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Review article

Context and trade-offs characterize real-world threat detection systems: A review and comprehensive framework to improve research practice and resolve the translational crisis

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ABSTRACT

A better understanding of context in decision-making—that is, the internal and external conditions that modulate decisions—is required to help bridge the gap between natural behaviors that evolved by natural selection and more arbitrary laboratory models of anxiety and fear. Because anxiety and fear are mechanisms evolved to manage threats from predators and other exigencies, the large behavioral, ecological and evolutionary literature on predation risk is useful for re-framing experimental research on human anxiety-related disorders. We review the trade-offs that are commonly made during antipredator decision-making in wild animals along with the context under which the behavior is performed and measured, and highlight their relevance for focused laboratory models of fear and anxiety. We then develop an integrative mechanistic model of decision-making under risk which, when applied to laboratory and field settings, should improve studies of the biological basis of normal and pathological anxiety and may therefore improve translational outcomes.

1. Introduction

Decision-making under risk is relevant to behavioral researchers from a variety of disciplines, including all those who study topics ranging from predator-prey interactions in the field to anxiety disorders in humans (e.g., Clinchy et al., 2011; Mobbs et al., 2018). Anxiety occurs

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Box 1
The distinction between anxiety and fear

We use the term anxiety to refer to a preparatory response to possible future threatening events, especially in situations where there is conflict between different goals, such as between avoiding a potential threat and being attracted to food. Anxiety is often seen and measured by increased vigilance or caution ('risk assessment') when moving around. By contrast, fear is a response to an unambiguous immediate threat. In nature, we might see animals increase their vigilance after detecting the scent of a predator because they are not sure whether the predator is there or not. By contrast, when predators are sighted, prey may freeze or flee rapidly. The latter demonstrates fear. Humans may be anxious when they oversleep their alarm clock and miss an important meeting. By contrast, humans may be fearful if they have been fired from a job and cannot produce income to pay for food or rent.

in response to risk and is generally related to a sense of apprehension. This apprehension results, in part, because there is a conflict between a potential threat and the potential of receiving a benefit such as foraging or potential mate (McNaughton and Corr, 2004) It may be quantified as increased vigilance and can become maladaptive when it interferes with otherwise necessary behaviors that enable survival (Box 1). Risk-related decisions are thought to maximize fitness; hence, individuals that make the right decisions are those whose genes are passed on to future generations. A key insight about these decisions is the involvement of trade-offs where the costs and benefits of risky behaviors are evaluated and the optimal outcome maximizes benefits while minimizing costs. Costs primarily ensue from the risk of predation, competition, disease and parasitism (Gallagher et al., 2017). Humans, especially in modern societies, additionally live with the risks of losing social status and employment (Björkqvist, 2001). A key lesson from behavioral ecology is that in order to optimize outcomes, individuals cannot avoid all risks; by doing so it would be impossible to acquire resources or mates (Blumstein, 2008).

Both, anxiety and fear, are emotional states, associated with physiological and psychological responses. Anxiety and fear are adaptive responses if it is possible to correctly differentiate safe and threatening stimuli. If individuals are unable to distinguish between threatening and safe stimuli, anxiety and fear may become maladaptive. If such a maladaptive state lasts longer, it becomes pathological and in humans we might diagnose an anxiety disorder. Decisions about risks may vary according to a range of internal factors (Kiyokawa et al., 2009) and the external environment (Campbell-Palmer and Rosell, 2011; Orrock and Danielson, 2009) at the time a threat is detected. For example, moon phase is known to influence antipredator decision-making in several prey species. Oldfield mice (*Peromyscus polionotus*) and woodmice (*Apodemus sylvaticus*) are more likely to respond to predator cues on full-moon nights when the mice are most visible, and hence vulnerable, to their predators (Orrock and Danielson, 2009; Orrock et al., 2004). By contrast tammar wallabies (*Notamacropus eugenii*) increase the time spent foraging under moonlight, suggesting that they feel safer under illumination when high visibility improves their ability to detect predators (Biebouw and Blumstein, 2003). Humans are also influenced by moonlight. In Tanzania, where lion attacks are common, the full-moon causes anxiety among people (Packer et al., 2011), ostensibly because the coming nights will be darkest. Among non-vertebrates, European leeches (*Hirudo verbana*) modify their behavior according to how deep they are within water, and whether they have been fed a blood meal (Palmer et al., 2014; Palmer and Kristan, 2011). Thus, there are a variety of ways that context (light, depth of water, or a meal in these cases) modifies decision-making based on the assessment of these factors.

Consequently, there is widespread recognition that trade-offs, and the context in which they are made, must be incorporated into models of decision-making (Caro, 2005; Lima, 1998). However, not enough laboratory research considers these cost-benefit trade-offs and contextual variables that characterize anxiety and fear in nature (Gray and McNaughton, 2000; McNaughton and Corr, 2004). This is especially important if we are to make progress in solving a crisis in translational biomedical research (Manjili, 2013) where results from preclinical studies cannot approximate pharmacological effects in clinical studies or real-world settings (Kinsella and Monk, 2009; Oppenheim, 2019), or similarly, in conservation and wildlife management where fear-based management tools cannot approximate outcomes from fear cues in the laboratory (Parsons et al., 2018).

For instance, an isolated laboratory rodent might be exposed to a specific stimulus that could generate fear or anxiety, but the type and extent of its behavioral response is shaped by other factors, such as the animal's current satiety status (internal drive; Lõhmus and Sundström, 2004) or the presence of further potential dangers (external context; Nersesian et al., 2012; Orrock et al., 2004; Parsons and Blumstein, 2010). Despite this potential of contextual variables to profoundly influence behavior (Wolff, 2003), many such variables are sacrificed in laboratory/neurobiological models specifically to improve power and replicability (Klumpers and Kroes, 2019). The resulting animal models allow us to use powerful approaches such as optogenetics and chemogenetics to understand neurobiological mechanisms underlying decision-making under risk. They also allow us to manipulate internal and external conditions we wish to understand, but cannot be directly manipulated in humans. Yet, these models are not intended to account for the influence of context in real-world decision making.

Here, we review and discuss the trade-offs that should be taken into account during antipredator decision-making in wild animals, and integrate them with neurobiological models of fear and anxiety. We emphasize the importance of internal drives and external contexts in decision-making via an integrative mechanistic model, for which we have summarized the neural basis for threat-induced defensive behaviors. While calls for real world models have been increasing over the past decade (Kinsella and Monk, 2009; Oppenheim, 2019), our approach is novel in that we develop a more integrative model that shows how decision-making in response to conflicting internal drives is influenced by fear and may result in anxiety. Lastly, following our review, we propose how decision-making research can be improved, and thereby facilitate new semi-realistic and naturalistic approaches. These outcomes are intended to address the growing bench-to-bedside gap in translational medicine (Manjili, 2013), while also enhancing wildlife conservation and management.

2. Controlled experiments versus real-world studies – costs and benefits

2.1. Benefits and costs of controlled laboratory experiments

Neuroethological laboratory experiments are often performed under standardized conditions where it is typical to modify only one critical variable while all others are fixed. Standardization can include the use of inbred strains of rodents and investigators' clothes behavior (Sorge et al., 2014), use of skincare products (Brower et al., 1998), sex, and reproductive status (Vaclavik et al., 2012), as well as user–not animal–defined timelines (Bruinsma et al., 2019). Nevertheless, attempts to totally control context remain illusory (Crabbe et al., 1999). Instead, standardization is expected to greatly reduce the variance in measurements created by 'irrelevant' contextual factors, which then makes it easier to detect the small effects of a targeted manipulation (Richter

Box 2
Neuroethological studies of threat-induced defensive behaviors, fear and anxiety

Neuroscientists have identified neural circuitries and neurotransmitter systems involved in behaviors induced by threat (for comprehensive reviews see Davis and Whalen, 2001; LeDoux, 2000; McNaughton and Corr, 2004; Phelps and Ledoux, 2005; Ullmann et al., 2013). For ethical reasons, physical encounters with live predators are typically not used in laboratory settings (Gluck et al., 2002). Therefore, predatory stimuli consist of predator models, silhouettes, scents and odors, calls, or artificial stimuli such as electric foot shocks (Duvarci et al., 2009; Pereira and Moita, 2016). In a simplified scenario (Fig. 1), the amygdala (AMY) is activated by the onset of clearly identifiable or specific predatory cues. If these stimuli are ambiguous and/or very general (i.e., they are neither clearly identifiable nor easily predictable), the bed nucleus of the stria terminalis (BNST) is activated (Duvarci et al., 2009; Goode et al., 2020). The AMY is thought to mediate a phasic, or punctuated, state of fear (red pathway in the figure below), while the BNST mediates sustained or continual fear that is akin to state of anxiety (orange pathway). The neural activity of the AMY or BNST, and thereby states of fear and anxiety, are modulated by several inputs including the hippocampus (HIP), which is important for contextual cues, encoding and memory processes.

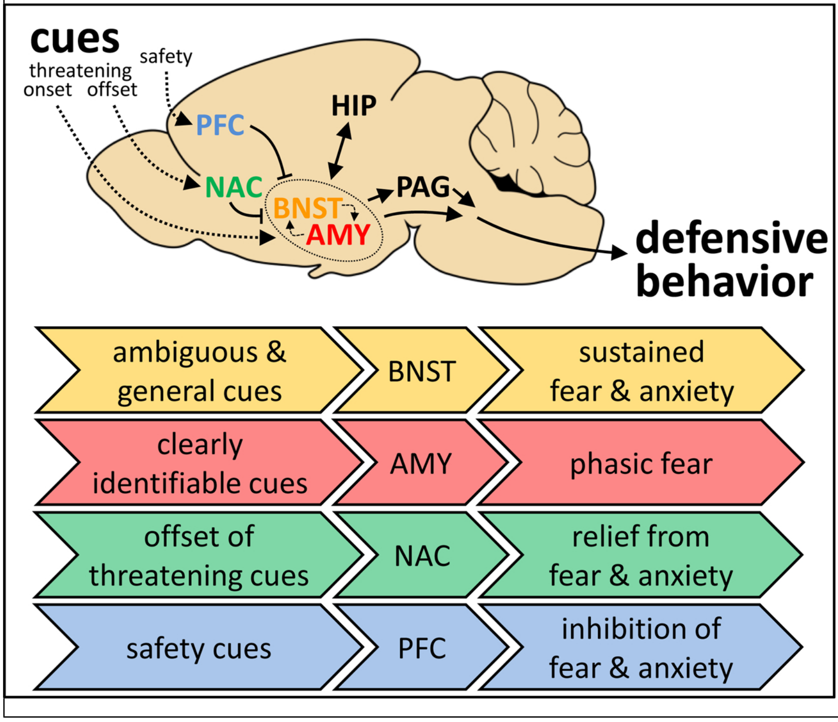
The states of fear and anxiety support and/or induce anti-predator behavioral responses that are supported and/or induced via projections from the AMY or BNST to midbrain and brainstem structures such as the periaqueductal gray (PAG). The latter brain site orchestrates defensive responses including freezing and escape behavior (Fadok et al., 2017; Vianna et al., 2003). The offset of threatening cues activates the brain reward system including the nucleus accumbens (NAC) which inhibits AMY/BNST activity and/or the descending pathways and thereby induces relief from fear and anxiety (green pathway). Safety-related cues activate the prefrontal cortex which inhibits BNST/AMY activity and thereby the expression of fear and anxiety (blue pathway).

With the help of innovative approaches such as viral vectors, optogenetics, chemogenetics, in vivo calcium imaging, whole brain imaging and single-cell mRNA sequencing (transcriptomics), our knowledge about the neuronal correlates of defensive behavior is steadily growing. We now have access to remarkable imaging techniques whose temporal and spatial resolution are orders of magnitude more precise compared to methods available just a couple of decades ago (Calhoon and Tye, 2015; Canteras and Graeff, 2014; Silva et al., 2016; Tovote et al., 2015). Despite these successes, there are limitations in how we incorporate this knowledge into real-world outcomes such as pharmacology and wildlife conservation.

So far, studies on innate/reflexive defensive responses, have identified only a few potential targets for the pharmacotherapy of anxiety disorders which are associated with exaggerated fear responses (e.g., specific phobia or panic attacks), such as the endocannabinoid system (Micale et al., 2013; Patel et al., 2017; Riebe et al., 2012). Even less progress has been made in the identification of drug targets for the therapy of fear-related anxiety disorders such as for Generalized Anxiety Disorder within the past 15 years (Millan, 2003). This might be ascribed to the simplicity of current test paradigms, which rely mostly on a putative approach/avoidance conflict between “the innate drive to explore novel environments” and the drive to avoid open, illuminated areas (Belzung and Griebel, 2001; Sousa et al., 2006). This conflict, however, is often only minor due to very limited appetitive drive in laboratory subjects.

In line with previous hypotheses (Gray and McNaughton, 2000; McNaughton and Corr, 2004), we propose that anxiety states emerge when animals are motivated to approach a resource (e.g., by hunger, thirst, social/sexual interest) despite the existence of risk-related cues. For instance, a coyote traversing the prairie will not approach a campfire unless it is hungry. The resulting approach-avoidance conflict will create an anxious state, which could be reversed by anxiolytic treatment (e.g., with benzodiazepines). If it is not hungry, then we can increase the dose until it falls asleep before moving closer to the campfire. If the conflicting drive of hunger is present, however, the animal will continue forward. Unfortunately, the latter situation is analogous to most experimental settings with laboratory rats and mice (Wolff, 2003), which rarely include antagonistic internal drives. In addition, pharmacological “validations” with benzodiazepines are often not instructive since they may simply ameliorate behavioral changes caused by the stressful injection procedure (Meijer et al., 2006). This creates a condition whereby we cannot generate reliable conclusions about the behavior of untreated animals. Together, this explains why our knowledge about the neuronal circuits involved in anxiety states is inferior, including the proposed role of the septal-hippocampal system (Gray and McNaughton, 2000).

Box Fig. 2: Neural basis for threat-induced defensive behaviors, fear and anxiety. The bed nucleus of the stria terminalis (BNST) is activated by ambiguous and general cues, whereas the amygdala (AMY) is activated by clearly identifiable cues that more precisely predict potential threats. The BNST and the amygdala then activate the periaqueductal gray (PAG) and/or other midbrain and brainstem sites engaged in defensive behaviors.



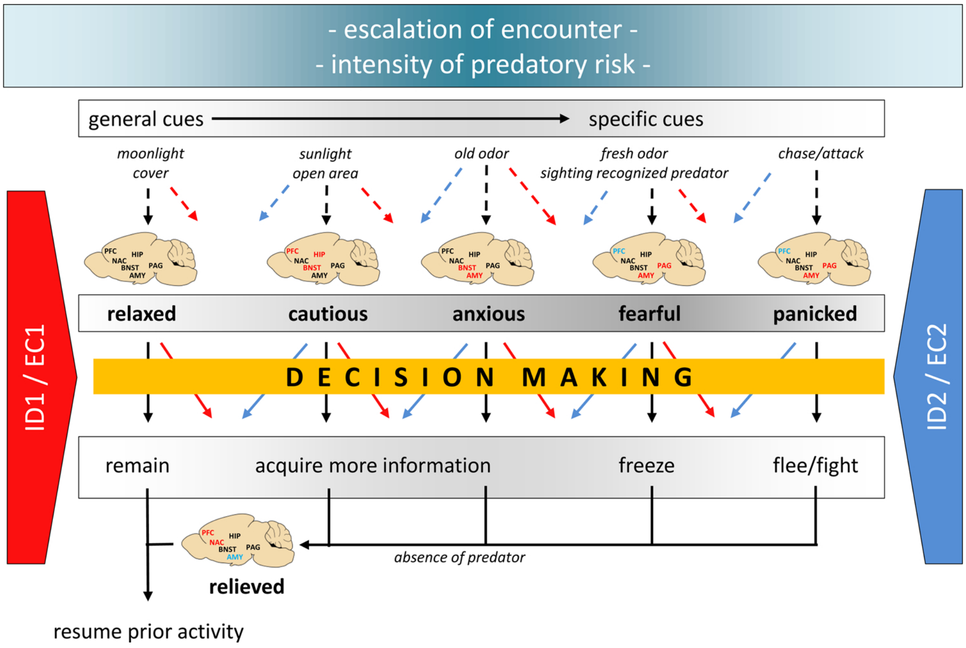


Fig. 1. Integrative mechanistic model for decisions made under risk. How cues influence decisions depends on a variety of contextual factors. For instance, a precise cue such as fresh predator odor (top gray bar) typically (black arrows) leads to a fearful internal state (middle gray bar) and an adaptive response such as freezing behavior (bottom grey bar). However, contextual factors including external context (EC, e.g., variable illumination [red to blue]) and internal drives (ID, e.g., variable hunger/thirst [red to blue]) may influence this process and lead to other behavioral responses (red/blue arrows). Therefore, the same cue may not always lead to identical or similarly safe responses in different contexts (black arrows). Over time, the absence of new risk cues, or changes in contextual factors should lead to a decline in anxiety and ultimately a resumption of prior activities. This process may also be accelerated or delayed by internal and external contextual factors. For abbreviations, see Box 2.

et al., 2009). Such focused approaches are helpful for studying the neurological or pharmacological basis of simple behavioral responses such as startle or escape (Wotjak, 2019). However, many laboratory tests are chosen somewhat arbitrarily, suggesting that we may be creating an evolutionary mismatch which could make our resulting inferences suspect (Mobbs et al., 2018).

However, research on many real-world pathologies such as stroke, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease are recognized as having been stifled by the narrow approach used in studying them (Oppenheim, 2019). This is especially true for diseases with pathological decision-making such as anxiety disorders, trauma- and stress-related disorders, or depressive disorders. In particular, research on these diseases would benefit from a different approach (Oppenheim, 2019; Wolff, 2003) that includes studies of outbred populations with highly-variable genes (Modlinska and Pisula, 2020), and with multiple animals exposed to competing stimuli in semi-realistic or naturalistic settings (Clinchy et al., 2011). These real-world conditions may include use of shelter (Bowen et al., 2012), different distances to threat cues, and the presence of conspecifics (Bowen and McGregor, 2014). Furthermore, dependent variables should be diverse and contextually relevant. For example, the freezing response in fear conditioning studies (Wotjak, 2019) could be considered along with other behaviors that are potentially modulated by fear, such as changes in grooming (Mooring and Hart, 1995; Smolinsky et al., 2009), resting or sleeping (Beauchamp, 2008), avoidance, flight, escape, or specific vocalizations (Loughry and McDonough, 1988).

2.2. *Benefits and costs of field experiments*

In ethological field studies, natural heterogeneity is typical as it is essentially impossible to control all contextual variables (e.g., weather, vegetation cover, animal energetic states). Field biologists therefore, compensate by aiming for sufficient replication and use complex statistical models to control for and explain as much variation as possible. However, the ecological literature also contains many studies that consider too few response variables. For example, field researchers may focus exclusively on the number of physical approaches an individual makes toward a scent in order to evaluate a potential wildlife deterrent (Garvey et al., 2016). Yet, this response alone does not consider predator inspection, the process whereby animals approach a scent to acquire more information about the predator (Banks et al., 2014; Fishman, 1999). Similarly, context may confound interpretation when a hungry animal elects to forage near a risky cue (Carthey and Banks, 2018). Thus, a suite of contextual factors including distance from shelter, social facilitation, age, type and strength or intensity of the fear stimulus may influence decisions (Parsons et al., 2018). Since these contextual factors can vary greatly between locations, studies of the same species using the same methods often produce different results (Apfelbach et al., 2005). Thus, we suggest that field researchers could also benefit from a better consideration of contextual cues (Owen et al., 2017). For instance, when three contexts (amount of shelter, distance from a cue, and intensity to the fear cue) are manipulated, a fear-cue can actually become an attractant, and vice versa (Parsons et al., 2018).

Compared to laboratory studies, researchers studying free-living animals often know little about how internal and external factors and prior experiences may influence their subjects' decisions. Internal factors like genotype, motivation, age, sex, disposition or personality (Wolf and Weissing, 2010) are rarely known in ecological field studies. The same is usually true for knowledge of body condition (e.g., nutritional state or percentage body fat), health or immune status (Poirotte et al., 2016), pubertal and ovarian/gonadal hormone levels, breeding status, satiety level, and parasite or disease status (Wingfield et al., 1990; Muller and Wrangham, 2004; Prokop et al., 2010). External factors like dominance status or position in a social network (Blumstein et al., 2017; Davis et al., 2009; Mady and Blumstein, 2017), and the presence or absence of con- and hetero-specific individuals (Drakeley et al., 2015; Jones et al., 2016; Patriquin et al., 2018) may influence risk perception. These variables can be specifically accounted for in laboratory studies, but cannot be easily controlled in field experiments. Prior experience may include inherited factors (Crews et al., 2012) maternal effects (Monk et al., 2000) and prenatal experience (Monk et al., 2012), epigenetic modifications (Monk et al., 2012), natal habitat experience (Davis and Stamps, 2004; Stamps and Swaisgood, 2007), food preferences (Symonds et al., 2006), as well as recent encounters with habitats, predators, or conspecifics (Blumstein et al., 2002). Such prior experiences can be more specifically controlled in laboratory studies.

These factors demonstrate why it is difficult to replicate laboratory research in the field and vice versa (Apfelbach et al., 2005; Oppenheim, 2019; Wolff, 2003). To find ways to mutually overcome these limitations, we discuss how external and internal factors influence decision-making under real-world conditions. Our first step is to understand the proximate basis of threat-induced behaviors, which is outlined in Box 2.

3. Towards an integrative mechanistic model of decisions made under risk

Behavioral decisions such as where to forage, when to rest, and with whom to mate all have consequences (Suraci et al., 2016). A large body of literature already considers decisions made under the risk of predation (Caro, 2005; Lima and Dill, 1990). Contemporary humans are not usually exposed directly to predation (but see Gurung et al., 2008; Packer et al., 2011), but are threatened by other factors including social pressure (Gurung et al., 2008; Stein and Stein, 2008), work or financial pressure, highly cognitive-demanding situations such as in heavy traffic (Knöll et al., 2018), or unhygienic living conditions (Soto, 2009). These threats induce psychophysiological and neurocognitive states that are similar to those observed under predatory threat in animals (Hagenaars et al., 2014; Mobbs et al., 2015, 2018; 2020). However, contemporary humans make decisions about how to respond to such cues associated with these threats based on evolved patterns of risk assessment, which mirror the well-studied decision-making processes undertaken by free-living animals avoiding predation. For example, in a shooting-decision task, police officers froze in anticipation of threat, as well as having bradycardia and stronger activation of defensive midbrain structures (Hashemi et al., 2019).

To highlight the importance of external contexts and internal drives in decision-making, we work from the external environment toward internal conflicting drives. We begin by presenting an integrative mechanistic model that recognizes context and trade-offs (Fig. 1). This model shows how fearful stimuli and the context in which they are presented alter a potential prey's emotional state. The model and alternative reactions are grounded in how fear and anxiety are reflected in neural activity (Box 1). Prey, or humans under duress, must trade-off the risks and rewards associated with a particular scenario before making a behavioral decision.

In laboratory studies, subjects with controlled and thereby very similar intensities of internal drives (ID; e.g., hunger, thirst, etc.) are exposed to a particular cue (Fig. 1 top gray bar) in a controlled and thereby similar external context (EC; e.g., illumination/availability of shelters). Since it is common to use genetically very similar and experimentally naive animals, the variation in reactivity to the cue produced is limited. As a result, the cue typically evokes similar emotional states (dashed black arrows and middle gray bar), and hence, similar decision-making and subsequent adaptive responses (solid black arrows and bottom grey bar). In contrast, in natural settings, each individual has different intensity of ID and faces the cue in a variable EC. In this situation, the differences in ID/EC pattern either intensifies (red dashed arrows) or attenuates (blue dashed arrows) the emotional state the cue has evoked. This process is further influenced by the large genetic variability of individuals in natural settings and their diverse set of previous experiences. Differences in EC then further modulate decision-making and thereby the subsequent behavioral response. That is, individuals in a safer or more dangerous EC chooses a weaker (blue solid arrows) or stronger (red solid arrows) behavioral response as compared to individuals in a neutral EC. For example, a satiated animal may freeze in response to detecting a fresh predatory odor. However, a hungry animal exposed to the same cue may make a decision that trades-off the need to acquire more food (blue dashed arrow). This could then lead to the decision to ‘actively acquire more information' rather than ‘freezing’, especially if further contextual variables such as the presence of shelter in the form of darkness or vegetation is present (solid blue arrow). In contrast, even a hungry animal may freeze when the same cue is presented together with bright illumination and no shelter (solid red arrow). In a satiated animal, the same cue may generate flight (red arrow).

In humans, internal drives and external context can lead to maladaptive decisions made under risk. Based on unfavorable experiences or contexts, otherwise potentially benign cues may be over-interpreted which may lead to anxiety disorders. Cognitive-behavioral therapy (CBT) then works as a psychological exposure-intervention with the goal to relearn appropriate risk assessments, and responses to cues (change red arrows to black arrows). For example, internal states reflected in endogenous testosterone levels in anxiety patients predict the efficacy of subsequent exposure-based CBT sessions (Hutschemaekers et al., 2020). Current pharmacological or neural (brain stimulation) interventions, on the other hand, target the neural response directly and hence reduce the expression of pathological behaviors, often without using context to remap the pathological relationship between affect and response (i.e., they simply weaken the black dashed arrows).

4. A comprehensive model of decision-making in response to conflicting internal drives

We next introduce a comprehensive model showing how the pattern of ID and EC may modulate the emotional state in Fig. 1. In natural settings, an individual usually detects multiple stimuli concurrently (Fig. 2A left). Although effects of each stimulus are analyzed individually in the laboratory (Fig. 2A middle), behavioral responses are determined by the combination of detected stimuli (Fig. 2A right). In the field of ethology, these questions are mostly analyzed by asking how EC affects appetitive or repellant drives. By contrast, in other research fields, such as neurobiology, endocrinology, and physiology, researchers seek to determine how ID modulates these drives (Fig. 2B). For instance, an individual's emotional state can be expressed as an integration (Fig. 2C gray arrow) of vertically connected vectors for the appetitive (Fig. 2C blue arrow) and repellant drives (Fig. 2C red arrow). Let's imagine a wild rat that detects peanuts and fresh fox odor simultaneously.

There are two ways that EC and ID could be integrated and influence the motivational state of the rat, and thereby, also the decision of how to respond behaviorally. First, EC and ID change the direction of the summation vector by changing the length of a repellant vector. For example, low illumination or a lack of shelter may decrease or increase the length, respectively. Similarly, repeated encounters with fox odor or experiences with near-capture may decrease or increase the length, respectively. Second, EC and ID change the direction of summation vector by changing the length of the appetitive vector. For example, hunger or satiety may increase or decrease the length, respectively. In both of these cases, the longer of the two vectors will be more prominent in determining the internal drive and thereby the decision an individual makes. This model can further illustrate the intensity of the conflict between the appetitive and the repellant drive, represented by the gray area between the vectors. Returning to our previous rat example, an individual may experience conflicting drives when the repellant drive is triggered by fresh fox odor (i.e., anxiety), but this may be ameliorated by the appetitive drive triggered by peanuts. If individuals continuously experience such extreme conflicts, anxiety may lose its adaptive value and become pathological.

In humans, chronic anxiety can lead to depression, social phobias, panic and ultimately, reduced quality of life (Gorman, 1996, 2004). Wild animals brought into captivity or otherwise protected from predation may exhibit loss of fear and anxiety (Carthey and Blumstein, 2018), and this is detrimental if animals are to survive within a predator-rich environment. Thus, it is often essential to recreate the conditions that contribute to anxiety (Blumstein et al., 2002; Griffin et al., 2000). Among humans, the opposite is true; we seek to ameliorate cues and contexts that produce anxiety.

5. An appeal for more integrative studies of decisions made under risk

This integrative, mechanistic model guides us to identify key contextual factors that influence experimental results in the laboratory and

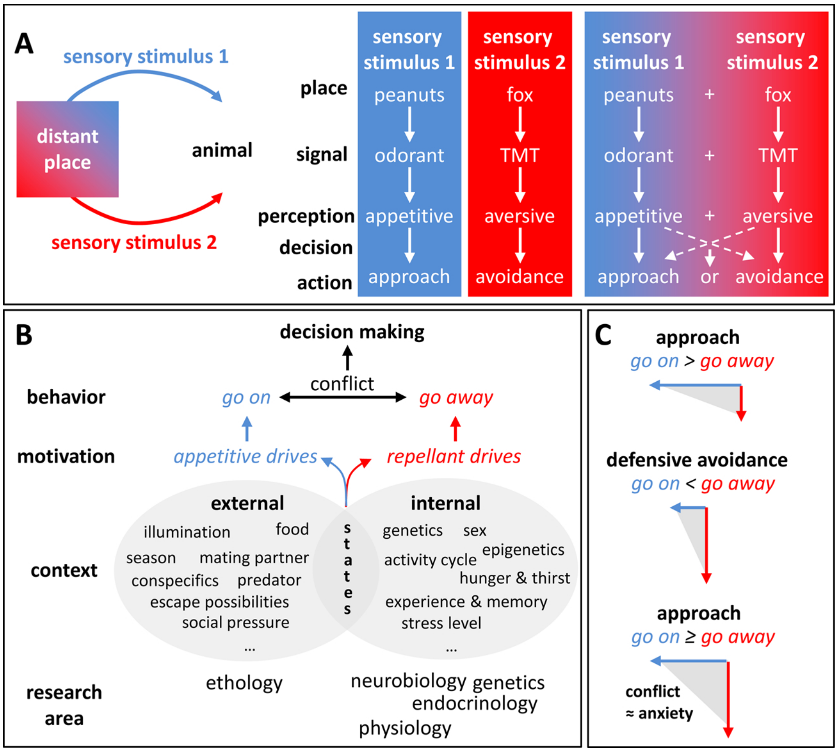


Fig. 2. Decision-making in response to conflicting internal drives may result in anxiety. A) An animal may perceive distinct sensory stimuli from a distant place which could signal reward (e.g., food–blue) or danger (e.g., predator–red). B) The process of decision-making depends on external and internal contextual factors which together define an animal's current state and, thus, affect the outcome of the conflicting situation. C) Anxiety emerges if the appetitive and repellent drives are similar in intensity.

field, under natural and pathological conditions. For instance, returning to Fig. 1, we can now appreciate how wild animals or humans with anxiety are affected in their decision making: low(er) risk cues may trigger higher risk emotional states (Fig. 1: red-dashed arrows, middle part of figure) and hence costly behavioral and physiological responses (Fig. 1: lower side of figure; red-solid arrows). The relevance of arousal and affective states on such cost-benefit analyses has been illustrated in recent computational work on risky decision-making in anxious individuals (Browning et al., 2015; Piray et al., 2019). Fig. 1 also illustrates that in the extreme case of anxiety disorders, low risk situations can elicit intense defensive behaviors – instead of relief-associated behaviors – even after the threatening cue has disappeared (see also Fig. 2). In this way, the model helps us understand how, where, and why mismatches between stimuli and responses occur and can be used to improve the designs of such studies by integrating or manipulating certain internal and external factors.

Given the importance of interactions between cue strength and type of representation (Fig. 1), as well as internal drives (Fig. 2) and prior experience, we suggest that it will be profitable to design experiments to systematically vary context both in the lab and in the field.

There are some laboratory protocols that have explicitly incorporated context (Kirlic et al., 2017; McDermott et al., 2018). Other examples include the Vogel conflict test where water-deprived animals gain access to a water bottle, but with the risk of punishment (Millan, 2003; Sousa et al., 2006), and the test of novelty-induced suppression of feeding (Bechtholt et al., 2007) where food-deprived animals can access food in a novel cage. Furthermore, there are varied approaches using prior aversive experience (e.g., early life stress) which do not only modulate anxiety in adulthood (O'Mahony et al., 2009) but also alter sensitivity to anxiolytic drugs (e.g., (Lakehayli et al., 2015). Social fear conditioning paradigms have been developed in which an approach to a strange conspecific individual was either punished (Toth and Neumann, 2013) or rewarded, enabling quantification of the approach-avoidance trade-off under acute threat in the light of reward or costly avoidance (Klumpers et al., 2018). The use of virtual reality for the study of anxiety also enables us to modify context variables in a controlled manner (Ben-Moussa et al., 2017).

We further suggest that analysis of a broader spectrum of active and passive defensive behaviors be considered. For instance, for exploration-based test paradigms (such as the elevated plus-maze, light-dark avoidance and open field tasks), it is important to consider factors other than only the position of the animal (in the open or enclosed arm). This includes not only measurements of locomotor activity to control for motor impairments or lack of motivation/exploratory drive, but also a detailed analysis of different behaviors in the different compartments of the setup.

For example, animals might actively explore a 'risky' compartment of an experimental apparatus to assess the risk but, if it is scared, it may freeze in that compartment and remain. This could mislead the researcher to assume this is a safe location for the animal. The same applies to the non-risky compartment in which an animal may express active exploration but could freeze or sleep. Without analysis of a broader spectrum of behaviors, it remains difficult to infer how risk is perceived. In human research, the increased use of virtual reality has the advantage that a broader spectrum of active and passive defensive behaviors can be tested, enabling us to study how context and treatment interventions influence a variety of decision-making behaviors (Ben-Moussa et al., 2017). At this point, such technology is unavailable for field studies, although technological advances in augmented reality might help provide an avenue for this approach (Bimber and Raskar, 2005).

But does incorporation of context help improve translational outcomes? There are a number of outstanding questions in this regard. For instance, we recognize that to add context we reduce, to some degree experimental control; is this ultimately useful? Can we improve translational outcomes more by increasing internal contextual variation (e.g., using different genetic strains, different phases of hormonal cycles, or 'personality' types of animals) or by increasing variation in the external context that animals experience (e.g., the structural complexity of the social and physical environment)? More generally, can a mechanistic understanding of the brain regions involved in risk assessment improve our understanding of behavior in the field, and can this be used to improve management interventions to conserve rare species or manage over-abundant species? Can insights from the field improve the design and interpretation of laboratory studies and can these improve translational outcomes? For example, it is well known that high testosterone levels are associated with reduced risk-and threat-avoidance, biasing the amygdala to social-threat approaches in animals and humans (Maner et al., 2008; Radke et al., 2015). Endogenous testosterone levels predict symptom reduction with exposure therapy in patients' social anxiety disorder (Hutschemaekers et al., 2020), but can treatment-efficacy be augmented using direct testosterone administration? Last, by analyzing non-overt behaviors (e.g., release of hormones and pheromones, ultrasonic vocalization, etc.) as well as overt behaviors in relevant contexts, can we expect to gain further understanding of key decisions about anxiety and fear? Time will tell and we hope that this updated review and framework stimulate the tests that will allow us to answer these questions.

Given the advantages and disadvantages inherent to both laboratory and field experiments, we encourage more future collaborative research amongst laboratory and field researchers (Davidson et al., 2019; Mobbs et al., 2018; Modlinska and Stryjek, 2016; Stryjek et al., 2012). For example, we will gain a better understanding of decision-making by testing wild animals in naturalistic and also under controlled laboratory conditions, and by focusing on only one or few specific cues and on the same subjects with different prior experiences and different internal drives. Some combined laboratory and field experiments already exist (Wolff, 2004). European leeches (*Hirudu verbena)* have been useful models in determining how multiple external and internal factors such as depth of water they are found in and how recent they have fed on a blood meal can contribute to maps of behavioral responses to stimuli (Palmer et al., 2014; Palmer and Kristan, 2011). Zebrafish (*Danio rerio*) have also been extensively studied for their behaviors such as shoaling, homeostatic and social dominance responses that vary according to external contexts such as light conditions and water flow, but also internal contexts such as developmental endocrine conditions (Aho et al., 2017; Gerlai, 2011; Ivy eat al., 2017). A potential shortcoming of these studies on poikilothermic animals is that they may have limited translational value because these species do not have the neurogenesis seen in homeothermic animals such as small mammals. Thus, if neurogenesis is important in the context of understanding and treating psychiatric diseases, studies of mammals may be required.

There are also attempts to bring laboratories into the field and to use enclosure studies in which wild animals can be tested under semi-natural conditions (Schmieder et al., 2012; Siemers and Schnitzler, 2004). Enclosure studies offer possibilities to narrow down the vast number of external factors potentially influencing decision-making and to better understand key trade-offs.

Laboratory animals, particularly the ubiquitous rodent models where pre-existing data are readily available (Whishaw and Kolb, 2004), could be tested under more natural conditions to study their decisions in more enriched environments. There is a growing desire to create alternative models to the laboratory rodent (Modlinska and Pisula, 2020; Stryjek and Modlinska, 2016). Such tests are becoming increasingly feasible given new approaches and technology (remote sensing and machine learning methods) to access and monitor wild rodents (Byers et al., 2017; Norris, 2019; Parsons et al., 2015). These experiments can be done in natural habitat enclosures or at least in more naturally enriched and less artificial experimental settings (Pisula et al., 2012; Stryjek et al., 2018; Stryjek and Pisula, 2008) than elevated plus-mazes or small, sterile boxes. We hope that by highlighting the importance of context in decision-making, new collaborations are formed and through them, and that we enhance our understanding of fear and anxiety in both the lab and the field to help resolve growing problems in translational research across disciplines.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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