

Anxiety: Here and Beyond

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Abstract

The future harbours the potential for myriad threats to the fitness of organisms, and many species prepare accordingly based on indicators of hazards. Here, we distinguish between defensive responses on the basis of sensed cues and those based on autocues generated by mental simulations of the future in humans. Whereas sensed threat cues usually induce specific responses with reference to particular features of the environment or generalized responses to protect against diffuse threats, autocues generated by mental simulations of the future enable strategic preparation for hazards that may not require an immediate response. The overlap of these mechanisms makes defence effective and versatile, yet can manifest as contemporary anxiety disorders in humans.

Keywords

anxiety, fear, prospection, threat management

Chance favours the prepared mind.

Louis Pasteur

In the course of life, animals are regularly confronted with indicators of potential threats. Anxiety is characterized by sensitivity to such indicators, manifesting in the form of coordinated mental, behavioural, and physiological response that prepares the animal for threat. We start by outlining selective pressures posed by some of the main types of threats faced by our forebears and highlight some of the key mechanisms involved in the management of these threats. We then delineate three categories of responses to threats. Threat cues can forebode specific or diffuse dangers, therefore leading to *targeted* or *generalized* responses, respectively (see Table 1 for glossary). Humans are also capable of mentally constructing potential threat scenarios on the basis of *autocues* in the absence of relevant sensory input, enabling strategic preparation for a variety of threats that do not require an immediate response and may occur even in the remote future. These are not meant to represent mutually exclusive categories; rather, they are proposed to capture different “levels” of threat

management that often overlap in humans. We appraise the strengths and limitations of the main research approaches used to study each of these and then outline avenues for future work, including at the intersection of these response types. Finally, we consider the implications of this approach for understanding some of the challenges facing the treatment of anxiety disorders.

The Evolutionary Significance of Threat

A *threat* is defined here as any entity or event that is expected to cause harm. *Ultimately*, threats are significant insofar as they could negatively affect the passage of an individual’s genes to the next generation. Though by no means exhaustive, the following list denotes some of the broad classes of threats that are thought to have played an important role in shaping threat management processes in various animal species:

- Attack threats refer to dangers posed by other animals (Barrett, 2005; Hart & Sussman, 2008; Mobbs, Hagan, Dalgleish, Silston, & Prévost, 2015).

Table 1. Glossary of terms.

Autocue: Self-generated prompt (i.e., not triggered by immediate sensory input).

Declarative knowledge: Information that can be explicitly recalled.

Emotionally competent: An entity or event that elicits the appropriate emotional response.

Episodic foresight: The capacity to imagine future scenarios and to use these imaginings to guide present action.

False alarm: A defensive response to a cue that is not indicative of an actual threat.

False negative: Failure to respond defensively to a cue that is indicative of an actual threat.

Generalized response: An anxiety response toward diffuse threat possibilities.

Hypervigilance: Alertness directed toward threat-related contexts or stimuli.

Mentally simulated associative learning: Learning a cue–outcome or action–outcome association on the basis of mental simulation.

Pessimism: A state of (exaggerated) expectation for the occurrence of a threat.

Prospective cognition: Future-oriented mental processes.

Semantic memory: Generic knowledge about the world, such as the meaning of words, or the names, properties, or locations of entities.

Sensory threat cues: Sensory information arising in the external or internal environment that is indicative of threat.

Targeted response: An anxiety response toward a specific threat.

Threat: Any entity or event that is expected to cause harm.

Ultimate: A type of explanation that focuses on the evolution of a trait, in terms of its adaptive significance and phylogenetic history.

- Resource threats refer to the possibility of running out of vital supplies such as food and water (Berridge, 2004; A. R. Damasio & Carvalho, 2013; Panksepp, 1982).
- Abiotic threats are dangers arising from the nonliving environment such as fluctuating temperatures and storms (Buss, 2009; Nesse, 1998; Orians & Heerwagen, 1992).
- Mate-selection threats are those involved in securing an effective reproductive partner, such as mating with a partner with poor genetic fit to the environment or low potential for investment in shared offspring in pair-bonding species (Geary, Vigil, & Byrd-Craven, 2004; Miller, 2011; Zietsch, Verweij, Heath, & Martin, 2011).
- Contaminative threats are borne by pathogens such as bacterial or viral infectious diseases (Fumagalli et al., 2011; Neuberg, Kenrick, & Schaller, 2011; Tooby & Cosmides, 1990).
- Social threats are dangers derived from conspecifics, such as aggression from another individual or group (Kurzban & Leary, 2001; Nesse, 2016; Trower & Gilbert, 1989).

Species and individuals may differ in the detection and management of such threats, based on vulnerabilities to different risks. Thus, whereas ungulates scan the horizon for terrestrial attack threats, monkeys also scan the skies for aerial attack threats. Similarly, within a species, different stages in life can reflect different vulnerabilities. For example, in humans separation anxiety appears to be highly prevalent among infants, reflecting the dangers posed by isolation from a caregiver at this vulnerable age; and social anxiety is common in adolescence, reflecting the importance of reputation management in the creation of cohesive social bonds (for review see Boyer & Bergstrom, 2011); and worries about the health and welfare of kin are common during the postreproductive lifespan, perhaps reflecting attempts to manage threats to inclusive fitness (for review see Miloyan & Bulley, 2015). Finally, individual learning experiences account for considerable

individual differences within the same species and life stage. In what follows, we discuss various examples of how associative learning shapes detection and responses to threat cues.

The Means of Threat Management

Upon detecting an *emotionally competent* threat cue, animals tend to exhibit cognitive (e.g., *hypervigilance*), physiological (e.g., cortisol secretion), and behavioural responses (e.g., fleeing; (A. R. Damasio, 1995; LeDoux, 2015b). Whereas fear refers to the class of defensive response that is triggered by manifest or immediate dangers, anxiety refers to the class of response to cues that may precede danger (Boyer & Lienard, 2006; Fanselow & Lester, 1988). The adaptive significance of fear and anxiety, then, lie in these responses minimizing harms to fitness (Cannon, 1916; Darwin, 1872; Marks, 1969).

The distinction between fear and anxiety corresponds loosely to the proposed neural dissociation between the fight, flight, freeze system (FFFS) and the behavioural inhibition system (BIS) with respect to the midbrain/brainstem and prefrontal cortex (Gray & McNaughton, 2003; McNaughton & Corr, 2004, 2008): Whereas the former is involved in immediate responses to acute threats (e.g., predation), the latter plays a role in avoidance or approach-oriented behaviours aimed at carefully gathering information about potential threats to inform response selection (Blanchard, Blanchard, & Rodgers, 1991; see also Mobbs et al., 2009; Mobbs et al., 2007).

There is an asymmetry between false alarms and false negative errors in the detection of threat cues. False alarms are ordinarily not particularly costly, only requiring the metabolic expenditure of mounting the response and the possible forsaking of other behaviours (an opportunity cost). In comparison, false negative errors may have a more acute cost to reproductive fitness: failing to respond to particular types of threat cues (e.g., those indicating potential predation) could quickly result in death. That is not to say that false alarms cannot be harmful:

High responsiveness to threat cues may lead to repeated opportunity costs that may turn out to be consequential. Nonetheless, natural selection appears to have shaped threat management processes to err on the side of caution in response to threat cues that could bear sudden, lethal consequences (Nesse, 2001).

Flexible responses to sensory threat cues do not necessitate explicit reasoning that the cues forebode danger. In fact, *declarative knowledge* is neither necessary nor sufficient to trigger appropriate responses upon sensing a threatening cue. For example, lesion studies indicate that individuals with damage to the amygdala, who are able to identify threatening stimuli and describe what the appropriate responses entail, fail to produce those responses on the basis of external sensory cues (Bechara et al., 1995; Feinstein, Adolphs, Damasio, & Tranel, 2011). Conversely, individuals with hippocampal lesions who are unable to explicitly recall information about threatening stimuli are able to produce the appropriate response when presented with the relevant cue because associative fear learning processes remain intact (Bechara et al., 1995). This is well illustrated in a classic example reported by neurologist Édouard Claparède (1911/1950). Hiding a tack in his palm, Claparède pricked one of his amnesic patients during a greeting handshake. On subsequent days, despite having no explicit memory of ever meeting her doctor, the patient refused to shake his hand. A subsequent neurological case study suggested that neither the hippocampi nor the amygdalae may be required for such learning to occur (Tranel & Damasio, 1993). Taken together, these findings indicate that declarative knowledge is neither necessary nor sufficient to trigger the appropriate defensive response.

However, declarative knowledge appears to be necessary (but not sufficient) to trigger the appropriate response on the basis of autocues in humans (A. R. Damasio, 2000; A. R. Damasio, Tranel, & Damasio, 1990; Suddendorf & Busby, 2005). For example, people with hippocampal amnesia seem to be impaired in their ability to imagine and prepare for future scenarios (Hassabis, Kumaran, Vann, & Maguire, 2007; Klein, Loftus, & Kihlstrom, 2002; Kurczek et al., 2015; Kwan, Carson, Addis, & Rosenbaum, 2010; but see Dede, Wixted, Hopkins, & Squire, 2016; Squire, McDuff, & Frascino, 2011; Squire et al., 2010); and although individuals with lesions to the ventromedial prefrontal cortex (vmPFC) are able to generate, entertain, and compare future plans, they often fail to prepare prudently for the future by engaging appropriate behaviours (A. R. Damasio, 2000; Harlow, 1848). We now examine the basic principles underlying associative learning about specific threats and some key strengths and limits with extant research approaches in this domain.

Defensive Responses to Sensed Cues: Specific Responses

Animals routinely respond to sensed cues that are indicative of potential threats. Pavlovian learning enables the acquisition of information about cues that precede danger, and a capacity for instrumental conditioning enables learning about threats that may emerge on the basis of particular behaviours. Associative

learning thereby allows animals to prepare for potential threats based on precedent (Öhman & Mineka, 2001). Higher order conditioning also enables individuals to learn about cues that previously surrounded, but did not directly precede, danger (Gewirtz & Davis, 2000). Although in laboratory studies higher order conditioning is often observed to be weaker and more transient than first-order conditioning, it can nonetheless be powerful. That defence responses are sometimes triggered among individuals with posttraumatic stress disorder (PTSD) following the perception of innocuous environmental cues (e.g., colours or sounds) that have long ceased to co-occur with threats serves to illustrate the flexibility and durability of these responses (Ehlers, Hackmann, & Michael, 2004).

Neural circuits underlying the acquisition of conditioned fear and the expression of threat-induced defensive reactions are highly conserved in mammals (for reviews see Johansen, Cain, Ostroff, & LeDoux, 2011; LeDoux, 2012). Darwin (1872) initially proposed that the expression of fear was shaped by natural selection. A century later, Marks (1970) observed that the stimuli and situations that most frequently comprise the objects of fears or phobias seem to bear adaptive significance. This same notion formed the basis of Seligman's (1971) proposal that humans are predisposed to learn about fear-relevant stimuli and situations that bear adaptive significance, which explains the rapid acquisition, persistence, and resistance to extinction of such fears. In humans, for example, heights and some species of animals are widely regarded as anxiety-provoking (Curtis, Magee, Eaton, Wittchen, & Kessler, 1998; Seligman, 1971). At the same time, Bolles (1970) proposed that different species of animals are predisposed to respond to punishments in different ways, suggesting that instrumental responses bear adaptive significance. Together, these observations undermined the assumption of equipotentiality that characterized the learning models of the time: it became increasingly implausible that any threat-related stimulus or threat-induced response could achieve the same potency as any other stimulus or response.

Bolles (1970, p. 32) also recognized that the experimental procedures used to study the learning models of the time seemed to be "totally out of touch with what is known about how animals defend themselves in nature." Almost 50 years later, we do not think that this limitation of experimental studies has been appreciated (see also Perusini & Fanselow, 2015). For example, applications of the Pavlovian conditioning paradigm typically consist of cues that immediately precede threats. In such scenarios, an animal is conditioned to exhibit a fear-like response to the conditioned stimulus (CS), given the imminence of the subsequent harm, rather than an anxiety response that is triggered when there is uncertainty about the unconditioned stimulus (US). An advantage of this approach is that it enables defence responses to be elicited reliably, which can be helpful for identifying proximate neurobiological mechanisms (e.g., Tovote, Fadok, & Lüthi, 2015). However, this approach is ineffective for investigating the dynamic relationships between animals and their environments that are so critical to understanding the expression of anxiety. For example, vervet monkeys in the wild sound unique alarm calls to indicate the presence of aerial or

terrestrial threats, and engage differential responses accordingly (Seyfarth, Cheney, & Marler, 1980). Indeed, laboratory-based methods necessarily limit the possibilities and uncertainties that animals face in their natural habitats (Bar-Yam, 2015). A resurgence of comparative observational studies aimed at uncovering complex relationships between animals and threat scenarios in their natural environments, where animals must frequently face trade-offs between threats and opportunities (for discussion in a predation context, see Lima & Dill, 1990), are needed to address these inherent limitations of laboratory studies. Laboratory studies, in turn, can be useful for understanding the proximate mechanisms underlying ecologically valid scenarios.

In the wild, a particular threat may occur with some frequency or cost in a specific context, or with varying frequencies or costs across multiple contexts; a threat could also co-occur with other threats or with the pursuit of opportunities, and such conflicts perhaps entail competing responses. Therefore, the mechanisms underlying specific defensive responses to external cues cannot be properly understood in isolation from these variables. For example, recent work has demonstrated that superb fairy-wrens increase nest vigilance after seeing a brood-parasitical Horsfield's bronze cuckoo near their nest (but not a harmless white-plumed honeyeater; Feeney & Langmore, 2015). However, nest attendance can attract predators, and therefore the wrens face competing threats (Davies & Brooke, 1988; Feeney & Langmore, 2015). Another host species, the reed warbler, similarly faces competing threats posed by the brood-parasitical common cuckoo and the predatory hawk (York & Davies, 2017). Recent findings suggest that the cuckoo is adept at exploiting trade-offs in its host's defensive behavioural repertoire: Upon surreptitiously laying its eggs in its host's nest, the cuckoo makes sounds similar to those of a hawk, which seems to reduce the host's nest vigilance and increases the success of the parasitic behaviour (York & Davies, 2017). These results suggest that there can be differential costs to engaging different defences, and specific threat cues may at times be ineffective for appropriately modulating defensive responses. We turn now to the topic of generalized responses.

Generalized Responses

Many animals benefit from the ability to prepare for diffuse threats on the basis of contextual (external or internal) cues that indicate vulnerability, even if such cues are not directly indicative of particular threats (Bateson, Brilot, & Nettle, 2011). Responsiveness to contextual cues is to some extent species-specific, reflecting the particular susceptibilities of different animals. For example, many prey animals show increased vigilance and precaution in open spaces, which entails regularly scanning the environment (Bednekoff & Lima, 1998; Underwood, 1982). Furthermore, individual vigilance tends to decrease as the group size in social prey animals increases, presumably in part because the probability of threat detection and subsequent response by some group member also increases, leading in turn to others being alerted (Bertram, 1980; Powell, 1974). An example for humans is that in urban environments,

people may be particularly attendant to dark alleyways or try to avoid them because of the conjunction of features that induce vulnerability (poor visibility, lack of escape routes, etc.).

Precautionary responses can also take a more protracted time course. For example, night-time is reliably associated with more cautious behaviours for species that are adapted to diurnal life. Likewise, nocturnal animals who are particularly active in the dark, such as rats, demonstrate anxiety-like profiles in brightly lit environments (Burman, Parker, Paul, & Mendl, 2009). More naturalistic observation studies are needed to understand how animals respond to contextual cues that are indicative of general vulnerability, especially when an animal is exposed to multiple threats that require differential or competing responses (Brilot, Bateson, Nettle, Whittingham, & Read, 2012). For example, mayflies residing near streams must contend with attack threats posed by fish and other insects, among other things (McIntosh & Peckarsky, 1999). Whereas the mayflies remain inconspicuous in response to cues of fish, they tend to drift away when faced with cues of other predatory insects. In the presence of both types of cues, the mayflies can modulate their responses based on other variables that indicate the likely presence of one predator type over the other (e.g., based on the time of day that each predator is most likely to be active).

Physiological parameters that signal vulnerability (e.g., injury, inflammation) may also result in elevated anxiety and reduced response thresholds to threats (Bateson et al., 2011). In humans, higher prevalence of anxiety symptoms and disorders are often observed in medical, relative to community samples, and in the context of chronic pain (Bryant, Jackson, & Ames, 2008; Katz, Pagé, Fashler, Rosenbloom, & Asmundson, 2014; Niles et al., 2015). In rats, there is some support for causality. For example, the administration of an inflammatory cytokine (interleukin-1beta) increases anxiety-like behaviours (Connor, Song, Leonard, Merali, & Anisman, 1998; Cragolini, Schioth, & Scimonelli, 2006; Maldonado-Bouchard et al., 2016), and anti-inflammatory treatment has been found to reduce these behaviours (Bayramgürler, Karson, Özer, & Utkan, 2013; Rodgers et al., 2014). Animals may also use such information from conspecifics to detect potential threats. For example, hard clams reduce feeding behaviour in response to predatory cues, such as chemosignals of crabs (Smee & Weissburg, 2006). A reduction in feeding behaviour has also been observed in response to chemosignals originating from injured conspecifics in the direct absence of predators. In this context, an injured conspecific appears to serve as a signal that a predator is likely near (see also Sullivan & Johnson, 2016).

Defensive Responses to Autocued Threats

Humans, and possibly some other species, are capable of mentally simulating the future in the absence of relevant sensory signals by engaging in *episodic foresight* (Michaelian, Klein, & Szpunar, 2016; Redshaw & Bulley, in press; Suddendorf & Corballis, 2007; Suddendorf & Redshaw, 2013), and can thereby "autocue" potential threats and engage in strategic preparation (see also Boyer & Bergstrom, 2011; Gärdenfors, 1995; Mobbs

et al., 2015; Pezzulo, 2008; Pezzulo & Castelfranchi, 2009; Pezzulo, Rigoli, & Chersi, 2013). Because the capacity for episodic foresight draws on a generative process by which information obtained through past experience is combined to form novel mental representations of future possibilities, a nearly boundless set of adversities and hardships can be imagined (Corballis, 2011; Suddendorf, 2013; Suddendorf & Corballis, 1997). This ability can be adaptive as it enables people to prepare for, avoid, defuse, or surmount anticipated difficulties (Bulley, Henry, & Suddendorf, 2017; Nairne & Pandeirada, 2008; Suddendorf, 2006). The flipside of entertaining manifold potential threats is that it can be a persistent and potent cause of distress (see the Mental Health Implications section in what follows).

Once a possible threat scenario has been autocued, one can take behavioural steps to avert its possible consequences: the making of a spear, for instance, in preparation for hunting or potentially encountering a hostile out-group. In the face of simulated upcoming problems, humans can go about gathering useful information and resources, crafting suitable tools, prioritizing certain activities, or forging tactical allegiances and sharing information. Humans also engage in deliberate practice in order to shape their future skill sets (Suddendorf, Brinums, & Imuta, 2016), for example by repetitively throwing a spear at a training target to increase accuracy and force. Although imagining a threat does not guarantee preparation and preparation does not guarantee effective management, these multifaceted advantages illustrate how future threats facing early hominins may have acted as an important selective pressure in the evolution of foresight.

Throughout the preceding discussion, anxiety was conceptualized as an overt response to threat rather than the subjective experience of threat. Ever since the work of James (1884) and Papez (1937), the overt and experiential features of emotion have been distinguished for conceptual reasons. Although these routinely occur in tandem, the overt (observable) responses that follow the perception of threat cues are usually referred to as the emotion of anxiety (A. R. Damasio, 1995), whereas the feeling of anxiety refers to the subjective experience of the cognitive and physiological changes that constitute the emotion (A. R. Damasio & Carvalho, 2013). Although the feeling of anxiety may not be integral to defensive responses based on sensed threat cues, in the context of autocues, which are divorced in time or space from the relevant threats, feelings likely play an important role in preparation, for example by enabling an individual to evaluate the potential consequences of future threats and determine the appropriate behaviours (A. R. Damasio & Carvalho, 2013; LeDoux & Brown, 2017). That people often exaggerate the way they will feel following future events (Wilson & Gilbert, 2005) may serve to bolster motivation and a sustained commitment to mitigate or avoid harm (Miloyan & Suddendorf, 2015). This might also explain the tendency of anxious individuals to frequently “overpredict” fear (Rachman, 1994). For instance, exaggerating the expected magnitude and consequences of an attack by a neighbouring group may serve to motivate the negotiation of a truce, defensive preparation, or even preemptive attacks (Tinbergen, 1968). A foundation for a neurobiological approach to feelings was outlined two decades

ago (A. R. Damasio, 1995), yet there has since been little progress in understanding the role of feelings in anxiety and the management of remote threats (see LeDoux, 2015a, for a recent survey).

Most studies to date in this domain have been cross-sectional, demonstrating that autocued threat detection is part and parcel of the anxiety profile in humans (MacLeod, 1996; MacLeod & Byrne, 1996). Longitudinal studies with repeated assessments are still needed to compare future-oriented thoughts and feelings at baseline, and actual decision-making and behaviours at follow-up (e.g., Spreng & Levine, 2013). Phenomenological approaches, such as daily life thought-sampling and self-report diary methodologies can be used in longitudinal designs to shed light on the emergence of future-oriented thoughts and feelings during real-life experience (Barsics, van der Linden, & D’Argembeau, 2015; Finnbogadóttir & Berntsen, 2011), even in patient populations (Feinstein et al., 2011). Such approaches may better enable causal attributions to be made about the role of prospection and feelings in human threat-related decision-making and behaviour.

Mentally Simulated Associative Learning

We now turn to the intersection of responses to sensed cues and autocues. Recent approaches have combined Pavlovian and category learning paradigms to elucidate the neurobiological underpinnings of anxiety generalization (Dunsmoor & Paz, 2015; Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2014; Lipp, 2006). A basic conclusion of these studies is that a threat-related member of a particular category can generalize to other members of that category (Dunsmoor, Martin, & LaBar, 2012; Dunsmoor & Murphy, 2015). For example, a dangerous encounter with a particular dog could facilitate anxiety responses to the sound of other dogs barking in the future, or even the mere sight of a doghouse. Generalization could be considered an adaptive learning rule inasmuch as the objects or categories are related in terms of the behavioural response required to avert harm (Brilot et al., 2012).

The category-specific organization of *semantic memory* (Caramazza & Mahon, 2003) was likely shaped by selective pressures to facilitate rapid recognition of external stimuli, information processing, and response selection (Boyer, 2015; Caramazza & Mahon, 2003; Delton & Sell, 2014; Dunsmoor & Murphy, 2015; Suddendorf & Corballis, 2007). Indeed, the principles by which these memories are organized appear to be phylogenetically conserved in mammalian species (Barker, Bird, Alexander, & Warburton, 2007; Tanaka, 1997). In humans, lesion and impairment studies have found that the retrieval of concrete entities (names of people, places, animals, objects) and action-concepts (e.g., cutting, running) via partially segregated neural systems (H. Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004) play a critical role in supporting episodic foresight (Irish, Addis, Hodges, & Piguet, 2012; Meyer & Damasio, 2009).

The reverse relationship, however, has been less well studied: Can imagining the relationship between a cue and outcome, or action and consequence, without actually experiencing these

events, produce associative learning? If so, the simulation of threat-related scenarios may facilitate or strengthen category learning by creating associations between cues and potential threats in a wider variety of contexts that one may encounter in the real world (see Dadds, Bovbjerg, Redd, & Cutmore, 1997). For example, a tribesman may simulate various types of raids by a neighbouring group. Repeatedly simulating threat-related scenarios—also a feature of anxiety—may strengthen these associations, leading to improved preparatory behaviours (e.g., around-the-clock border surveillance), and possibly to the persistent worrying that is characteristic of anxiety disorders (Watkins, 2008).

We now wish to highlight two observations related to this idea that mental imagery could facilitate learning (Bower, 1972; Paivio, 1969). First, imagination is associated with similar patterns of neuronal activity as perception (Moulton & Kosslyn, 2009; Pearson, Naselaris, Holmes, & Kosslyn, 2015). Second, a number of studies suggest that procedural (motor) imagery improves skill acquisition in the absence of actual motor behaviours, in part because imagined movements engage similar neural activity as evoked by real movements (for reviews see Beilock & Lyons, 2012; Denis, 1985; Mulder, 2007). We hypothesize that imagining stimulus–stimulus or action–outcome pairings enables Pavlovian or operant learning to take place. Strengthening cue–cue or cue–outcome associations across various contexts by engaging mental simulations would therefore be hypothesized to facilitate more rapid or efficacious deployment of defensive measures in the future, in response to signals whose significance one has learned through simulation, rather than on the basis of previous physical encounters. One way to test the hypothesis could be to have participants engage in mentally simulated associative learning about a threat cue, before presenting the trained and novel cues visually in a conditioning task to determine if defensive responses are more rapidly acquired or more so engaged in response to the trained cues.

As it is not feasible to prepare for every threat possibility due to constraints of time and resources, deliberate preparation is typically restricted to what people judge to be the most pressing issues. Nonintentional mental simulation, for instance in the course of mind-wandering, also leads people to autocue threats (Baird, Smallwood, & Schooler, 2011; Killingsworth & Gilbert, 2010). This can be anxiety-provoking (Finnbogadóttir & Berntsen, 2011; Perkins, Arnone, Smallwood, & Mobbs, 2015), but it may be functional in that it sometimes facilitates preparation without requiring deliberation (Baird et al., 2011; Stawarczyk, Cassol, & D’Argembeau, 2013).

Mental Health Implications

Ultimately, the observation that threat management mechanisms bear adaptive significance suggests that anxiety disorders can be appropriately conceptualized as dysregulated defences, rather than defects (Marks & Nesse, 1994; Nesse & Williams, 1995). For example, it seems surprising from today’s perspective that the 1949 Nobel Prize in Medicine was awarded for the

discovery of prefrontal leucotomy as a treatment for emotional disorders. Despite being an effective (albeit arguably barbaric) means of eliminating distress, tampering with prefrontal circuitry turned out to have costly and unintended consequences that were not fully appreciated until decades later (A. R. Damasio, 2000; A. R. Damasio et al., 1990). It is now better understood that any neurobiological disturbance resulting in a pronounced reduction of anxiety bears a risk of introducing other problems that stem from a lack of wariness (Feinstein et al., 2011). These observations suggest that interventions for anxiety disorders do not require eradication of the responses, but careful modification.

A given psychosocial intervention might successfully demonstrate to the anxious individual that there is an absence of threats based on the (auto)cues that the individual regularly adheres to, perhaps leading to a reduction in anxiety. However, this method alone may often lack long-term efficacy (excluding, perhaps, cases of stimulus-bound specific phobia) because the mechanisms underlying the anxiety response do not easily confuse absence of evidence for evidence of absence. For example, although conditioned responses are effectively extinguishable, they frequently succumb to relapse (Vervliet, Craske, & Hermans, 2013), particularly when individuals confront the relevant threat cue(s) again in different contexts (Bouton, 2002) or in threatening or unsafe environments (Goode, Kim, & Maren, 2015). This challenge has led recently to an assessment of virtual reality as a way to extinguish phobias in various contexts in an attempt to prevent relapse (Dunsmoor, Ahs, Zielinski, & LaBar, 2014).

However, relapse may not occur specifically—or mainly—in response to contextual cues. A more general possibility is that a reduction of anxiety at one level of response (e.g., to specific cues) may not necessarily generalize to other levels (e.g., to contextual cues or autocues). To our knowledge, it remains unclear whether the extinction of a conditioned response also leads to a cessation of responding on the basis of autocuing the associated conditioned stimulus, and this remains an important direction for future research. It also remains unexamined whether the imagination of threat-related scenarios can result in mentally simulated reinstatement of anxiety at lower levels of response. If such reinstatement is possible, then attempts to improve upon existing interventions by extinguishing a specific response over multiple relevant contexts may also turn out to lack efficacy. A more effective approach may require extinction of the pertinent response types over the relevant contexts.

Caution should be taken to avoid making two assumptions. The first assumption is that an anxiety response that appears to be costly in one context is not beneficial in other contexts. For example, if a patient presents with excessive anxiety about animal attack threats, demonstrating frequent avoidance of situations where s/he would expect to encounter animals, successful treatment may ultimately entail reducing avoidant behaviours, or perhaps even training the individual to take on more exploratory behaviours if the probability of an attack in their usual environment is deemed to be sufficiently low. However, this could render the individual more vulnerable to contaminative

Table 2. Defensive responses on the basis of different types of threat cues.

| | Example(s) | Stimulus/cues | Emotion | Response |
|---------------------------|--|---|---------|---|
| Imminent danger | Faced with a predator or shortage of oxygen | Specific external (sense perception) or interoceptive (physiological state of the body) | Fear | Fight-or-flight (panic, freeze, flight, aggression) |
| Sensed threat cues | | | | |
| Specific | Rustle in leaves | External | Anxiety | Specific responsiveness (hypervigilance, scanning environment, proceeding with caution, withdrawal) |
| General | Darkness or injury | Nonspecific contextual or interoceptive | Anxiety | General wariness (precaution, hypervigilance, lower response threshold to a variety of threat cues) |
| Autocued threat | Imagining an animal attack before a trip to the wilderness | Mentally simulated | Anxiety | Advanced and flexible precautionary measures (e.g., acquiring tools, practicing skills, provisioning resources) |

threats. The purpose of this example is not to suggest that contaminative threats should always warrant significant precaution; rather, it is to illustrate that successful treatment in one context could be harmful to the individual in a different context. The second assumption that we caution against is that maladaptive anxiety at one level of response is also maladaptive at another. For example, a conditioned fear of insects may interfere significantly with one's daily life, and therefore prove to be maladaptive. However, the ability to anticipate proximity with venomous insects, for example in the context of an upcoming hiking trip, and to take appropriate precaution, is clearly adaptive. The cost of eradicating an important defence is perhaps higher than the cost of excessive anxiety (see also Nesse, 2001).

Despite any benefits to fitness afforded by autocued defensive responses, the capacity to imagine future threats comes hand-in-hand with costs to mental health. People can worry about numerous possibilities that are outside of their control, are very unlikely to ever occur, or that may occur sufficiently far in the future that they need not be of immediate concern (MacLeod, Tata, Kentish, & Jacobsen, 1997). Excessive anxiety about the numerous threats that one could face at any time would stifle adaptive behaviour. For example, it is not practical to obtain and carry antivenoms for every creature that may bite or sting you on a trip through Australia. Increased expectations of threat-related future events, coupled with the belief that the future no longer holds the possibility for rewards in store may lead to a sense of hopelessness about one's future that can be depressing and lead to suicidal thoughts (MacLeod, 1996; MacLeod & Byrne, 1996; MacLeod, Rose, & Williams, 1993; Miloyan, Pachana, & Suddendorf, 2014; Roepke & Seligman, 2015).

The perhaps distinctly human impetus to exchange information about imagined future scenarios is an important influence on autocued responses, in that people can learn about what and what not to be anxious about from others (Suddendorf, 2013). We think this provides another layer of explanation for why some individuals become excessively cautious in proportion to the hazards in their environments. For example, people who are frequently warned about threats by others, or who frequently discuss threatening scenarios with others in unchecked fashion,

may be likelier to mentally simulate these diverse threat possibilities. People who are particularly empathetic may be especially susceptible to the contagion of anxiety from others (Shu, Hassell, Weber, Ochsner, & Mobbs, 2017). Conversely, people's anxiety can be alleviated through comments of others (e.g., when children are reassured that there are no monsters). The interpersonal exchange of information may keep the engagement of autocued defensive responses within reasonable bounds most of the time, if people are exposed to an appropriate balance of threat-related and "safe" information (including corrective feedback) from other people.

Conclusion

The future harbours diverse threats to reproductive fitness. The sensory perception of a threat cue can result in targeted responses to specific threats or trigger states of generalized anxiety that result in reduced response thresholds to a variety of subsequently perceived cues. Humans also have the ability to autocue defensive responses by imagining future threat events, and thereby to strategically prepare for future hazards (see Table 2). We have appraised the relative strengths and weaknesses of the predominant research paradigms that have been used to study each of these response types, and recommended alternative approaches for overcoming their limitations.

Together, these functionally related and overlapping, yet distinct defensive response processes enable versatile and effective preparation for potential threats. Novel research approaches are needed to understand how the capacity to envisage and prepare for threats in the absence of environmental cues interact with lower level mechanisms underlying defensive responses to sensed cues in the context of threat management, as well as how and when this process goes awry in the case of anxiety disorders.

Declaration of Conflicting Interests

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