode space in operational rather than metric terms. Specifically, this discovery involved analysis of 105 ventral premotor cortex mirror neurons from two monkeys. Each monkey was tested in a fixed primate chair, with the reach of its arm defining a peripersonal space within which it could contact and grasp objects. Outside this reach was extrapersonal space such that the monkey could observe an experimenter touching and grasping objects, but could not reach these objects itself. About half of the motor neurons tested responded to the experimenter's actions regardless of whether they occurred in the peripersonal or extrapersonal space, whereas about a quarter responded only to events in the peripersonal space, or, in the extrapersonal space. When a transparent panel in the primate chair was closed and the monkey could still see but could no longer reach objects that had previously been located in its peripersonal space, changes were seen in about 40% of the mirror neurons that had

shown selectivity in responding, depending on the location of the event. These changes involved both sets of selective mirror neurons, with some that had previously responded to events in peripersonal space ceasing to respond when the monkey could no longer reach the object, and with some that had previously responded only to events in extrapersonal space now responding to events that had previously been inside the monkeys reach but were no longer reachable by the subject.

These findings provide an almost eerie echo of two crucial factors in the control of defensive behavior. First, about 50% of the mirror neurons were responsive not only to distance, but to a particular type of distance; the distance over which the subject was capable of acting and potentially controlling the action, given its specific and highly familiar situation; the primate chair. Second, and even more remarkably, a subset of these neurons reacted quickly and appropriately to changes in that functional distance. While, given the way in which mirror neurons are identified (i.e. in terms of responsivity to both action and observation of similar actions by another) this phenomenon may certainly be interpreted in the context of the subject's ability to imitate behaviors, it may also have nothing to do with imitation but instead reflect a determination that is functional in a more general context: Can I complete or control this action, to produce some particular (successful) outcome? In this particular situation, the barrier makes potential actions that might have been completed (grasping the object) impossible. It simultaneously indicates that the experimenter's action of grasping the object (located in what was previously the subject's peripersonal space) can be successful, without possible competition or interference from the subject. In both cases, the mirror cells could be interpreted as responding to changes in the predicted outcomes of actions by the subject itself, or by another.

It is in the context of defense that such determinations are perhaps most crucial. First, defensive distance, the distance between the subject and the other, has a clear and strong influence on the form of defensive behavior: Flee or attack? Freeze or attack? Flee or freeze? Threat or attack? These crucial decisions are made in the considerable part on the basis of defensive distance. More specifically, Caggiano et al. (2009) data indicate that mirror neurons are responsive to barriers, even when these are transparent. The differences in defensive behavior seen when a place of protection is available (e.g. Blanchard, 1997) make it clear that somewhere in a rodent brain is a system capable of attending to, detecting and responding to a barrier or other protective feature between the animal and a threatening stimulus. In short, in defensive situations, neurons with these features would be invaluable in enabling the animal to more precisely evaluate the possible outcomes of its actions in terms of success or failure in avoiding, evading, thwarting, or frightening a potential attacker. They would function to increase the chance of success of individual defenses, based on some basic features of the environment and defensive distance that constitute core expediting stimuli for defense.

An additional function hypothesized for mirror neurons is that of facilitating the subject's understanding of the emotions of others, by enabling them to imitate facial expressions indicative of emotionality (Iacaboni, 2009). While this seems unlikely to be useful to prey in the context of interactions with predators, an important additional aspect of defense is in the context of conspecific attack. Is it of value to an animal to be able to "read" the facial expressions—or possibly other gestures—of a conspecific that is in a position to attack the subject, and may or may not do so? If an ability to interpret the emotion-based intentions of conspecifics works for empathy, why not for the equally intense emotions expressed by a conspecific attacker? Monkeys and man, the species in which mirror neurons have been identified, do have a wider and more expressive range of facial expressions than do rodents, but there is no real reason to believe that the functions ascribed to mirror neurons are to be found exclusively in the area of hand and facial movements. Experienced observers can tell, with a very high degree of probability, that one rat is about to attack another, even if knowing nothing of the history or current circumstances of the two animals; piloerection is the cue. As in the case of defensive distance, or, changes in peripersonal vs extrapersonal space due to the presence of barriers, gestures of another may contain information that is potentially determinative of the firing of mirror neurons. And, all of this information may provide strong clues as to the success, or otherwise, of actions that the subject might take in threatening situations.

To be clear, these considerations do not indicate that defense, or more specifically RA, represents the behavioral outcome of activation of systems reflected in mirror neuron firing. What the studies described do indicate is that some mirror neurons are demonstrably performing functions similar to those embedded in the patterning of defense; functions that we have ascribed to RA. They add to information indicating that RA and its analytic functions are found in both rodents and humans, and that activation in a set of common neural structures may occur in the context of threat detection and analysis.

In summary, these studies strongly suggest that RA is an important evolved biobehavioral pattern; one that may be influential in shaping the form and outcome of a variety of significant behavioral systems. The pharmacological link between RA and drugs effective against particular anxiety disorders suggests that this link may be selective, and that the RA process is involved, to different degrees, in a variety of threat-related psychopathologies. In the context of the present special issue, deficiencies in the ability of RA to predict that specific actions will be successful, or indeed that actions already performed have been successful, may have dramatic effects on the duration and form of defense (see articles on OCD in the current issue). These analyses extend the range of anxiety-related psychopathologies in which RA deficiencies may be an important factor.

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