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# The nature and neurobiology of fear and anxiety: State of the science and opportunities for accelerating discovery

Shannon E. Grogans [a], Eliza Bliss-Moreau [d,e], Kristin A. Buss [f], Lee Anna Clark [g], Andrew S. Fox [d,e], Dacher Keltner [h], Alan S. Cowen [i], Jeansok J. Kim [j], Philip A. Kragel [k], Colin MacLeod [l], Dean Mobbs [m,n], Kristin Naragon-Gainey [o], Miquel A. Fullana [p,q], Alexander J. Shackman [a,b,c,*]

[a] Department of Psychology, University of Maryland, College Park, MD 20742, USA
[b] Neuroscience and Cognitive Science Program, University of Maryland, College Park, MD 20742, USA
[c] Maryland Neuroimaging Center, University of Maryland, College Park, MD 20742, USA
[d] Department of Psychology, University of California, Davis, CA 95616, USA
[e] California National Primate Research Center, University of California, Davis, CA 95616, USA
[f] Department of Psychology, The Pennsylvania State University, University Park, PA 16802 USA
[g] Department of Psychology, University of Notre Dame, Notre Dame, IN 46556, USA
[h] Department of Psychology, University of California, Berkeley, Berkeley, CA 94720, USA
[i] Hume AI, New York, NY 10010, USA
[j] Department of Psychology, University of Washington, Seattle, WA 98195, USA
[k] Department of Psychology, Emory University, Atlanta, GA 30322, USA
[l] Centre for the Advancement of Research on Emotion, School of Psychological Science, The University of Western Australia, Perth, WA 6009, Australia
[m] Department of Humanities and Social Sciences, California Institute of Technology, Pasadena, California 91125, USA
[n] Computation and Neural Systems Program, California Institute of Technology, Pasadena, CA 91125, USA
[o] School of Psychological Science, University of Western Australia, Perth, WA 6009, Australia
[p] Adult Psychiatry and Psychology Department, Institute of Neurosciences, Hospital Clinic, Barcelona, Spain
[q] Imaging of Mood, and Anxiety-Related Disorders Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer, CIBERSAM, University of Barcelona, Barcelona, Spain

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ABSTRACT

Fear and anxiety play a central role in mammalian life, and there is considerable interest in clarifying their nature, identifying their biological underpinnings, and determining their consequences for health and disease. Here we provide a roundtable discussion on the nature and biological bases of fear- and anxiety-related states, traits, and disorders. The discussants include scientists familiar with a wide variety of populations and a broad spectrum of techniques. The goal of the roundtable was to take stock of the state of the science and provide a roadmap to the next generation of fear and anxiety research. Much of the discussion centered on the key challenges facing the field, the most fruitful avenues for future research, and emerging opportunities for accelerating discovery, with implications for scientists, funders, and other stakeholders. Understanding fear and anxiety is a matter of practical importance. Anxiety disorders are a leading burden on public health and existing treatments are far from curative, underscoring the urgency of developing a deeper understanding of the factors governing threat-related emotions.

## 1. Introduction

Fear and anxiety play a central role in the lives of humans and other mammals, and there is an abiding interest among scientists, clinicians, philosophers, artists, and the public at large in understanding their nature, identifying their biological underpinnings, and determining their contribution to other psychological processes, from cognition and decision-making, to health and disease. Over the past 50 years, methods for eliciting, assessing, and analyzing fear and anxiety have become increasingly refined, and techniques for making sense of the underlying

* Correspondence to: Department of Psychology, University of Maryland, College Park 20742, USA.
*E-mail address:* shackman@umd.edu (A.J. Shackman).

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neurobiology have become more powerful and precise (Fox, Shackman, 2018; Fox and Shackman, 2019; Machado, Kauvar, and Deisseroth, 2022). The more than dozen mini-reviews that make up the bulk of the present Special Issue embody many of these exciting developments and underscore the important advances that have already been made (Fullana and Shackman, in press). Despite this progress, it is clear that our understanding remains far from complete.

Here we provide a virtual roundtable discussion focused on 7 fundamental questions about the nature and biological bases of fear and anxiety. Kenrick and Funder argued that "science best progresses through multiple and mutually critical attempts to understand the same problem" (Kenrick and Funder, 1988, p. 32), and the side-by-side responses that make up this roundtable discussion provide a valuable opportunity to sharpen constructs, identify unspoken assumptions, and highlight weaknesses in theory and the underlying evidentiary record. A central goal of the roundtable was to take stock of what we have already learned and inspire the next generation of empirical research and conceptual work. Accordingly, much of the discussion focused on the most urgent next steps, with implications for training and funding the next generation of affective scientists. Each of the 7 questions was addressed by a collection of experts chosen to represent a broad spectrum of disciplines and methodological approaches (Table 1). By design, the discussants included a mix of genders and professional experience, from 'rising stars' to internationally recognized senior investigators. At the end of each section, the Editors have written an Afterword, highlighting points of consensus and disagreement, and key avenues for future research.

**Question 1**. ***Conceptual Framework: How do you conceptualize fear, anxiety, and related constructs, such as panic? Do you view them as discrete emotions, dimensions, hybrids, or human constructions?***

**Bliss-Moreau:** Fear, like all emotions, is socially constructed and emergent. To say that emotions are socially constructed means that they are realized via the combination of more basic or fundamental ingredients, some of which are dependent upon features of social life, including culture, language, and interpersonal relationships (Hacking et al., 1999). Emergence is the process by which a phenomenon comes to be that which is greater than and/or cannot be reduced to its parts. To say that fear is emergent means that an instance of fear, whether it be a person's own experience or their perception of fear in another, cannot be reductively explained by the ingredients required to make the emotion; instead, the process involved in making emotions builds instances of emotions that are greater than the sum of their parts. The ingredients of emotions can be discussed as either psychological phenomena, biological phenomena, or both, but ultimately, psychological phenomena emerge from biological ones.

Constructivist theories of emotion posit that fear and other discrete emotions come to be when people predictively make meaning of physiological signals from their bodies related to *allostasis* (i.e., the biological processes that anticipate future needs and proactively regulate homeostasis) using culturally derived notions of what specific emotions are (i.e., emotion concepts) (Barrett, 2017b; Bliss-Moreau, 2017, 2020; Bliss-Moreau and Rudebeck, 2021; Boiger and Mesquita, 2012; Clore and Ortony, 2013; Cunningham et al., 2013; Lindquist et al., 2015; Russell, 2003). The experience of, and meaning making about, such physiological signals, however, need not always become an emotion—the processing of allostatic signals can result in the experience of affect without being transformed into emotion. Affect—a psychological state characterized by some degree of valence/hedonics (ranging from very negative to very positive) and some degree of experienced physiological arousal or activation (ranging from very activated to very deactivated)—emerges from sensory information from the physiological systems of the body (interoceptive information) that may be integrated with sensory information from the environment (exteroceptive information). As such, in addition to serving as the necessary (but not sufficient) foundation for the emergence of emotions, affect serves as a barometer that provides information about an organism's place in the world and guides behavior to ensure effective allostasis and ultimately the ability to meet evolutionary challenges via regulation of the internal milieu and behavioral mechanisms (Barrett and Bliss-Moreau, 2009; Barrett and Russell, 1999).

Support for constructivist views exists across all levels of analysis. In the central nervous system, meta-analytic evidence demonstrates that emotions are realized by distributed neural networks that are not specific to traditional discrete emotions; indeed, there is considerable neuroanatomical overlap between specific emotions (Kober et al., 2008; Lindquist, Wager, Bliss-Moreau et al., 2012; Lindquist, Wager, Kober et al., 2012; Wager et al., 2015). Similarly, in the autonomic nervous system, there are not patterns that correspond with specific emotions; instead, variability in parasympathetic and sympathetic activation across instances of emotions is the norm (Siegel et al., 2018). Evidence from developmental and cross-cultural studies demonstrates that emotions are inexorably linked to one's concepts of emotion (Hoemann et al., 2019, 2020; Mesquita, 2022). Emotion concepts are abstract by nature because they are not linked to statistical regularities in the body or the environment (Barrett, 2017a; Hoemann et al., 2019; Mauss and Robinson, 2009) and therefore must be socially learned (Borghi, 2020; Borghi et al., 2018). As a result, emotion concepts are acquired in social contexts and shaped by social and cultural norms. There is enormous cultural variation not only with regard to what emotion concepts people have but also what specific emotion concepts mean and whether or not emotions are experienced as existing within an individual or between individuals (Mesquita, 2022). This true for all emotions, including fear, which has long been argued to be 'universal' (Ekman and Cordaro, 2011; Keltner et al., 2019). For example, recent lexical analyses demonstrate that only 21.5% of global languages examined have a word for fear and 13% of those same languages have the related concept of anxiety and, further, the meaning of the concept fear varies across languages (Jackson et al., 2019). Finally, when a negative high arousal affective state is induced, it can be transformed either into fear or anger, depending on the conceptual information available in the moment (Lindquist and Barrett, 2008).

Emotion concepts link experiences and perceptions that vary with regards to the triggering stimuli and the contexts in which they occur, their physiological manifestations, and their outputs (including behaviors). Fear is fundamentally related to instances of threat, even if those instances vary within or across individuals. Animals with the capacity for abstraction—namely humans—populate the fear concept with instances of both abstract threats (e.g., death, climate change, financial crashes) and concrete threats (e.g., venomous snakes, the sound of footsteps in a dark alley, peering over the edge of a tall cliff). Animals lacking the capacity for abstraction (or with lesser capacity for abstraction, if it is considered as a continuum) likely only experience concrete threats as threatening. Additionally, it is unclear to what extent animals without the capacity for abstraction link varied instances of threat to each other—the basis of a concept of fear—particularly if they are highly differentiated in terms of their sensory experience. Different types of threats (e.g., predators, aggressive conspecifics, pain) in different contexts (e.g., escapable or not) generate different types of physiological reactions (e.g., increased heart rate, changes in blood pressure) and behaviors (e.g., fleeing, freezing, fighting) which have dissociable neural substrates (Blanchard and Blanchard, 1988; Gross and Canteras, 2012; Lang et al., 2000; LeDoux, 2000; Roelofs, 2017). Human scientists look at those instances and behaviors in animals and call them, collectively, fear, but the extent to which animals link them together or experience them as similar is unclear.

**Buss:** My research program is founded on a biopsychosocial conceptual framework that is informed by 3 key theories, all of which focus on fear as a state that is distinct from other negative emotions, such as anger and sadness. First, is Goldsmith's temperament theory (Goldsmith et al., 1987; Goldsmith and Campos, 1982). Second, is Campos' functionalist approach to emotion (Barrett and Campos, 1987; Campos et al.,

1994). Third, is discrete emotion theory (Ekman, 1992; Ekman et al., 1983; Izard, 1971). Although these 3 theories suggest specific distinctions between different emotions, debates about what is and what is not an emotion, or how to define emotions per se do not guide my work. Instead my research is focused on understanding the processes that account for and predict individual differences in the tendency to express signs of fear and anxiety, including pathological fearful behaviors and anxiety symptoms. I have argued that fearful tendencies are stable across development, and what develops becomes more complex—making it challenging to distinguish what is emotion, what is temperament, what is personality, and what is psychopathology (Buss et al., 2019; Buss and Kiel, 2013; Buss et al., 2015). Finally, my definition of anxiety is guided mainly by temperamental and developmental psychopathology frameworks of anxiety development, especially the transformative work of Jerome Kagan, Nathan Fox, and their collaborators (Fox and Pine, 2012; Garcia-Coll et al., 1984; Kagan, 2008).

Although the distinctions among emotions are not cut-and-dry, a robust literature supports their utility for predicting different outcomes. For example, we have provided evidence for the differentiation of fear, sadness, and anger in infancy and toddlerhood across multiple studies. First, we documented distinct patterns of regulatory behaviors in 6-, 12-, and 18-month old infants, and demonstrated that anger in 12- and 18-month-olds was more likely be alleviated by these regulatory behaviors than fear (Buss and Goldsmith, 1998). Second, we showed that when toddlers look to their caregivers for help during fear- and anger-eliciting situations, facial expressions of sadness were more prevalent than fear and anger, respectively (Buss and Kiel, 2004). This is consistent with evidence that caregivers are more likely to respond to child expressions of sadness than anger (Huebner and Izard, 1988). Our study was the first to show that this is also true for fear (versus sadness). Third, in the identification of the dysregulated fear profile (Buss, 2011), sadness and distress crying loaded on a different factor than fear reactions (e.g., bodily freezing). Moreover, only fear reactions were predictive of development of maladaptive withdrawal (Buss, 2011) and anxiety symptoms (Buss et al., 2013).

**Clark:** From my phenomenologically grounded perspective on emotions, fear and anxiety—and related constructs, such as panic and worry—are best conceptualized as continuous dimensions of subjective states that overlap in some ways but are distinct in others. For example, all of these feelings are negative emotional states, but fear and panic are more immediate and fleeting states—typically with a clear referent (e.g., a rattlesnake, a sudden large lurch in an airplane)—whereas anxiety and worry are more future-focused, diffuse, and persistent. The terms we use to describe emotions are, of course, language-based human constructions and, as such, they vary across languages and cultures. However, in all cases, they reference the experience of at least somewhat similar feeling states, which vary in the extent to which individuals are consciously aware of the feeling.

It is likely that the specific quality of these feeling states varies across individuals—this is currently unknowable, as we have no way, and may never have any way, of actually feeling what another person feels—but there are clear correlations between the types of external stimuli to which people are exposed and the terms they use to describe the resulting emotions, so it is reasonable to conclude that their feelings states are similar. That said, although in the aggregate there are physiological associations with these feelings, between-subjects correlations of subjectively reported feeling states with physiological markers of them are consistently low (e.g., Siciliano, Anderson, and Compas, 2022) to moderate (e.g., Liu et al., 2019). Whether there are consistent within-subjects correlations has not been systematically examined, so it is possible that individuals' response patterns differ from others' but are consistent across time for themselves. This is an important area for future research.

**Fox:** My fear and anxiety research is driven by the desire to decrease human suffering. I do not believe that it is scientifically beneficial to hold strong beliefs about the nature of these constructs. I am not convinced that contemporary use of these terms for emotion concepts—either in the lab (e.g., fear, anxiety, panic) or the clinic (e.g., specific phobia, generalized anxiety)—accurately captures the underlying essence of the wholistic experiences or provides a clear path to alleviate suffering. Put another way, I do not think that the concepts of 'fear' and 'anxiety' capture the complexity of the subjective experience (i.e., they are not 'natural kinds'), nor do I think they accurately reflect the underlying biological mechanisms (i.e. they do not 'carve nature at its joints').

It is nearly impossible to agree on terms to describe subjective (i.e., phenomenological) experiences. Researchers, clinicians, and lay-people have yet to agree on definitions for traditional emotion words. According to the Oxford English Dictionary, the word *Fear* can be used to describe: "a feeling of a state of alarm or dread", "an apprehension toward potential danger", "uneasiness toward impending danger", "uneasiness toward the prospect of some possible evil", or even "anxiety for the safety of a person or thing". This is further complicated by different cultures having subtle (and not-so-subtle) differences in definitions for emotion words (Fox, Shackman, 2018; Jackson et al., 2019; Lindquist et al., 2022; Russell and Sato, 1995). Words can be enculturated and learned, resulting in many-to-one emotion-to-word mappings. This is not unique to emotions, for example, there can be many-to-one color--to-word mappings, as an English speaker without exposure to a variety of words for colors, might use the word 'pink' rather than 'salmon.' Similarly, emotion words, such as 'fear' may reflect linguistic limitations and not be a full and accurate reflection of our experience (akin to catch-all colors, such as pink). Emotion-related words are intended to describe phenomenological concepts, which themselves may be phenomenologically heterogeneous. With this in mind, researchers must take care not to mistake differences in the linguistic expression of emotions, or emotion categories, as differences in emotions per se.

Although recent years have seen some researchers re-defining 'fear' and 'anxiety' to indicate 'phasic' and 'sustained' fear, respectively (Avery et al., 2016; Davis et al., 2010; Lebow and Chen, 2016), the lack of clarity on precisely what is 'phasic' and what is 'sustained' undermines the utility of this distinction (Daniel-Watanabe and Fletcher, 2022; Shackman et al., 2016; Shackman and Fox, 2016). Moreover, although initial theories suggested there are dissociable substrates for phasic and sustained threat responding, an increasing number of studies have failed to support this hypothesis (Fox and Shackman, 2019; Hur et al., 2020; Shackman and Fox, 2021). Others have suggested that the central states resulting from various threats are differentiated based on pre-, circa-, and post-threat responding (Fanselow et al., 2019; Fanselow and Lester, 1988; Mobbs et al., 2020; Moscarello and Penzo, 2022). This definition seems to be a step forward, but it is unclear whether it is sufficiently precise to capture the complexity of the underlying biology (though attempts have been made), or if it fully characterizes the environment (e.g., Is circa-strike equivalent to a high-probability threat?). There may be different biological states that can be associated with a given word, even those used in more recently established scientific models of fear and anxiety. I posit that understanding the biology will prove more fruitful in disambiguating these experiences for the purpose of intervention. Thus, my preferred approach would aim to uncover the psychological nature of fear and anxiety by refining our understanding of the biological processes that underlie the processing of potential threats, both real and imagined (see below). By understanding the biological mechanisms of fear and anxiety, we can adjust, adjudicate, and advance our psychological understanding of these concepts (Shackman and Lapate, 2018).

My research program is motivated by the hypothesis that the underlying biology is more likely to map on to the underlying essence of emotion, or at least that it will enable increased precision and clarity relative to broad-based phenomenological descriptors. If we can understand the neurobiology of threat responding, we may be able to develop new hypotheses about the kinds of interventions most likely to decrease suffering. Importantly, if interventions can be targeted at

biological mechanisms, rather than emotion-word concepts, it may enable more effective treatment. Accordingly, my whole-hearted endorsement of specific definitions or theories of emotion would require they be linked to specific biological mechanisms and/or motivate experimentally falsifiable hypotheses. Rather than risk artificial precision, I prefer loose definitions that intentionally encompass multiple aspects of threat responding. I hope that we can increase our biological understanding to the point that we can develop new emotion terms and concepts that better match the underlying biology.

In sum, I do not believe that popular conceptual models of fear and anxiety match the underlying biological mechanisms, which will make it difficult to develop individualized (or stratified) treatments and/or truly understand emotions.

Nevertheless, I will outline 3 *weakly* held beliefs about the psychological nature and organization of fear and anxiety:

a) *The words we use to classify affective states are imprecise.* Catch-all terms such as 'fear' or 'anxiety' likely encompass a number of phenomenologically and biologically distinct experiences, which often occur in concert or rapid succession ('one-to-many') (Adolphs et al., 2019; Fox and Shackman, 2018).
b) *Conversely, subjectively indistinguishable affective states may reflect multiple distinct biological causes ('many-to-one')* (Holley and Fox, 2022). The 'panic' that we experience when being threatened with a knife is likely to be biologically distinct from the 'panic' evoked by $CO^2$ inhalation (Feinstein et al., 2013; Fox, 2018; Khalsa et al., 2016).
c) *A single theoretical model may not be optimal for understanding different aspects of emotion.* I hypothesize that constructivist models will best describe the words and concepts that we use to describe feelings, whereas other frameworks—evolutionary, appraisal, discrete/basic, dimensional, or hybrids—may be more useful for understanding the mechanisms, which emerged over the course of evolution, and that transform emotion-relevant information into survival-promoting responses (Adolphs et al., 2019; Fox, Lapate et al., 2018; Holley and Fox, 2022; Moors et al., 2013). I am intrigued by the possibility that biology can guide the creation of new emotion concepts, which could help guide interventions aimed at decreasing suffering.
d) *As we move toward developing better models to describe the landscape of affective states, we must incorporate additional features.* Understanding affective states may require dimensional models that encompass multiple discrete dimensions (e.g., valence, arousal, etc.), from which a new subjective experience can emerge. However, I suspect that there are far more dimensions than most theorists currently recognize. For example, bi-dimensional (i.e., valence and arousal) models do not adequately explain the divergent experience, expressions, or behaviors that distinguish 'fear' from 'disgust' (Susskind et al., 2008). I anticipate that the biological substrates of a given experience of anxiety/fear will reflect at least 4 dimensions: (1) the type of threat, (2) the perceived probability of threat, (3) the perceived adaptive response, and (4) the perceived cost/benefit of engaging in this adaptive response (Holley and Fox, 2022; Mobbs et al., 2020; Moscarello and Penzo, 2022). Each of these features is likely to be important, and may require multiple distinct dimensions to fully characterize the variety of behavioral responses and subjective experiences, not to mention the variation in the biological underpinnings. In the end, I believe that what we currently call 'fear' and 'anxiety' will encompass a substantially larger number of distinct states. The extent to which these states reflect shared neural substrates remains unclear.

**Keltner & Cowen:** There may be no constructs that have dominated the science of emotion to a greater extent than 'fear' and 'anxiety.' The field-shaping search for fear- and anxiety-related neural circuitry, fight-or-flight peripheral physiology, patterns of cortisol release, and influences of fear and anxiety upon cognitive processes, all speak to the centrality of these phenomena in the science of emotion (Kreibig, 2010; Lerner and Keltner, 2001; Rodrigues et al., 2009).

The literature has largely treated *fear* in a singular or monolithic fashion, presupposing that the varieties of fear likely have similar neurophysiological correlates. Anxiety is often conceptualized as the trait-like or clinical manifestation of excessive fear, differing from state-like fear in terms of intensity, frequency, or duration (Rosenberg, 1998). This set of assumptions has many origins, including the legacy of early arguments for Basic Emotion Theory (Ekman, 1992), with their focus on six emotional states—anger, disgust, fear, sadness, surprise, and happiness. The monolithic treatment of fear has been reinforced by constructionist approaches to emotion, which apply the 'fear' label to feelings as divergent as those associated with physical threat and those associated with excitement before a sporting event (Wilson-Mendenhall et al., 2015).

We depart from these assumptions by offering a new conceptual and methodological approach to the study of fear and anxiety—and emotion more generally—that we call Semantic Space Theory (Cowen, Sauter et al., 2019; Cowen and Keltner, 2018, 2021; Keltner, Brooks and Cowen, in press). Semantic Space Theory posits that any subjective realm—sensations in the body, scents, tastes, moral intuitions, aesthetic reactions to music or visual art, and emotions—is defined by 3 properties. First, a space of subjective experience is defined in terms of its *dimensionality*: in terms of emotion, how many kinds of emotion are distinguished within a space? The Basic Emotion Theory legacy is deep, and oriented the field to six emotions. Semantic Space Theory departs from this framework and raises questions about how many distinct emotions warrant empirical study. Is 'fear' all there is to this space of subjective experience? Is 'anxiety' the same as 'fear,' simply differing in terms of intensity, frequency, or duration? Are there varieties of fear with meaningful differences in need of neurophysiological study?

The second property of semantic spaces is the *distribution* of states within the space: What is the structure of emotional states along their dimensions? Are the boundaries between distinct categories of experience sharp or fuzzy? *Within* an emotion category, are there nuanced variations in experience that individuals reliably distinguish by applying more granular terms like 'horror' or 'anxiety?' *Between* emotion categories, are there boundaries that separate classes of experiences people label with one word or another—either 'fear' or 'disgust' for example—or is there meaningful overlap between categories traditionally considered discrete?

The third property of a semantic space is *conceptualization*: what concepts most precisely and reliably capture people's implicit or explicit differentiation of subjective experiences and emotional properties of stimuli, such as expressive behaviors or pieces of art? What taxonomy is sufficient to explain the variations in emotional response? Do experiences and expressions correspond to specific emotions (e.g., awe, fear, surprise) or broader affect and appraisal evaluations such as valence and arousal or certainty, as posited in appraisal and constructivist theories?

Recent work by our team (Supplementary Note 1.1) reveals that emotion is high dimensional; that the boundaries between emotion categories are not discrete, but are instead bridged by smooth gradients of meaning and blended experience; and that people more reliably conceptualize emotional experience in terms of discrete concepts than dimensions, such as valence or arousal (Cowen and Keltner, 2021).

A careful examination of the space in which 'fear' is located makes the case for distinguishing at least 4 kinds of experience commonly conflated in studies of 'fear' and 'anxiety' (Supplementary Note 1.2). *Fear* is mostly evoked by physical threat (e.g., spiders, heights). *Horror* is elicited by depictions of gore, death, and destruction. *Anxiety* is associated with epistemological uncertainty, and is elicited by stimuli that upset, challenge, or subvert the individual's stable understanding of the world. *Awkwardness* is associated with social separation and rejection concerns and is elicited by violations of social norms or the sense of exclusion. Studies of emotional expression demonstrate that fear, anxiety, horror, and awkwardness are reliably communicated by distinct

vocal and facial signals (Brooks et al., in press; Cowen and Keltner, 2020). In short, recent work fractionates fear into at least 4 kinds. They are evoked by distinct threats: physical, existential, epistemological, and social. They appear to trigger qualitatively different experiences and are likely subserved by distinct neurophysiological processes.

**Kim:** I subscribe to Bolles' concept (1967) that *fear* is "a hypothetical cause [motivation] of behavior" and that its main purpose is to keep organisms alive. Thus, predators (in animals) and perpetrators (in humans), electric shocks (both animals and humans), and stimulation of specific brain regions that produce defensive reflexes—such as the periaqueductal gray (PAG), hypothalamus, and amygdala, and hypothalamus (animals and humans)—would satisfy the objective criterion of fear. Of course, the subjective experience of fear would differ between humans and animals, say rodents, but this would hold true for almost all biological processes, such as pain, hunger, etc.

As a researcher who works with rodents, I know that it is debatable whether rats and mice show *anxiety* as it is defined in human psychology and medicine. We should acknowledge that not all human traits and psychopathologies can be modeled in animals. Alternatively, we still may not have figured out a good way to measure anxiety in animals based on their natural behavior.

On the other hand, rodents can be used to study *panic*, which is usually defined as an uncontrollable, frightened reaction. For example, when awake patients' dorsolateral PAG is stimulated, they describe what sounds like a panic episode (Nashold et al., 1969; Amano et al., 1982). The uncontrollable frightened reaction can be induced in cats and rats by stimulating the same region of the PAG (Bandler and Depaulis, 1991).

My personal view, which is by no means unique, is that fear, anxiety, and panic all share the same basic defensive system (see for example, Bliss-Moreau's response), but they differ in terms of the degree of engaging other neural structures, with panic and anxiety being the most and least autonomous, respectively (see my response to Question 2). The type of adaptive response to threat situations would be determined both genetically and experientially.

**Kragel:** I conceptualize fear and anxiety as solutions to ancestrally recurring challenges to the survival of a species (Cosmides and Tooby, 2000; Nesse and Ellsworth, 2009), a view consistent with functional accounts of emotion (Anderson and Adolphs, 2014; Keltner and Gross, 1999; Zych and Gogolla, 2021). Facing a complex environment with a large behavioral repertoire, and repeated encounters with specific situations (e.g., familial loss, obstructed goals, and predation), organisms that engage in certain behaviors will have increased fitness. This suggests the function of emotions is to select situationally appropriate behaviors through probabilistic or semiflexible mappings from sensory inputs to behavioral outputs (Adolphs and Andler, 2018; Scarantino, 2017). Accordingly, sensory representations of threats, associated action tendencies, and the neural processes that relate the two are part of what makes fear and anxiety distinct from one another, and from other emotions.

The utility of this classic view has been questioned because of the considerable variability in the antecedent events, behaviors, and brain activity associated with different emotions (see Bliss-Moreau's response to this question, and also Barrett, 2006; Lindquist et al., 2012; but see Loaiza, 2021). In short, the events that lay people label as 'fear' and 'anxiety' are thought to be too variable for them to be observer-independent natural kinds. This suggests that human emotion involves abstraction beyond associations linking perception and action, and that cognitive or constructive processes are needed to explain how humans conceptualize, communicate about, and experience emotion (Clore and Ortony, 2013; LeDoux and Brown, 2017; Oatley and Johnson-Laird, 2014).

Viewing emotions as adaptive functional states, patterns of cognitive appraisals, or psychological constructions seem like fundamentally opposing views, but they have much in common. For instance, a single episode of fear could be identified based on the proximity and certainty of threat (Fanselow and Lester, 1988), patterns of cognitive appraisal (Moors et al., 2013), or differences in pleasantness and arousal (Russell, 1980), to name a few. Debates about the nature of emotion tend to be anchored on the assumption that there is only one correct definition for a given emotion—as natural kinds, prototypes, ad-hoc categories, human constructions, or something else. I do not think it is productive to view these definitions as mutually exclusive, insofar as emotional states involve multiple components (e.g., sensory, evaluative, visceral, skeletomotor, motivational, phenomenological) that are implemented in separable brain systems. A single instance of human emotion can be meaningfully characterized using multiple prescriptive labels, such as 'biologically basic fear,' 'predator fear,' 'cognitively appraised fear,' and 'psychologically constructed fear.' Because theories tend to focus on different aspects of fear and anxiety, they can be viewed as complementary explanations of human behavior and brain function (cf. Fox's response to Question 1).

**MacLeod:** Variation in emotion is likely continuous on multiple dimensions, including intensity, qualitative aspects of subjective experience, cognitive content, physiological state, and behavioral characteristics. Nonetheless, there is value in creating distinct emotional categories by labeling, and thereby differentiating, particular combinations of emotional signs and symptoms. Doing so delivers the twin benefits of focusing research efforts on emotional 'regions' (e.g., clusters, families) of shared interest, and facilitating communication of the resulting findings. Nevertheless, I think it prudent for investigators to bear in mind that the distinctions between the emotional categories we construct should not obscure the commonalities that connect them.

Regardless of the theoretical perspectives from which our models are constructed, the most powerful accounts will identify the mechanisms that underpin symptomatology shared across multiple emotional categories, while also illuminating the differences in such mechanisms that account for the discrepant patterns of symptomatology that distinguish categories of emotion. Thus, research guided by the information-processing perspective has revealed that depressive and anxiety disorders are both characterized by cognitive biases that favor the selective processing of negative information, but it has also demonstrated that the operation of such selectivity in memory is a more robust feature of the former, while the operation of such selectivity in automatic attentional processing is a more robust feature of the latter. Similarly, although attentional bias to negative information is a shared characteristic of all anxiety disorders, research has shown that the nature of the negative information implicated in such attentional bias differs between alternative categories of anxiety disorders, for example implicating negative social information in social anxiety disorder, fear-related information in specific phobias, trauma-relevant information in PTSD, and a broader range of negative information in generalized anxiety disorder.

Although the convention of constructing emotional categories, such as fear or anxiety, enables researchers to focus their efforts more sharply on understanding the nature and biological bases of specific clusters of emotional symptomatology, such specialization must not blind us to the equally important need to understand the mechanisms that connect such clusters. When multiple people work on a given jigsaw, progress can potentially be enhanced by dividing the puzzle into distinct areas, so that each person can focus on one particular section. But unless the puzzle solvers also endeavor to identify how the edges of the areas they each are working on connect with those that adjoin them, the bigger picture will not emerge. Likewise, dividing anxiety disorders into separate categories facilitates progress in our understanding of the mechanisms that underpin the symptomatology associated with each such category. But understanding the mechanisms that transcend multiple categories of anxiety disorder, and those that also contribute to other types of emotion, is of equal importance if we are to advance overall understanding of emotional experience, disposition, and dysfunction.

**Mobbs:** *Fear* occurs when a threat is present, imminent, and directed at the agent, whereas *Anxiety* is a future-oriented state triggered by

prospective danger (Mobbs, 2018; Grupe and Nitschke, 2013; Borkovec, 1985). *Panic* occurs when a threat is highly potent and proximal, leaving little room for coordination of behavioral strategy and resulting in a lack of behavioral control. These categorical definitions are anchored in 3 key dimensions: (a) the spatiotemporal proximity of threat, (b) the potency or intensity of threat, and (c) the degree of uncertainty (Fanselow and Lester, 1988; Mobbs et al., 2020). These definitions are also tied to specific environmental conditions, and suggest that fear, anxiety and panic—or what I collectedly term *defensive states*—evolved to overcome predation and other obstacles to survival. I hold a functionalist and dimensional perspective on defensive states. Functionally, they are survival strategies evolved to combat both specific and general ecological threats. Dimensionally, I see these strategies as existing on a spectrum: as the threat gradient increases, the agent shifts from panic, to fear, to anxiety (Mobbs et al., 2020). Further, I would expect a certain degree of synergy (e.g., a persistent state of anxiety potentiating fear responses when threat is encountered) and waxing and waning between defensive states. This conceptualization has implications for how we study emotions and how they are represented in the human brain.

One model that depicts the natural conditions of threat is the threat imminence continuum (Fanselow and Lester, 1988). This model encompasses a *pre-encounter phase*, where there is a possibility of encountering threat, which is the prototypical model of anxiety. The model also includes a *post-encounter phase*, in which threat is present but has yet to attack. I believe that the post-encounter phase is the key switch between anxiety and fear, and that this switch is determined by the proximity of the threat (Mobbs et al., 2020). Finally, the model includes a *circa-strike phase*, where the agent is being actively attacked, which serves as a model of intense fear (Mobbs et al., 2007, 2010; Moscarello and Penzo, 2022; Mobbs, 2018). Across these contexts, the spatiotemporal properties and predictability of threat alters defensive states (Mobbs et al., 2020). In my view, 'fear' and 'anxiety' are just adaptive defensive responses to these, and maybe other, contexts. Therefore, in this model, we do not need to use the terms of fear and anxiety. We can do a better job tying defensive states to specific ecological conditions and in turn characterize their adaptive behavior. Pre-encounter anxiety, for example, will drive an animal to avoid locations associated with potential harm (Cunningham et al., 2006). Such a strategy may involve simple internal interoceptive states (Barrett and Simmons, 2015; Klein et al., 2021) or more complex prospective strategizing through cognitive heuristics (Suddendorf and Corballis, 2007; Mobbs et al., 2015; Qi et al., 2018).

**Naragon-Gainey:** Fear and anxiety are facets of negative affect that serve the evolutionary function of protecting the organism from danger. Fear is a response to current threat and anxiety to future or potential threat. Of note, it is the *perception* of a threat, rather than the objective presence of a threat, that triggers the experience of fear or anxiety, and so individual differences in threat identification and appraisal contribute to variation in emotional responding. Like many other emotions, fear and anxiety can be conceptualized as momentary states or as stable traits (DeYoung et al., 2022; Fleeson, 2001). Trait levels of fear and anxiety are thought to reflect individual differences in the strength and sensitivity of the behavioral inhibition system (a biobehavioral motivational system that serves to protect organisms from danger), which is very closely linked to the broader dimensions of neuroticism and trait negative affectivity (Barlow et al., 2014; Watson et al., 1999).

Building upon these definitions, I view fear and anxiety (and other emotions) as hierarchical in structure and dimensional in nature. Fear and anxiety are specific manifestations of a broader construct of negative affect, which is separable from positive affect and its facets. This hierarchical structure is evidenced by frequent co-occurrence of anxiety and fear with other negative emotions (e.g., sadness, anger, guilt, shame, irritability) (Watson et al., 1999). Importantly, the covariance of different types of negative affect is not only evident at the trait level, but also within-persons during momentary states, as people often report experiencing multiple facets of negative affect at once (Posner et al., 2005; Watson et al., 1999). Furthermore, there is evidence for continuous gradations in the subjective experience of anxiety and fear, as well as only loose coupling of the subjective experience of these emotions with behavioral or physiological responses (DeYoung et al., 2022; Hollenstein and Lanteigne, 2014; Posner et al., 2005). Based upon this evidence, I primarily view fear and anxiety as dimensional states subsumed within the broader dimension of negative affect. However, the shared variance between these facets does not preclude distinctions at the lower order level, and so negative affectivity facets such as fear and anxiety can still exhibit qualitative differences (e.g., different functions and underlying motivations; distinct physiological activation).

**Question 1 Afterword**.

The *"shoddy and inept application of words lays siege to the intellect in wondrous ways…words clearly force themselves on the intellect, throw everything in turmoil, and side-track men into empty disputes, countless controversies, and complete fictions."*—Francis Bacon (Barber, 2017, p. 500).

*"Much of what [fear and anxiety researchers] disagree about is semantic…But to say the differences are semantic does not mean they are unimportant. Words are powerful. They underlie our conceptions and shape the implications of our theoretical points of view, and they influence what others conclude about our research."*—Joseph LeDoux (Mobbs et al., 2019, p. 1209).

What is the nature of fear and anxiety? How should they be defined? How many relevant states are there? How universal are they? How sharp are the boundaries between them? Are feelings special or just one feature among many?

Although many of the theoretical debates within the science of fear and anxiety are philosophical—and cannot be resolved by new experimental data—the choices we make about nomenclature and theory can have important consequences for the design, evaluation, and larger significance of our empirical research, and ultimately for the development of more useful tools for treating pathological fear and anxiety (Mobbs et al., 2019).

Recent years have witnessed a vigorous debate about the nature of fear, anxiety, and other emotions, with leading theorists challenging the canon of facts and assumptions that has inspired and guided the field for the past 50 years (Adolphs and Anderson, 2018; Adolphs et al., 2019; Barrett, 2017; Barrett et al., 2019; Cordaro et al., 2015; Crivelli and Fridlund, 2019; Ekman, 2016; Ekman et al., 1983; Ekman et al., 1969; Fox et al., 2018; Keltner et al., in press; Krumhuber and Kappas, 2022; LeDoux, 2014, 2021, 2022; Lindquist et al., 2022; Mobbs et al., 2019; Ortony, 2022; Russell, 2022). Despite this theoretical tumult, there was a remarkable—albeit far from perfect—degree of consensus among the discussants about the nature of fear, anxiety, and related states. All of them seem to agree on 7 key features:

1. **Threat is the Common Antecedent.** Fear, anxiety, and other closely related states are triggered by perceived threats, real or imagined, internal or external. Several discussants emphasized the utility of distinguishing these momentary states from more stable trait-like propensities (Shackman and Fox, 2018; Shackman et al., 2018).
2. **Fear is Arousing and Negative.** Fear and related states are arousing and unpleasant. Humans and animals will work to avoid cues and contexts that elicit such states (Rolls, 2018).
3. **Threat Responses are Scalable.** Fear and related states are scalable, *not* all-or-nothing. They can be stronger or weaker in intensity (Adolphs and Anderson, 2018).
4. **Threat Responses are Complex and Multicomponential.** Fear and related states encompass alterations in multiple systems, including conscious conscious experience (feelings), cognition, peripheral physiology, and overt behavior. Clark and Naragon-Gainey remind us that the degree of coupling between subjective, somatic, and behavioral responses to threat is typically modest (Lang, 1994; Shackman et al., 2013).

5. **The Brain is Crucial.** Once perceived, threat triggers a sequence of events. The brain is a necessary intermediary between threat and fear- and anxiety-related responses.
6. **Fear is Not One Thing.** Different types of threat generate different responses. The discussants were unanimous in rejecting early variants of basic emotion theory, which lump terror, panic, dread, fear, anxiety, apprehension, and trepidation into a single weakly differentiated family of fearful states (Ekman and Ekman, 2022). A number of discussants went a step further, distinguishing 3 or more states.
7. **Fear and Related States are Evolutionarily Endowed, But Flexible and Probabilistic.** Fear and related states are shaped by natural selection and probabilistically enhance biological fitness, even if specific instances are maladaptive or pathological. Most of the discussants emphasized the flexibility and probabilistic nature of fear-related states, highlighting the myriad ways in which context (e.g., opportunity for escape), experience, learning, and culture can sculpt subjective and objective responses to threat.

Although there was consensus that different types of threat can trigger distinct emotional states, there was less agreement about how to best fractionate those states.

Clark, Kim, Mobbs, and Naragon-Gainey draw a distinction between *fear* (a phasic response to clear-and-immediate threat) and *anxiety* (a sustained response to uncertain-or-distal threat) (Beckers et al., in press; Casey et al., 2013; Davis et al., 2010; Shackman and Fox, 2016). To this, Clark, Kim, and Mobbs add *panic* (an intense, uncoordinated response to direct signs and symptoms of physical harm). All of these theorists and MacLeod seem to view these categories as rough heuristics, rather than observer-independent natural categories. As MacLeod notes, "there is value in creating distinct emotional categories by labeling…Doing so delivers the twin benefits of focusing research efforts on emotional 'regions' (e.g., clusters, families) of shared interest, and facilitating communication."

Keltner and Cowen fractionate fear into 4 discrete states. Based on distinctive constellations of facial expressions, vocal signals, subjective experiences, and antecedents, they distinguish *fear* (triggered by acute physical threat), *anxiety* (triggered by uncertain threat), *horror* (triggered by existential threat, including signs of gore, death, and destruction), and *awkwardness* (triggered by actual or potential social separation, social rejection, or the violation of social norms). They argue that the boundaries between these 4 (and other) emotional states are fuzzy, bridged by smooth gradients of blended experience and expression. Although she adopts a different conceptual framework, anchored in statistical models of verbal reports, Naragon-Gainey also emphasizes the frequent co-occurrence and blending of fear, anxiety, and other negative emotions (e.g., sadness), which give rise to the broader construct of negative affect.

Mobbs and Fox emphasize the importance of going beyond heuristic categorical descriptions (e.g., 'fear'), telling us that that threat-elicited states emerge from more fundamental dimensional processes. For Mobbs, these include the proximity, intensity, and uncertainty of threat. Fox highlights an overlapping set of dimensions, including the type of threat, the perceived probability of threat, the perceived adaptive response, and the perceived cost of executing that response.

The discussants staked out divergent perspectives on emotion language. All acknowledge that the words that lay people and scientists use to describe emotion can vary substantially across individuals, languages, cultures, and contexts. Clark emphasizes evidence of consistency between specific kinds of threat (antecedents) and verbal report (consequents). On this basis, she suggests that the underlying mental and neurobiological states are relatively consistent and universal. Fox and Bliss-Moreau reject this one-to-one perspective. Fox tells us that seductively simple catch-all terms, such as '"fear' and 'anxiety,' [neither] capture the complexity of…subjective experience (i.e., they are not natural kinds)…[nor do they] accurately reflect the underlying biological mechanisms (i.e., they do not carve nature at its joints)." He argues that such terms likely "encompass a [much larger] number of phenomenologically and biologically distinct experiences." Bliss-Moreau draws on evidence of linguistic differences in emotion words to drive home a similar point. She notes that only 1 in 5 languages has a word for fear, only 1 in 8 has a word for anxiety, and the meaning of those words varies substantially across linguistic groups. For her, emotional feelings are human cultural constructs that are imposed upon nature (like constellations), rather than observer-independent natural categories (like stars).

All of the discussants agree that fear, anxiety, and related emotional states are complex, encompassing changes in multiple response systems, from subjective feelings of apprehension and terror to overt changes in behavior and physiology. Theories of emotion—basic emotion, appraisal, constructivist, and so on—are often viewed as equally applicable to all of these responses. Kragel and Fox raise the intriguing counter possibility that different models may be optimal for understanding subjective feelings versus more objective signs (for related perspectives, see Mobbs' response to Question 3 and LeDoux, 2022). As Fox notes, "I hypothesize that constructivist models [of the kind espoused by Bliss-Moreau] will best describe the words and concepts that we [humans] use to describe feelings, whereas other frameworks… may be more useful for understanding the mechanisms, which emerged over the course of evolution, and that transform emotion-relevant information into survival-promoting responses."

Lisa Feldman Barrett has written that theoretical "commitments and assumptions are…tools that influence (and constrain) the process and products of scientific inquiry" (Mobbs et al., 2019, p. 1213). Indeed, as we shall see, the conceptual frameworks laid out by the discussants here motivate and fundamentally shape their responses to many of the subsequent Questions considered by the panel.

### Question 2. *Animals: How should animal models inform our understanding of human fear and anxiety ('forward translation')? How should evidence gleaned from humans inform animal models ('reverse translation')?*

**Bliss-Moreau:** Constructivist approaches ask when in evolutionary time, and therefore where in the phylogenetic tree, did the ingredients of emotion emerge, which gives insights into which animals may have emotions and also sets the stage for studying homologous ingredients in the animal species in which they exist (Bliss-Moreau, 2017). The physiological processes from which affect emerges and valence is encoded are likely universally present in animals with brains capable of prediction. It is likely, however, that there is variation across the animal kingdom in animals' abilities to represent affective feelings of pleasantness and unpleasantness consciously. Although there is ample evidence that many animals have the capacity for generating and using concepts, the capacity for abstract concepts is likely much more limited in the animal kingdom, making the existence of emotions likely limited to a small number of species. As a result, the likelihood of finding an animal homolog of human fear is low (particularly in the species most typically used as models in biomedical and psychological science) which makes the popular practice of trying to find evidence of fear homologs in humans and our model species (e.g., freezing) unlikely to be successful. An alternative and likely more fruitful approach is to focus on how affect is realized in animal models—its central and autonomic nervous system neurobiology, and how it is shaped by context, changes over the lifespan, and drives behavior. If the goal is to understand fear or anxiety, then the focus becomes negative, high arousal affective states, which can very likely be modeled in a wide variety of animal species. Over long durations of time, momentary affective states are thought to become more pervasive mood-like states (Bliss-Moreau and Rudebeck, 2021), so considering the temporal dimension of affect may be key in the distinction between how we model phenomena in animals related to fear versus related to anxiety.

**Buss:** Animal models help to strip away some of the extraneous

psychological factors that can detract from theoretical and empirical work focused on process and mechanisms. That is not to say that psychological factors, like subjective perceptions of emotional experiences or appraisal, are not important, but they are not central to the early life development of individual differences in emotion. Moreover, I do not think that conscious emotional appraisals are the driving force behind individual variation in fearfulness or anxiety development.

Yes, animal models should inform our understanding of human fear and anxiety. Our dysregulated fear work was heavily inspired by Ned Kalin's work in non-human primates—in particular, the Human Intruder Paradigm he developed to examine individual variation in fearfulness across different threat contexts (Kalin, 1993, 2003; Kalin et al., 1998). This research, together with my own, elucidates adaptative and maladaptive (or less adaptive) fear responses to different situations and identifies processes and contexts that increase risk for anxiety development (Buss et al., 2013; Buss and McDoniel, 2016).

**Clark:** Given that animals cannot tell us how they are feeling the way people can, we must infer their feeling states entirely from their behavior, which limits how much we can learn about human emotions from animal models, particularly given the low between-subjects correlations between human feeling states and their purported physiological markers. That said, where there are reliable stimulus-response relations that have established correlates to human feeling states (e.g., snakes generally induce both avoidance behavior and fear), we may be more able to study animal than human brain processes, from which we may then be able to devise ways of determining whether the same processes are at work in human brains.

**Fox:** Optimal progress toward understanding and alleviating human suffering requires both *translation* and *reverse translation*. Although we can best study subjective experience in humans, these feelings emerge from, or are related to, behavior, peripheral physiology, distributed neural circuits, cell-types, molecules and neurotransmitters, along with genes and gene regulation. Nearly all of these biological processes are more readily deciphered in nonhuman animals. Animal models can be leveraged to develop testable hypotheses for human research (translation), and should be guided by our understanding of what leads to suffering in humans (reverse translation). Each animal model has its strengths and weaknesses, and research in humans, nonhuman primates, rodents, and other species has each contributed to our current knowledge in important ways.

Animal models are critical for elucidating the complex biology that underlies fear and anxiety. The tools commonly available for studying the human brain are largely constrained to studying aggregate brain responses across hundreds of thousands of neurons. It has become abundantly clear that this level of description is insufficient, as research in rodents has identified subsets of neurons in threat-relevant regions, such as the amygdala, that have a distinct impact on the behavioral and physiological responses to threat (Fadok et al., 2017; Haubensak et al., 2010; Li et al., 2013; Viviani et al., 2011). Linking basic neuroscience findings to our understanding of human fear and anxiety, will require cross-species research and an open dialogue between clinicians and basic scientists working with different species (Fox and Shackman, 2019).

Having said that, it is important to remember that evolution is not necessarily linear or additive—studies in animals cannot be assumed to apply to humans. Although many molecules, cell types, and circuits have been evolutionarily conserved, they can differ in important ways across species. For example, researchers have identified a class of striatal interneuron (thought to have emerged through a developmental repurposing of dopaminergic periglomerular cells of the olfactory bulb) that is present in primates, but not rodents (Krienen et al., 2020; Schmitz et al., 2022). This example underscores the complexity of cross-species translation, and why specific cell-types, and their functional roles, cannot be assumed to be conserved across species. Rodent studies implicating a specific cell-type or projection in threat processing are most useful when they can provide testable hypotheses about the experience of fear and anxiety in humans.

Nonhuman primates are of particular importance for translating findings to humans. Nonhuman primates are more likely to share biological substrates of fear and anxiety with humans because of their relatively recent evolutionary divergence from humans (e.g., 25 MYA for rhesus macaques vs. 80 million years for mice and rats). This shared biology, combined with similarities in socio-emotional development, in a species amenable to experimental manipulation, make nonhuman primates a crucial part of the research ecosystem; the translation and reverse translation used to link animals to humans, can be facilitated by translation and reverse translation between nonhuman primates to other animal models. As a nonhuman primate researcher, a major goal of my current research program is to determine the relevance of mechanisms discovered in rodent models to individual differences in dispositional fear and anxiety in monkeys.

Finally, if our ultimate goal is to inform our understanding of human fear and anxiety, we will need to incorporate increased precision in the way that we describe our research (Fox, Lapate, Davidson, and Shackman, 2018). Experiences of fear and anxiety are heterogeneous (see my response to Question 1). It follows that, fear- and anxiety-related psychopathologies are complex and heterogeneous. As such, there are likely to be a myriad of heterogeneous neural alterations that can give rise to these disorders. Thus, even a *complete* understanding of a specific threat-relevant process, such as Pavlovian tone-shock conditioning, is unlikely to provide a direct route to effective treatments for anxiety and affective disorders. Often, as scientists we are rewarded for 'pitching' or oversimplifying our findings. Unfortunately, this is often antithetical to closing the gap between basic and clinical science. Small differences in the paradigm, context, or stimuli may result in very different outcomes, and these differences can be exacerbated when adapting paradigms across species (Shackman et al., 2016). Interdisciplinary efforts demand accurate and precise communication across disciplines. Rather than purport to study 'fear' or 'anxiety' we must find a way to engage with non-experts while clearly communicating our paradigms and phenotypic measures, leaving the door open to re-interpretation and synthesis of individual research findings. To this end, computational models may be especially helpful (see my response to Question 5).

**Keltner & Cowen:** Animal models have been central to understanding human fear and anxiety and paved the way for major conceptual advances. LeDoux's classic work on fear conditioning and the amygdala laid a foundation for understanding the role of that brain region in human emotion, and the kinds of more automatic, unconscious appraisals that are generative of emotion (Rodrigues et al., 2009). Panksepp's work on multiple species oriented the science of emotion in humans to the PAG, which is thought to encompass seven emotion-specific circuits, including panic (Panksepp, 2009). More recently, studies using optogenetics suggest that the dorsal raphe nucleus may be central to coordinating diverse fear-related responses, with stimulation of the same neurons inducing either freezing or fleeing behavior depending on the nature of the threat (Cowen, 2019; Seo et al., 2019). The paradigms, precise measures, and behavior-focused methods of the study of fear and anxiety in nonhuman species have been critical to advances in emotion science.

As detailed above and in Supplementary Note 1.1, our own recent work suggests that there are significant variations in the kind of fear one might observe in nonhuman species—physical, existential, epistemological, and social—with distinct physiological correlates. Recent advances in studies of nonhuman fear lend credence to this hypothesis. Indeed, a recent review of the immobilization or flight response to imminent predation (physical threat) finds that the neurophysiological profile of this kind of fear involves connections between the amygdala, PAG, and dorsal raphe nucleus, and shifts in parasympathetic control of the autonomic nervous system that enable particular kinds of attention (e.g., Roelofs, 2017). By contrast, recent advances in the study of submissiveness—most closely akin to the fear of social separation we observe in humans—focus on interactions between dopaminergic

pathways, the HPA axis, and sex hormones (Giacolini et al., 2020). For social mammals, the fear of isolation or exclusion from the group is profound (Leary and Baumeister, 2000). Recent advances in the study of the fear of social separation and loneliness—in humans and non-humans—is documenting the role of other patterns of neurophysiology involving the anterior cingulate cortex, insular cortex, prefrontal cortex, and other regions (Vitale and Smith, 2022).

**Kim:** Current animal models of fear assume that stimulus-stimulus (S-S) Pavlovian conditioning and stimulus-response (S-R) instrumental conditioning can help us understand human fear and fear disorders. Conversely, human studies employing similar fear conditioning paradigms strive to corroborate animal findings. In doing so, we have made tremendous progress in understanding the behavioral principles and neuronal mechanisms of associative fear memory. However, the knowledge we gained from these lines of research is limited because 'procedurally pure' laboratory fear conditioning rarely happens in nature and, second, Simulus-Stimulus (S-S) and Stimulus-Response (S-R) fear models cannot account for all the different actions and decisions that animals and people make when they are frightened in the real world. For example, Thorndike (1900) has argued that learning can best be studied under artificial situations that inhibit potentially competing instinctive activities. If so, fear conditioning studies in the confines of small chambers (rodents) and sitting passively in front of monitors (humans) may be overstating the importance of learning in both normal and abnormal fear. Utilizing more ecologically pertinent risky circumstances is likely to be beneficial for both preclinical and clinical studies of fear and anxiety (Mobbs and Kim, 2015).

**Kragel:** Animal models provide a means of measuring and manipulating brain function with a level of precision that is impossible to achieve in healthy humans. Processes that are most likely to be conserved across species—such as those involved in hedonic, appetitive, and defensive behaviors—can be studied in animal models to pinpoint the contribution of specific neuronal populations (Berridge and Kringelbach, 2015; Janak and Tye, 2015). Comparing findings from laboratory studies in animals to those from neuroscientific research in humans can reveal points of convergence and divergence across species. Research using fear conditioning exemplifies this approach (Delgado et al., 2006; Lonsdorf et al., 2017), with studies in rodents (Gross and Canteras, 2012; Johansen et al., 2010; Tovote et al., 2015), non-human primates (Antoniadis et al., 2007; Resnik and Paz, 2015), and humans (Bechara et al., 1995; LaBar et al., 1995, 1998), demonstrating the involvement of the amygdala, hypothalamus, and PAG in learning about and responding to threats. To the extent that the behaviors controlled by this network (e.g., orienting, emotional learning, avoidance) are central to fear, findings at the level of individual cells and neural ensembles identified in animal models can inform human work.

Another example of this translational approach comes from efforts to understand how emotional information reaches the amygdala. In rodents, visual threat signals are conveyed through multiple pathways. One of the most important projects from the retina to the superior colliculus, to the pulvinar, and finally on to the amygdala (Shi and Davis, 2001; Wei et al., 2015). This pathway targets one of many interdigitated populations in the basolateral amygdala, populations that are involved in a wide variety of emotional behaviors, from pain (Corder et al., 2019) to reward learning (Hu et al., 2021; Servonnet et al., 2020). Due to the interdigitation of these populations and the limited precision of conventional human neuroimaging techniques, it has been difficult to functionally distinguish this pathway from other amygdala circuits. In a recent study, we used a combination of ultra-high-field MRI, an experimental paradigm encompassing multiple types of aversive stimuli (auditory, visual, mechanical, and thermal), and a multivariate index of functional connectivity to identify a polysynaptic pathway from the superior colliculus to the amygdala (via the pulvinar) that was uniquely associated with the aversiveness of exteroceptive stimuli (Kragel et al., 2021). These observations suggest that the 'low road' identified in rodent fear conditioning studies is conserved in humans, and is relevant to understanding how our brain transforms sensory inputs into emotional experiences. More broadly, this research shows how animal models can provide specific hypotheses for human research, and guide the development of new analytical tools. It also illustrates how neurobiological accounts of defensive behavior derived from animal models may explain some, but not necessarily all aspects of fear and anxiety in humans. Although we found that the normative aversiveness of stimuli covaried with connectivity in this subcortical pathway, online measures of self-reported aversiveness were better explained by predictive models that included signals distributed across multiple brain systems (Čeko et al., 2022), including activity in the amygdala and PAG as well as the insula, prefrontal cortex, and posterior parietal cortex—regions hypothesized to mediate the conscious experience of fear (LeDoux and Brown, 2017).

The gap in the amount of information conveyed by signals in subcortical pathways and patterns distributed across multiple brain systems highlights one potentially fruitful approach that combines forward and reverse translation. Circuits identified in nonhuman animals can constrain models of affective phenomena in human research; for example, by serving as a minimal set of features that can serve as inputs to predictive models or as targets for causal interventions. If additional neural substrates are necessary to accurately predict or decode emotional experience in humans, then the homologs of these substrates should be assessed in animal models to more precisely determine their contribution to behavior (e.g., causal status, cellular and molecular underpinnings). Iteratively applying this bi-directional, recursive approach should converge on a set of structures that are similar in function across species and that maximally explain human behavior.

**MacLeod:** When designing studies to advance understanding of psychological functioning, we are often faced with the need to balance the benefits of ecological validity against the benefits of experimental control. Ideally, what we examine should closely approximate the naturalistic occurrence of the specific psychological phenomenon that is of interest to us, but our capacity to adequately test the theories under scrutiny will often depend on our ability to constrain irrelevant variables and to systematically manipulate the independent variables implicated by those particular theories. Often, to achieve such experimental control, it may be necessary to compromise the degree to which the object of study closely matches the psychological phenomenon of interest. When the psychological phenomenon of interest concerns human fear and anxiety, ecological validity will be greatest when this is investigated using studies that employ human participants. Whether or not such human studies of fear and anxiety would be unduly compromised by an inadequate capacity to constrain irrelevant variables, or to manipulate the variables implicated by the theories under test, will depend entirely upon the specific nature of these particular theories. If the theoretical position under scrutiny can be tested only by constraining, say, genetic variation in ways that could not realistically be achieved using human samples, or by direct manipulating, say, neural structures using lesions, then it could become necessary to compromise ecological validity by conducting such studies on non-human animals. However, support obtained for the theory from studies conducted on animals could not be represented as compelling evidence of its validity in humans, just as lack of support would not permit the strong conclusion that the theory is invalid with respect to human fear and anxiety. Although I can envisage circumstances under which—in order to test very particular types of theoretical accounts concerning human fear and anxiety—the constraints associated with human testing might justify the use of some animal studies, I cannot envisage the reverse. It is a perfectly legitimate academic objective to advance understanding of fear and anxiety in non-human animals, but studies designed to test theories concerning fear and anxiety in animals will have the greatest ecological validity when carried out using the animals that these theories concern, and by instead using human participants methodological control would likely be compromised rather than enhanced. I should note that these above reflections pertain to the use of animal studies to *test* hypotheses

concerning human fear and anxiety, and to studies using human participants to *test* hypotheses concerning fear and anxiety in animals. In contrast, I have no such concerns about the use of findings from animal studies, and from human studies, to *inform the development of hypotheses* concerning human fear and anxiety, respectively. The formation of hypotheses is an inductive reasoning process that can be enriched by metaphor and analogy, so drawing upon theoretical models of animal emotion when developing hypotheses concerning human emotion, and vice versa, may stimulate the generation of plausible and powerful ideas. However, the validity of such hypotheses will be determined only by testing the predictions they generate. In my view, it will be best whenever possible to evaluate the validity of hypotheses concerning human fear and anxiety by testing the predictions they generate concerning human fear and anxiety, and to evaluate the validity of hypotheses concerning fear and anxiety in non-human animals by testing the predictions they generate concerning fear and anxiety in such animals.

**Mobbs:** Animal research is extremely important for informing human models, yet for obvious reasons their applicability is limited. Behaviorally, we have learned a great deal from animals and how they respond to different types of threat (e.g., *thigmotaxis*, the propensity to maintain close proximity to a wall or other physical enclosure and avoid open areas). However, few labs are measuring such rich behavioral information in humans (cf. Kim's response to Question 2). Therefore, computational ethological approaches to human neuroscience are critical in reducing the behavioral gap between animal and human research (Mobbs et al., 2021). Examples include Paul Pauli's group at the University of Würzburg, which provided some of the first studies of human thigmotaxis (Gromer et al., 2021), and Karin Roelofs' group at the Donders Institute, which devised reliable ways to measure freezing in humans (Klaassen et al., 2021; Roelofs and Dayan, 2022). Our work using virtual ecologies has demonstrated panic-related motor errors as well as thigmotaxis in humans (Mobbs et al., 2009). Other novel behavioral measures have also been proposed (Mobbs et al., 2021). It is early days, but more effort needs to be made in developing paradigms that produce better measures of behavior and reduce the behavioral gap between human and rodent work (Mobbs et al., 2021).

On the neurobiological level, there are other issues. The techniques used on rodent research are much more advanced and have orders-of-magnitude better spatial and temporal precision (e.g., optogenetics, calcium imaging). Further, the causal nature of this work and the ability to elicit real-life threatening paradigms (or at least in the mind of the rodent!), make animal models very powerful tools for understanding how the brain responds to threat. Still, the rodent brain has evolved under very different pressures and the evolutionary gap between humans and rodents is estimated to be 96 million years (Nei, Xu and Glazko, 2001). Despite this gap, many believe that we share much of the same circuitry. The main issue is that when we contemplate the neural representations of higher-order conscious feelings, we have no animal model. As LeDoux and Pine rightly noted, conscious feelings are the defining features of human fear and anxiety (LeDoux and Pine, 2016). This conscious feeling of knowing that you are in danger and the ability to engage metacognitive strategies to tackle the threat, are certainly more complex in humans. Here we need more and better theory on how and why human defensive states were evolutionarily configured in this way. We also need to develop paradigms that facilitate the process of understanding what is and what is not conserved across rodent and human brains (Terburg et al., 2016).

**Naragon-Gainey:** Animal models can be informative for understanding human fear and anxiety with regard to observable behaviors (presuming we know how to correctly translate them into equivalent human behaviors or inferred motivations) and neurobiological or physiological patterns. Observations in animals may suggest areas of interest for further study in humans or bolster confidence in cross-species features of fear and anxiety. Nevertheless, they need to interpreted cautiously, insofar as subjective experience is a core component of typical and pathological fear and anxiety in humans (Taschereau-Dumouchel et al., 2022). Given our inability to understand animal's subjective experiences, or how these experiences may manifest differently across species, we are limited in the translational inferences that can be made.

**Question 2 Afterword.**

More than a century ago, Darwin emphasized the shared origins and essential continuity of the emotions in humans and animals (Darwin, 1872/2009). Today there is a general scientific consensus that the neurobiological underpinnings of core features of fear- and anxiety-related states, traits, and disorders can be modeled in animals, enabling identification of the circuits responsible for detecting and learning about different kinds of threat, mounting adaptive behavioral and physiological responses, and choosing between competing response options (e.g., freeze or flee; Adolphs and Anderson, 2018; Barrett, 2017; Fanselow and Pennington, 2018; Fox et al., 2018; Pine and LeDoux, 2017; Taschereau-Dumouchel et al., 2022). It is clear that animal models enable a degree of resolution, precision, and control that is impossible to achieve in routine human studies. These technical strengths open the door to identifying the molecules, cell types, and circuits that are necessary and sufficient for assembling a variety of defensive responses to threat in mice, rats, monkeys, and other model species; motivating the investment of billions of biomedical research dollars over the past several decades (Fox and Shackman, 2019). But what about feelings, the hallmark of human emotion for many theorists (Mobbs et al., 2019)? How relevant are these tantalizing mechanistic discoveries to the everyday experience of fear, anxiety, and panic? To the subjective symptoms used to diagnose anxiety and trauma disorders? With this tension in mind, we asked the discussants to consider whether and how animal models should inform our understanding of human fear and anxiety.

Keltner-Cowen and Buss express the most unconditional support for animal models of fear and anxiety, perhaps reflecting their longstanding empirical focus on the same kinds of behavioral and observational measures that are the mainstay of animal research (Table 1). Although acknowledging the importance of feelings, Buss emphasizes that "they are not central to…individual differences in emotion," particularly in young children, a position reminiscent of that held by many behavioral neuroscientists and animal modelers, including early work by LeDoux (Berridge, 2018; Fanselow and Pennington, 2017; LeDoux, 2000).

For the remaining discussants, subjective experience plays a central role in human emotion (cf. Question 1), and they expressed greater hesitation about the value and reach of animal models. Cautions, caveats, stipulations, and provisos abounded. Mobbs adopts the most categorical position, telling us that, although animal research has proven invaluable, when it comes to "conscious feelings, we have no animal model." Bliss-Moreau, Clark, Kragel, and Naragon-Gainey adopt similar perspectives. Aside from the impossibility of asking rats and mice to report their conscious experiences, Clark reminds us that fearful and anxious feelings are, more often than not, weakly correlated with behavioral and physiological responses to threat in humans. For her, this weak association across emotion readouts (i.e., low 'convergent validity') reinforces the concern that mechanistic insights gleaned from the study of freezing and other defensive behaviors in animals are unlikely to translate to a deeper understanding of clinically relevant symptoms of fear and anxiety in humans.

Kim and Bliss-Moreau highlight other limitations of animal models. Kim tells us that "it is debatable whether rats and mice show *anxiety* as it is defined in human psychology and medicine….not all human traits and psychopathologies can be modeled in animals." Bliss-Moreau raises a related point, suggesting that humans "populate the fear concept with instances of both abstract threats (e.g., death, climate change, financial crashes) and concrete threats (e.g., venomous snakes, the sound of footsteps in a dark alley, peering over the edge of a tall cliff). Animals… with lesser capacity for abstraction…likely only experience concrete threats as threatening" (see also her response to Question 1).

Among the discussants who highlighted limitations of animal models

**Table 1**
Discussant demographics and scientific expertise.

| Name | Title | Sex | Country | Expertise | Developmental Chapter | Population | Species | Methods |
|---|---|---|---|---|---|---|---|---|
| Eliza Bliss-Moreau | Professor | F | USA | Comparative and Translational Affective Science | Lifespan | Typical/ Atypical | Multiple | Behavioral/Observational, Eye Tracking, Psychophysiology, Neuroimaging, Focal Brain Perturbations |
| Kristin A. Buss | Professor | F | USA | Affective Science, Developmental Psychopathology, Temperament, | Youth | Typical | Humans | Assessment, Behavioral/Observational, Psychophysiology, EEG/ERP, Neuroendocrine |
| Lee Anna Clark | Professor | F | USA | Clinical Psychological Science and Personality | Youth, Adults | Typical/ Atypical | Humans | Assessment |
| Andrew S. Fox | Associate Professor | M | USA | Translational Affective Neuroscience | Youth, Adults | Typical/ Atypical | Monkeys, Humans | Behavioral/Observational, Neuroscience, Genomic, Transcriptomic, Neuroimaging, Neuroendocrine, Computational Modeling |
| Dacher Keltner | Professor | M | USA | Affective Science | Adults | Typical | Humans | Behavioral/Observational, Psychophysiology |
| Alan S. Cowen | CEO | M | USA | Computational Affective Science | Adults | Typical | Humans | Computational Modeling |
| Jeansok J. Kim | Professor | M | USA | Behavioral Neuroscience | Adults | Typical | Mice, Rats | Neurophysiology |
| Philip A. Kragel | Assistant Professor | M | USA | Cognitive and Affective Neuroscience | Adults | Typical | Humans | Behavioral/Observational, Computational Modeling, Neuroimaging |
| Colin MacLeod | Professor | M | Australia | Cognition and Emotion | Adults | Typical/ Atypical | Humans | Cognitive/Experimental |
| Dean Mobbs | Professor | M | USA | Affective Neuroscience | Adults | Typical | Humans | Behavioral/Observational, Computational Modeling, Neuroimaging |
| Kristin Naragon-Gainey | Associate Professor | F | Australia | Clinical Psychological Science | Adults | Typical/ Atypical | Humans | Assessment, Ecological Momentary Assessment (EMA) |

of fear and anxiety, Fox articulates what is perhaps the most balanced perspective. For him, human studies and animal models are complementary. He emphasizes that, "optimal progress toward understanding and alleviating human suffering requires both *translation* [animals → humans] and *reverse translation* [humans → animals]. Although we can best study subjective experience in humans, these feelings emerge from, or are related to, behavior, peripheral physiology…circuits, cell-types, [and] molecules…Nearly all of these…processes are more readily deciphered in…animals."

Building on this foundation, Fox, Clark, Kragel, MacLeod, and Mobbs all underscore the value of animal models for developing testable hypotheses for human research. As MacLeod notes, "The formation of hypotheses is an inductive reasoning process that can be enriched by metaphor and analogy, so drawing upon…animal [research] when developing hypotheses concerning human emotion…may stimulate the generation of plausible and powerful ideas…[Of course,] the validity of such hypotheses will be determined only by testing the predictions they generate" in humans.

Several panelists suggest that the likelihood of successful translation of knowledge from animals to humans is greatest when similar paradigms and readouts are used (Clark, Fox, Kragel, and Mobbs). As Fox notes, "Animal models…should be guided by our understanding of what leads to suffering in humans …Small differences in the paradigm, context, or stimuli may result in very different outcomes, and these differences can be exacerbated when adapting paradigms across species." Adopting a longer-term perspective, Kragel tells us that "iteratively applying this bi-directional, recursive approach should converge on a set of structures that are similar in function across species and that maximally explain human [fear and anxiety]." Going beyond assays, Buss and Fox underscore the unique value of nonhuman primate research, telling us that the likelihood of successful translation to humans is increased because humans and monkeys share comparatively similar genomes and brains (including a well-developed prefrontal cortex) and a common repertoire of socio-emotional responses to different kinds of threat.

**Question 3.** ***How are fear, anxiety, and related constructs organized in the brain? Are some regions more central than others? Is there an 'anxious brain?' Are there distinct kinds of fear embodied in dissociable or overlapping circuits? How does the brain dynamically choose the most adaptive response to threats that vary across multiple dimensions? Do different circuits compete for control over behavior ('biased competition')?***

**Bliss-Moreau:** There are not discrete neural circuits for specific emotions. Fear and other emotions instead emerge from activity in neural networks responsible for domain general functions related to survival, such as regulating allostasis, making predictions/inferences, and organizing sensations and percepts to navigate the environment more effectively (e.g., in psychological parlance, the use of *concepts*). Affect emerges from activity in a distributed brain network that is responsible for processing signals from the body (*interoception*) and using those signals to regulate physiology predictively to meet the body's dynamic and changing needs (*allostasis*), referred to as the *interoceptive-allostatic network* (or the allostatic-interoceptive network) (Barrett and Simmons, 2015; Kleckner et al., 2017). This network includes regions of posterior insula responsible for sensorimotor integration, primary interoceptive cortex located in the granular regions of insula (dorsal and mid-to-posterior), visceromotor agranular/dysgranular regions of anterior cingulate cortex and anterior insula, amygdala (specifically central amygdala, which plays a role in visceromotor functions), and the subcortical and brainstem nuclei that receive information from and are directly responsible for regulating peripheral physiological systems (e.g., hypothalamus, PAG, etc.). When rodents are exposed to different types of 'fear'-relevant stimuli, different patterns of activity in these subcortical elements are activated (Gross and Canteras, 2012), suggesting that instances of affect are flexibly configured based on environmental context and behavioral affordances. In humans, the transformation of affect into a discrete emotion, such as fear, occurs (in psychological terms) when conceptual knowledge and language are integrated into the representation, and neural regions involved in conceptualization and linguistic process are active during discrete

emotions (Lindquist, Wager, Kober et al., 2012; Satpute and Lindquist, 2021). Importantly, brains are degenerate (Edelman and Gally, 2001), meaning that more than one neural ensemble can generate the same psychological output—there are, essentially, many neural pathways to the same emotion. For instance, recent neuroimaging work reveals degenerate patterns of activity during self-generated anxiety and anger (Doyle et al., 2022).

**Fox:** The capacity to adaptively respond to different kinds of threats across varied natural contexts has been a constant throughout evolutionary time. As such, the capacity to avoid threats is necessarily instantiated in the brain systems of fish and fruit flies, as much as mice and humans. It follows that threat-relevant brain systems are likely to be instantiated across the molecular, cellular, and distributed brain systems that we share with long-extinct common ancestors, as well as more recently evolved human brain systems.

Within this framework, we can reasonably hypothesize that there exist brain systems that are specific to detecting and responding to specific kinds of threat (e.g., looming aerial predators), as well as systems that are well-suited to provide a broader, generalized, framework for detecting and responding to threat. If a system is useful for avoiding death in fruit flies and humans, it seems likely that it was useful for our last common ancestor and that the biology that underlies this system is likely to be conserved to a greater or lesser degree. In contrast, if there is a particular set of threats that are uniquely applicable to particular species, or rely on a capacity that is unique to some species, it is unlikely that the biological substrates that enable processing of these threats are evolutionarily conserved. In addition, because evolution necessarily builds on what has come before, it is likely that these systems work in concert to enable adaptive threat responses.

With this in mind, I have outlined a number of considerations for understanding the organization of fear- and anxiety-relevant circuits in the human brain in Supplementary Note 3.1, and summarize 3 key predictions here:

a) *Threat-processing is not instantiated in a single unified brain circuit.* Different kinds or classes of threats are likely processed in partially independent brain systems. Evidence for this is abundant. For example, patient S.M., who, despite having bilateral destruction of her amygdalae and purporting not to experience fear a variety of lab and naturalistic contexts, does experience fear when confronted with a $CO^2$ inhalation challenge (Feinstein et al., 2011, 2013; Khalsa et al., 2016). This study, supported by a plethora of animal work, demonstrates that multiple circuits can trigger an experience that we might call fear (see Supplementary Note 3.1 for additional examples).
b) *Fear- and anxiety-related neural circuits are distributed across most of the brain, including the most basic sensory regions.* For example, plasticity in auditory cortex is required for tone-shock classical conditioning (Letzkus et al., 2011). Thus, even if a brain region is not considered to be a source of the emotion, learning in these regions may still play a critical role in the processing and filtering of threat-relevant information, biasing people to perceive threat in ambiguous contexts and/or toward extreme responses.
c) *Because distinct cell-types within specific brain regions can differentially contribute to varied responses, measures of aggregate brain activity will be insufficient to fully understand the neurobiology of fear and anxiety.* To understand how various features of a threatening context—type, intensity, probability, imminence, certainty, opportunity for avoidance, and so forth—trigger fear and anxiety, researchers will need to integrate biological insights from animal models to test targeted hypotheses in humans (see my responses to Question 2 and Question 5).

**Keltner & Cowen:** Semantic Space Theory suggests the need to go beyond the search for one-to-one mappings between six kinds of emotion and coarse brain regions (see our response to Question 1). Emotions are systemic states with recurrent dependencies on sensory processing, cognitive appraisal, autonomic physiology, expressive behavior, and decision-making. Thus, by their very nature, emotions are embodied in widely distributed and overlapping neural circuits. As dynamic, holistic states, emotions can be thought of as modes of brain activity, just as walking and running are different modes of human locomotion. There are no singular anatomical centers of walking or running, but a wide range of distributed musculoskeletal adaptions have evolved to support each of these modes of movement. We must think analogously when it comes to emotions and the brain.

With this in mind, a recent study by our group collected whole-brain fMRI responses to over 2,000 emotionally evocative videos and used statistical modeling approaches to differentiate neural representations of a wide range of emotions, broad affective features such as valence and arousal, and semantic and visual features (Horikawa et al., 2020). Dozens of emotions evoked by video could accurately be differentiated from patterns of brain activity. As expected, such differentiation was not observed in simple one-to-one mappings between specific emotions and brain regions (e.g., fear and amygdala) but in complex configurations across multiple brain networks.

The patterns of brain activity that mapped to specific emotions were highly consistent across subjects. This implies that they are not encoded in arbitrary brain networks, as implied by constructionist approaches to emotion (Barrett, 2017; Lindquist et al., 2022). Specific emotions explained greater variability in brain activity than affective dimensions in every cortical and subcortical region of the brain, including the amygdala and brainstem, as indexed by cross-validated predictive models. This study suggests that specific emotions are primary in the representation of emotion throughout the brain, consistent with behavioral findings from Semantic Space Theory (Cowen and Keltner, 2021; Keltner et al., in press).

Although emotion-related neural activity is distributed across the brain, causal evidence from animal studies point to specific regions playing a disproportionate role in modulating specific emotional states. In the case of fear and related emotions, this likely includes the amygdala, PAG, and dorsal raphe nucleus.

**Kim:** The amygdala and its associated structures (e.g., PAG, hypothalamus.) serve as a *central defensive system* in the mammalian brain against external threats from the environment. Again, the degree of engaging other neural structures might lead to fear, anxiety, phobia, panic, and so on. A useful analogy would be the common ingredients in bread (i.e., flour, salt, water). Other neural structures would be specific ingredients (e.g., yeast, egg, sugar) that can be added to these foundational ingredients to produce different types of bread (e.g., flatbreads, sourdough, cake). Ingredient imbalances may serve as a metaphor for pathological fear, anxiety, and panic.

**Kragel:** A growing number of studies have begun using multivariate models to examine how fear, negative affect, and related constructs are represented in the human brain (Braem et al., 2017; Faul et al., 2020; Kassam et al., 2013; Kim et al., 2017; Koizumi et al., 2016; Saarimäki et al., 2016; Shinkareva et al., 2020; Staib et al., 2020; Visser et al., 2013). One family of models—termed brain signatures or neuromarkers—includes features from multiple brain systems and is designed to be evaluated on independent samples from the same population under different experimental conditions (Kragel et al., 2018). This enables the models to be shared and used prospectively to validate mental constructs—to identify whether different theoretical conceptions of fear and anxiety are respected by the brain.

A number of multivoxel signatures have been developed to detect variations in mental states related to fear. These include models that capture Pavlovian auditory threat (vs. safety) cues (Reddan et al., 2018), phenomenologically distinct states of fear evoked by film and instrumental music (Kragel and LaBar, 2015), variation in self-reported aversiveness produced by different types of noxious stimuli (Čeko et al., 2022), and variation in feelings of fear evoked by photographs of predators and other naturalistic threats (Zhou et al., 2021). All of these signatures have been cross-validated using held-out data, and all show a

degree of generalizability (see, e.g., Sicorello et al., 2021; Zhou et al., 2021). All rely on activity distributed across multiple brain systems, *not* isolated brain regions. And although there is notable variability in the patterns that define these signatures (Clark-Polner et al., 2017), all 4 signatures include positive contributions (i.e., signature weights) in the amygdala, midbrain (in the superior colliculus and extending into PAG), and right inferior frontal gyrus (Supplementary Note 3.2).

The overlap in data-driven brain signatures trained using radically different paradigms, problems (e.g., regression to predict self-reported feelings and classification of different stimulus contingencies), and approaches argues against the position that there is little-to-no consistency in emotion signatures across experiments and labs (Barrett, 2017; Barrett & Satpute, 2019; Clark-Polner et al., 2017). At the same time, this emerging body of work is broadly consistent with proposals that emotion involves interactions between subcortical and cortical networks spanning multiple brain systems (Barrett and Satpute, 2013; Pessoa, 2017), rather than a single dedicated circuit or system. Findings from multiple studies show that subcortical circuits are not unique in their predictive capacity, as signals from networks beyond the amygdala and interconnected defensive circuitry are necessary to accurately predict fear experience (Taschereau-Dumouchel et al., 2020; Zhou et al., 2021). It is important to note, however, that regions conveying information useful for prediction may not play a causal role in defensive behavior or subjective feelings—manipulations such as trancranial magnetic stimulation, transcranial ultrasound (Legon et al., 2014), and temporal interference (Grossman et al., 2017) are needed to verify the contribution of these brain regions to behavior.

Further, the overlap between signatures shown in Supplementary Note 3.2 aligns with multiple hypotheses about the neural networks that coordinate defensive behavior and fear experience in humans that should be evaluated in future work. The network of subcortical regions shared across signatures—including the amygdala and PAG—may function as an integrative hub within a larger network in which more peripheral regions represent aspects of fear experience that vary across situations. Activity within this core subcortical network may reflect the features of evolutionarily important threats that cut across specific instances of fear (Öhman and Mineka, 2001). Alternatively, it might capture the activity of adjacent, but distinct circuits that process modality-, situation-, or context-specific threat cues, such as perceptual features associated with predators or social signals from conspecifics (Gross and Canteras, 2012). However, because past studies have only examined brain responses to one or a few manipulations at a time, it remains unclear which of these accounts most parsimoniously explains human brain function. Work that systematically samples and models more varied manipulations of threat and fear across different contexts is needed to adjudicate between these different theoretical accounts.

**MacLeod:** To be perfectly honest, I don't know how fear and anxiety are organized in the brain, as the topic falls rather far from my expertise as a cognitive-experimental psychologist. Consequently, I considered skipping this question. However, in the spirit of stimulating discussion, I thought that it might be a little more provocative to respond by considering whether it matters how fear and anxiety are organized in the brain. And to maximize provocation, I will start by suggesting that it does not. The theoretical questions central to my own area of research concern the nature of the cognitive processes that operate to elicit and sustain elevated anxiety and dysfunction—including attentional bias, distorted interpretation, negative expectation, and maladaptive belief—whereas the applied questions in my research area are centered on whether the manipulation of these cognitive variables can serve to attenuate anxiety vulnerability and dysfunction therapeutically. The locus of such cognitive processes within the brain is largely irrelevant when it comes to answering these questions. One sometimes encounters the view that because emotional experience, like all psychological experience, must inevitably emerge from brain activity, it follows that the study of brain activity will consequently enable superior understanding of such psychological experience. However, such a claim is akin to arguing that, because the brain is a structure comprised of atoms, the best understanding of psychological experience will result from the study of atomic structure. The important thing, in my view, is to ensure that the level of analysis adopted within any given research program is the level required to answer the specific questions that this particular research program is designed to resolve. Of course, it follows from this that my deliberately provocative response, suggesting that the organization of fear and anxiety within the brain does not matter, is a narrow view that can be defended only with respect to questions such as those typically addressed within my own area of research. Determining the answers to other types of important questions, such as whether the application of transcranial direct current stimulation to particular brain regions may alleviate fear and anxiety, will likely depend very heavily upon our knowledge of how fear and anxiety are organized in the brain. Although my own expertise does not enable me to comment with authority on the nature of this organization, the breadth of cognitive processes that are implicated in fear and anxiety justifies speculation that a diverse array of neural systems is likely to be involved. We know that elevated fear and anxiety are associated with alterations of associative memory, impaired attentional control, elevated worry about the future, biased selective processing across multiple sensory modalities, and dysfunctional patterns of overt behavior. Therefore, even if the anxiety response consistently involves activation of the amygdala, the processes that trigger such activation, and that operate to govern expression of anxious symptomatology, clearly must involve multiple neural regions that include, but will likely not be limited to, the temporal lobes, prefrontal cortex, orbitofrontal cortex, visual cortex, auditory cortex, and motor cortex. The degree to which it is likely to be of value to study the activation of these various neural systems directly within any particular research program conducted to advance understanding of fear and anxiety, will depend upon the precise nature of the specific questions that this particular research program is designed to answer.

**Mobbs:** The human brain is an extremely complex organ that encompasses both low-dimensional reflexes and high-dimensional representations. There are several things to consider: First, neural systems can be prepared innately for certain classes of stimuli (e.g., looming; Schiff et al., 1962). The brain also has a powerful set of learning systems, including those that learn from direct experience, vicariously, inferentially and further cross-fertilized through meta-learning. Higher-order abilities (e.g., inferring danger, prospection, metacognition and conscious feeling states) make it extremely difficult to separate these different processes. Next, depending on the conditions (e.g., level of threat imminence), the same threat can engage different neural systems. It is important to note that some environments are multidimensional and entropic, leading to a set of neural systems that need to be versatile and flexible. In the context of cognition, a multidimensional world will likely result in high-dimensional neural representations. A final comment is that these circuits change over development (e.g., from caregiver protection to flight and fight; Sullivan and Opendak, 2018) and across sexes (Choleris et al., 2018).

Given the changing and interactive nature of the brain, one must have a neurobiological model that can accommodate the multidimensional aspects of the world. Population coding presents one account, which comes from the belief that it is neuronal populations—*not* individual neurons—that serve as the fundamental computational unit (Saxena and Cunningham, 2019). Population coding is how the brain integrates multiple processes and performs complex computations. Ebitz and Hayden put forward the example that cognition plays multiple roles, including attending to a stimulus, keeping information in mind, planning, behavioral control, action execution, and outcome expectations (Ebitz and Hayden, 2021). Ebitz and Hayden's suggestion underscores the importance of understanding human defensive states as a dynamically integrated, holistic system. Therefore, examining the function of neurons in isolation, and linking them to specific behaviors or cognitive states fails to capture how the brain works in the real world. It is the

dynamic processes between populations of neurons that captures the mechanisms behind cognition and behavior.

We and others have recently proposed that population codes can account for the parallel and integrated processes needed across changing levels of threat and uncertainty (Headley et al., 2019; Mobbs et al., 2020). Further, such accounts can theoretically support other theories including constructivist theories (Barrett, 2017) and those that separate conscious feelings from defensive behaviors (LeDoux and Pine, 2016; Mobbs et al., 2019). These population codes need to construct an action plan based on internal states and sensory information that form representations of the external world (Flavell et al., 2022). Conscious fear and anxiety would also be represented in these population codes and integrated into the action plan, depending upon the spatiotemporal level of threat (Fanselow, 2018; Mobbs et al., 2020). Under urgent escape, the population codes will be focused upon reactive defensive reaction, whereas successful evasion allows time for cortical populations to inform reactive defensive responses (Mobbs et al., 2020).

In the context of the debates between constructivist and domain-specific models of the brain (see Adolphs and Feldman-Barrett debate; Adolphs et al., 2019), I take a hybrid view. That is, I see the brain as a set of population codes that construct representations of the world and summate through specialized brain structures that have evolved for survival purposes (e.g., natural and sexual selection). Therefore, I do not see these theories as contradictory. As I mentioned above, I believe that there is overlap between defensive states and that anxiety would just be a prospective representation of a potential threat that will increase autonomic reactions, raise conscious awareness of these feelings, and drive behavioral avoidance.

**Question 3 Afterword.**

When expressed too intensely or pervasively, fear, anxiety, and panic can be debilitating (APA, 2022). Anxiety and trauma disorders are the most common psychiatric illnesses and existing treatments are far from curative for many patients (Shackman and Fox, 2021). For many scientists and funders, these sobering clinical observations are sufficient to demand a deeper understanding of the underlying neurobiology. For others, the search is motivated by the more fundamental scientific belief that mechanistic understanding can inform and constrain basic psychological models of fear, anxiety, and other mental states, which would otherwise remain anchored exclusively in behavioral observation and introspective report (Fox et al., 2018; Tinbergen, 1963). With these general considerations in mind, we asked the discussants to consider how fear, anxiety, and related constructs are organized in the brain.

All agree that fear and anxiety encompass virtually the entire brain—including regions involved in basic sensory and motor functions—and not just the 'usual suspects' implicated in focal perturbation and recording studies (Li and Keil, in press; Shackman and Fox, 2018). As Keltner and Cowen note, fear and other "emotions are…states with recurrent dependencies on sensory processing, cognitive appraisal, autonomic physiology, expressive behavior, and decision-making. Thus, by their very nature, they are embodied in widely distributed and overlapping neural circuits."

Beyond this general point of agreement, there was less consensus about the precise neurobiological architecture of fear and anxiety. Nevertheless, Fox's framework seems to capture the general spirit of the other neuroscience contributors' responses. Building on the conceptual foundations laid out in Question 1, Fox hypothesizes that:

1. **Threat-Processing is Not Instantiated in a Single Unified Circuit (Many-to-Many).** The universe of potential threats, defensive responses, and conscious experiences is vast. Most of the discussants agree that this enormous psychological space encompasses multiple brain circuits, and not isolated fear or anxiety centers (Bliss-Moreau, Keltner-Cowen, Kim, and Mobbs).
2. **Multiple Circuits Can Trigger Similar Signs and Symptoms (Many-to-One).** Drawing on a rich body of mechanistic work, Fox reminds us that dissociable neural circuits can trigger similar, perhaps even identical, feelings and defensive behaviors (Supplementary Note 3.1). Bliss-Moreau articulates an overlapping position, emphasizing that multiple neural pathways can produce the same conscious feeling ('equipotentiality').
3. **Some Circuits are Narrowly Tuned to Specific Kinds of Threat (One-to-One).** Fox suggests that some neural systems are specific to detecting and orchestrating defensive responses to specific kinds of threat. Mobbs makes a similar point, emphasizing that some circuits are "prepared innately for certain classes of stimuli," such as looming aerial predators.
4. **Other Circuits are Broadly Tuned to a Variety of Threats (One-to-Many).** Nearly all of the discussants agree that some circuits are broadly engaged by a range of threats (Fox, Bliss-Moreau, Kim, Kragel, and Mobbs). As Kragel notes, this "may reflect the features of evolutionarily important threats that cut across specific instances of fear." More metaphorically, Kim tells us that "The amygdala and its associated structures…serve as a *central defensive system* in the mammalian brain against external threats from the environment…[while] the degree of engaging other [circuits] might lead to fear, anxiety, phobia, panic, and so on. A useful analogy would be the common ingredients in bread (i.e., flour, salt, water). Other neural structures would be specific ingredients (e.g., yeast, egg, sugar) that can be added to these foundational ingredients to produce different types of bread." For Bliss-Moreau, shared circuits may reflect the linguistic and abstract reasoning processes that underlie the conscious awareness of emotional feelings.
5. **Some Regions are More Critical Than Others.** As Keltner and Cowen note, "although emotion-related neural activity is distributed across the brain, [some]…regions play…a disproportionate role in modulating specific emotional states" (for a related perspective, see Berridge, 2018). Nearly all of the discussants highlighted the special significance of regions implicated by lesion and other kinds of mechanistic work, including the extended amygdala, hypothalamus, PAG, rostral cingulate, insula, and orbitofrontal cortex/ventromedial prefrontal cortex (OFC/vmPFC).
6. **Distributed Circuits are Key, and Can Compete for Control of Behavior.** All of the neuroscientists emphasized the importance of anatomically distributed networks and functionally distributed signatures, codes, and representations. In the **Supplement**, Fox goes a step further, and describes how the brain can overcome the complexity posed by the vast universe of possible threat-response mappings, a fundamental question for many fear and anxiety researchers (Fox et al., 2018). He begins by reminding us that every defensive response cannot be "implemented at the same time—an animal cannot flee while it is freezing," or foraging for that matter (Holley and Fox, 2022; for a related perspective, see Mobbs et al., 2020). He then highlights evidence from tracing and perturbation experiments in mice indicating that threat microcircuits are interconnected, with multiple points for competitive interactions and mutual inhibition, providing a mechanism for selecting the most adaptive response to a particular threat scenario (Supplementary Note 3.1).

The discussants diverge somewhat on the question of localization. Building on the conceptual framework outlined in her response to Question 1, Bliss-Moreau tells us that fear, anxiety, and other emotions are not natural kinds, they do not reflect invariant neurobiological substrates, and that they have no consistent 'fingerprints' in the brain. Although there may well be an emotional brain, for her, none of its constituents are specific to fear, anxiety, or any other discrete emotional feeling. Keltner and Cowen stake out the opposing position, telling us that recent neuroimaging research—in particular work which begins to grapple with the complexity of fear, anxiety, horror, and awkwardness (cf. Question 1)—is beginning to reveal "patterns of brain activity that mapped to specific emotions…[and that] were highly consistent across subjects. This implies that [these patterns] are not representations of

[socially or culturally] learned concepts encoded in arbitrary brain networks." Drawing on recent efforts to devise multivoxel brain 'signatures' of fear-related states, Kragel describes an intermediate perspective (Supplementary Note 3.2). While acknowledging that machine-learning has produced brain-emotion mappings that differ across paradigms, laboratories, and analytic approaches, Kragel emphasizes evidence of consistency across brain signatures, including engagement of the amygdala and PAG. Kragel hypothesizes that these core regions "may function as an integrative hub within a larger network in which more peripheral regions represent aspects of fear experience that vary across" threatening cues and contexts, a position that dovetails with Kim's bread-making metaphor (Question 3).

MacLeod, an experimental psychopathologist, stands apart from the neuroscientists. Adopting a more skeptical position, he writes that "in the spirit of stimulating discussion, I thought that it might be a little more provocative to…consider…whether it matters how fear and anxiety are organized in the brain. And to maximize provocation, I will start by suggesting that it does not." In short, he asks, what is the value of studying the brain for understanding the psychological nature and cognitive constituents of fear and anxiety (Grupe and Nitschke, 2013; Hur, Stockbridge et al., 2019)? Can affective neuroscience really provide insights that go beyond the reach of more traditional measures—behavior, ratings, and peripheral physiology? This is not an isolated, abstract, or purely rhetorical concern. MacLeod is hardly alone in questioning whether neuroscience can provide theoretically or practically important evidence and hundreds of millions of research dollars have been spent on the assumption that it can (Hur, Tillman et al., 2019). While it lies beyond the scope of the present discussion, a variety of work suggests that neurobiological data *do* have value for thinking about the nature of emotion. They can be used to quantify and tease apart implicit, reflexive, and automatic processes that are opaque to introspection and hopelessly muddled in behavioral assays (e.g., alterations in attentional capture or general threat reactivity vs. alterations in self-regulation). They can reveal deep mechanistic links between seemingly disparate psychological constructs or experiences, and they can be used to adjudicate between different theoretical models (cf. Bliss-Moreau and Keltner-Cowen's responses). Finally, neurobiological evidence can prompt the division of mental processes that might otherwise be considered one and the same (e.g., long-term vs. working memory, wanting vs. liking reward). In fact, it was evidence of dissociable neural substrates that prompted many scientists to fractionate fear into distinct states of fear, anxiety, and panic (Davis et al., 2010; Fox et al., 2018; Fox and Shackman, 2019). As Kent Berridge noted elsewhere, "studies of the brain can sometimes produce psychological surprises that have useful implications for thinking about disorders as well as normal functions. Those surprises can then help to reshape thinking about psychology in useful ways that might never have occurred if the brain studies had not been done, or their results had not turned out as they did." (Berridge, 2018, p. 91).

Still, MacLeod's response, which is grounded in rigorous cognitive psychological models of fear and anxiety, serves as a useful reminder that mindless neuroscience will not do. Neurobiological research, while valuable, is clearly not sufficient. "Without well-characterized behavior and theories that can act as a constraint on circuit-level inferences, brains and behavior will be like two ships passing in the night" (Krakauer et al., 2017, p. 484). Our neurobiology can only be as strong as our psychological models and behavioral assays, a point driven home time and time again in the discussants' responses to the prompts that follow. In short, scientists who view emotion through the lens of the neurobiology have much to learn from their non-neuroscientist colleagues. Likewise, students of emotion who do not "do neurobiology" have much to gain by attending to the discoveries of affective neuroscience.

**Question 4.** ***What mechanisms underlie the development and maintenance of pathological fear and anxiety? Is the search for biological markers of cross-cutting processes and mechanisms likely to be more fruitful than the search for markers of traditional diagnoses? Should the focus be on finding new therapies or better understanding old ones?***

**Bliss-Moreau:** The question is predicated on the idea that there are genuine categorical differences between 'normal' and 'pathological' fear and anxiety. That is just not true, whether one considers the biology or psychology of fear and anxiety. Constructivist approaches to emotion and other theoretical landscapes that recognize variance to be normative (e.g., evolutionary biology) do not draw hard boundaries between pathological and non-pathological. In this view, 'pathological' is not a biologically meaningful category (for a constructivist approach to depression see Shaffer et al., 2022), and health and illness in mental life emerge from complex systems (Fried, 2022). Further, these perspectives recognize the importance of context for shaping experience, and thus, a phenomenon that appears pathological in one context may be adaptive in another. 'Disorders,' in the DSM sense, are organizational structures constructed by humans. They do not represent real biological categories and so chasing their biological mechanisms is unlikely to generate insight. Studying the component mechanisms that are biologically real and then targeting therapies relative to those mechanisms is likely to be the more fruitful approach. For example, 'pathological' anxiety might arise from overgeneralization of stimuli or contexts that are associated with instances of fear or a hypersensitivity to physiological states leading to too many states being conceptualized as fear.

**Buss:** Both reactive and regulatory processes underlie the development of pathological fear and anxiety. These processes can be observed and quantified in multiple ways, from the biological to the environmental level of analysis. Taking work on dysregulated fear as an example, we have demonstrated that this behavioral profile is associated with both reactive biomarkers, such as the error-related negativity (Brooker and Buss, 2014) and cortisol (Davis and Buss, 2012); and regulatory biomarkers, including respiratory sinus arrhythmia (Buss et al., 2018) and delta-beta coupling (Phelps et al., 2016). In addition to these individual processes, our work has found robust evidence for environmental and familial factors—such as anxiety-promoting parental behaviors (i.e., overprotection)—that potentiate the risk of anxiety development in dispositionally fearful children (Kiel and Buss, 2011, 2014).

I would also like to briefly highlight the value of the National Institute of Mental Health's Research Domain Criteria (RDoC) initiative, which provides a robust framework for understanding the mechanisms that contribute to the development of typical and atypical anxiety (Conradt et al., 2021; Durbin et al., 2022; Ostlund et al., 2021). The utility of RDoC derives from its focus on cross-cutting processes and mechanisms, rather than discrete diagnoses. In my own work, it provides a framework for understanding the heterogeneity that we observe across development.

**Clark:** Like many other types of psychopathology, pathological fear and anxiety develop from perturbations in the biopsychosocial processes through which these emotions serve their adaptive function of alerting us to current and future real or potential danger, which may be physical (e.g., a vehicle speeding straight at us) or psychological (e.g., an upcoming exam). Classical conditioning and variants thereof (e.g., observational conditioning) is well established as one process through which pathological fear in particular, and to a lesser extent anxiety, develops. Other processes include social reinforcement and instructional learning. However, not everyone who undergoes conditioning develops pathological fear or anxiety, implicating individual differences in susceptibility.

These individual differences include innate temperament, and the personality traits that develop thereupon. Relevant examples of aspects of basic temperament include variation in vigilance for and sensitivity to aversive stimuli, the intensity (mild to panic) and type of response (fight, flight, freeze), and soothability following the offset of the challenge. These processes align well with an extended family of closely related traits, including neuroticism/negative affectivity, anxiety sensitivity,

and behavioral inhibition. Research has linked these traits to the function of specific brain regions (e.g., amygdala, bed nucleus of the stria terminalis, hippocampus and anterior cingulate) and to neurotransmitter activity (e.g., serotonin, GABA). Furthermore, molecular genetic studies are beginning to identify genetic variants that are linked to differences in the function of fear- and anxiety-relevant neural circuits, such as the hypothalamic-pituitary-adrenal axis.

Other types of individual differences include those anchored in traumatic experience (e.g., age of onset, duration, intensity) and the availability and effectiveness of subsequent support and intervention, including self-support and emotion regulatory skills. Believing that one has control over potentially fear- or anxiety-evoking situations also lowers risk of developing this type of psychopathology. A variety of cognitive biases (e.g., threat sensitivity) and interpersonal factors (e.g., attachment style, dependency, hostile criticism from significant others) also play a role. Given this dynamic causal complexity, longitudinal research beginning very early in life is sorely needed (Clark and Watson, 1994; Zinbarg et al., 2015).

With regard to the question of whether process-focused (e.g., RDoC) approaches to discovery will be more fruitful than categorical ones (e.g., DSM), a resounding *Yes* from me. It is now well established that the current set of 'official' diagnoses are not 'natural kinds' (i.e., entities that have relatively clear boundaries and reasonable within-category similarity), but instead are both highly comorbid and internally heterogeneous (e.g., Clark et al., 2017; Forbes et al., 2023). Increase in knowledge from studying these non-discrete hodgepodges of signs and symptoms has plateaued and turning research efforts to other levels of analysis is now more likely to yield new knowledge. However, it will be important not to reify the current RDoC structure, but truly to treat the model as a set of hypotheses to be tested and revised based on empirical results.

With regard to the question of whether we should focus on searching for new therapies or understanding existing ones, I maintain that the focus should be on finding ways to use research results concerning mechanisms and processes that lead to pathological fear or anxiety to inform new treatments. That said, it may be possible to modify current treatments to this end as well.

However, it is even more important to develop public-health-focused awareness and prevention programs with the goal of informing teachers and parents of major factors in the development of pathological fear and anxiety, and ways to develop good mental and behavioral health habits designed to reduce the incidence of pathological fear and anxiety. Our field has a woeful lack of knowledge regarding how to prevent or at least reduce the incidence of virtually all types of psychopathology, and there continues to be a dearth of research into prevention methods. The British are way ahead of the U.S. in terms of public-health campaigns regarding mental health and we would do well to emulate them (see https://www.nhs.uk/mental-health).

**Fox:** Fear and anxiety can be adaptive. It is only when these feelings are extreme, contextually inappropriate, or otherwise maladaptive that they become pathological. Thus, it seems prudent to theorize there is no mechanism that is uniquely associated with pathological fear and anxiety. Rather, I would hypothesize the processes and mechanisms that underlie fear and anxiety are shared between adaptive and maladaptive anxiety. Categorical and/or qualitative distinctions between non-pathological fear/anxiety and psychopathology are unlikely to help us understand treatment. That said, it is unclear if there are any current nomenclatures for describing fear- and anxiety-related states, traits, or disorders that will ring true with the underlying biology (see my responses to Question 1 and Question 3).

In my view, current efforts to develop fear/anxiety biomarkers have a low chance of success, given the potential for many-to-one mappings between the brain and emotion. Thus, I am wary of biomarkers without a clear understanding of mechanism and a refined nomenclature for fear and anxiety (see my responses to Question 1 and Question 2). Nevertheless, I believe that we will, in time, be able to identify biomarkers or other measures that will reflect the underlying pathophysiology and be useful for guiding treatment. I just do not think that this will precede a refined understanding of the biology that underlies threat processing. Rather, I propose that putative biomarkers should be drawn from animal work (translation) or considered high-priority targets for future animal work (reverse translation). To reiterate, the development and maintenance of pathological fear and anxiety must be studied in humans, while the biological processes that underlie threat-related pathophysiology are most amenable to research in animals (see my responses to Question 2 and Question 3).

With respect to studying new or old treatments, I do not believe it is either/or. It is currently unclear precisely *how* current therapies work. A refined understanding of the mechanisms by which current therapies function at a cellular and molecular level may lead to increased efficiency and more effective application of these treatments. At the same time, it is unlikely that optimal treatment will be derived from current treatments. Current treatments are only partially effective and come from an incomplete understanding of the mechanisms that underlie fear- and anxiety-related suffering.

In time, understanding the precise biological mechanisms of fear and anxiety can lead to treatments that are more directly targeted at the biological alterations that generate the experience of suffering. It is becoming increasingly clear that not every anxiety disorder presentation (or moment of experienced anxiety, for that matter) reflects the same underlying biological mechanisms. Rather, there are many-to-one and one-to-many relationships between biology and fear/anxiety.

In addition to trying to improve treatments in the short-term, we should be engaging in long-term efforts to better understand the mechanisms that give rise to an individuals' suffering. Ultimately, I believe that this understanding will be required to develop optimal individualized or stratified interventions, whether psychosocial or biological.

**Keltner & Cowen:** Semantic Space Theory points to several tractable approaches for understanding when fear and anxiety become disruptive or pathological (Keltner and Kring, 1998). Each of the 4 kinds of fear that we have identified might be inappropriate to the context (e.g., a person fears death when base rates of this possibility do not warrant such a fear—e.g., flying). An episode of fear might persist for too long; for instance, a person might ruminate about social separation for days after an ambiguous remark.

Discoveries grounded in Semantic Space Theory also provide preliminary evidence for a new approach to treating clinical fears—that of positive interventions (Pressman et al., 2019). This work is grounded in the assumption that the experience of positive emotions—such as amusement, love, awe, or excitement—are effective means of repairing and reducing fears. Consider awe. Recent work provides compelling evidence that brief experiences of awe are a central process by which several interventions—nature immersion, contemplation, and psychedelics—reduce maladaptive fear-related processes, including chronic stress, PTSD, and elevated stress-related peripheral physiology (Monroy and Keltner, 2022).

**MacLeod:** Undoubtedly, the development and maintenance of fear and anxiety reflects multiple mechanisms. Advancing understanding of how such mechanisms contribute to fear and anxiety requires adoption of 2 quite different, but ultimately complementary, research approaches. The first approach is reductionist in nature and involves the clear conceptual delineation of these different mechanisms, and the development of measures that can sensitively assess each as precisely as possible. In contrast, the second approach is guided by the goal of synthesis and involves developing and testing accounts of how these mechanisms operate together to shape the occurrence and expression of anxiety and fear. This latter approach is necessary to determine which mechanisms represent independent pathways to fear and anxiety, which mechanisms moderate the degree to which other mechanisms serve to drive fear and anxiety, and which mechanisms mediate the impact of other mechanisms on fear and anxiety. Within my own research

field—which is focused on the information-processing mechanisms that contribute to fear and anxiety—greatest emphasis to date has been placed upon the former of these two approaches. This has resulted not only in the successful delineation of distinct cognitive biases (e.g., of interpretation, appraisal, expectancy, and attention), each associated with fear and anxiety, but also to the differentiation of multiple subtypes of each bias. Thus, researchers investigating the attentional bias to negative information now draw a distinction between automatic and controlled facets of this attentional bias, and between biased attentional engagement with and biased attentional disengagement from negative information. Although such reductionism provides a firm foundation for synthesis, I think we have yet to see such synthesis come to fruition. All too few studies investigating the cognitive basis of vulnerability to fear and anxiety include measures of multiple cognitive processes, and fewer still are designed to test clearly articulated hypotheses concerning the independence or interdependence of different cognitive processes in the determination of such vulnerability. The time is now ripe for such integrative work (see my response to Question 5).

Although it is my conviction that our goal should be to understand the processes that underpin the development of anxiety disorders, it does not necessary follow from this that I believe the search for biological markers of such processes will be more fruitful that the search for biological markers of disorders. The identification of markers—biological or otherwise—will be of greatest value when the nature of the marker serves to advance understanding of the processes that underpin anxiety. It is quite possible that a biological marker of a process known to be associated with anxiety dysfunction could be identified, without this marker serving to illuminate understanding of how this process operates to produce or maintain dysfunctional anxiety. Conversely, it is possible that a biological marker of an anxiety disorder could be identified, the specific nature of which strongly suggests the operation of hitherto unknown process in the determination of this anxiety dysfunction. The latter instance of biological marker research would, in my view, have been more fruitful than the former. Likewise, I believe that enhanced understanding of the processes that underpin therapeutic improvement will be the key to improving therapeutic efficacy. Therefore, I do not consider the objective of better understanding past therapies to represent an alternative to the goal of finding more effective new therapies. Rather, both approaches should go hand-in-hand, such that the enhanced understanding of therapeutic processes resulting from the former type of research activity serves to shape the latter type of research activity by informing the development of new therapies that can harness these better understood therapeutic processes more effectively.

**Mobbs:** From a functionalist perspective, defensive states are merely survival strategies. They produce integrated internal states, including hormonal and autonomic states, subjective conscious feelings, and defensive behaviors that are computationally tractable. Given the complexity of defensive responses, the systems that support them can breakdown in many different ways (e.g., synaptic disconnection, hyper- or hypo-connectivity, misconnection). Further, and as I noted previously, one would expect that defensive responses are scalable and intercorrelated (e.g., fear follows anxiety and anxiety follows fear). This suggests that pathological affective disorders should, and indeed are, comorbid (e.g., 30–63% of anxiety disorder patients meet criteria for concurrent MDD) (Fava et al., 2000; Brown et al., 2001). Therefore, we need to consider the integrated nature of the defensive states when attempting to understand affective psychopathology.

Concerning the case for biomarkers, one should aim to measure both individual brain regions and distributed population codes in healthy individuals and across different defensive states. These neuronal populations will reflect the defensive state that the individual is in, reflecting the parallel and integrated defensive states, including conscious feelings of fear or anxiety, the autonomic state, and the preparation and executions of the defensive actions, and so on. In clinical populations, population codes will reflect a dimensional biological marker that will characterize the patients' maladaptive defensive states. One could also supplement categorical approaches, such as the DSM, by statistically segregating population codes by anatomy to create more specific markers that include autonomic disturbances, maladaptive behaviors or feelings. Yet, examining the entire population code should result in more accurate predictions as it is likely that affective disorders are not always due to specific regions going awry. Further, these biomarkers should be used in parallel approaches, including computational psychiatry, which will further help classify different affective disorders (Huys, Maia and Frank, 2016).

**Naragon-Gainey:** Although there are numerous causal factors, I view avoidance as the core proximal factor contributing to pathological fear and anxiety, wherein risk is greatest for psychopathology when avoidance is broad, context-insensitive, and/or associated with substantial impairment or distress (Arnaudova et al., 2017). Although avoidance of external stimuli (e.g., situations, objects, people) is common in pathological fear and anxiety, I argue that it is *experiential avoidance*—the negative evaluation of internal stimuli associated with fear or anxiety (e.g., feelings, thoughts, physical sensations) and attempts to avoid these internal events—that is most important for pathological anxiety and fear (Hayes et al., 1996). Perceiving fear and anxiety as unacceptable experiences contributes to difficulty tolerating uncertain or potentially negative outcomes (i.e., intolerance of uncertainty) and engaging in perseverative negative thinking (e.g., worry or rumination) to try to prevent such outcomes (McEvoy and Mahoney, 2013). Furthermore, negative evaluation of anxiety and fear likely promotes heightened allocation of attention to potentially threat-relevant information and negative interpretive biases, resulting in more intense and frequent perceptions of threat (Mathews and MacLeod, 2005). Efforts to get rid of feelings, sensations, or thoughts related to anxiety are also associated with avoidant coping and ineffective emotion regulation. Although all of these behaviors are ostensibly aimed at reducing anxiety and fear, ultimately, they tend to promote distress and overt avoidance (Barlow et al., 2014). As this feedback loop continues, avoidance may become generalized, habitual, and impairing, leading to clinically significant symptoms (Arnaudova et al., 2017). Although avoidance (broadly defined) appears to be a necessary proximal risk factor, high neuroticism is a key distal risk factor that promotes experiential avoidance, but it is not sufficient to cause pathological fear or anxiety (Barlow et al., 2014; Shackman et al., 2016).

With regard to biology and biomarkers, subjective experience and behavior has primacy over biology when it comes to understanding and treating psychopathology (Taschereau-Dumouchel et al., 2022). That is, if we could alter the physiological or neural responding that we believe underpins anxiety but there was no corresponding improvement in psychosocial functioning, distress, or quality of life, I do not think we've treated the 'cause' of pathological anxiety in any meaningful sense. Given that it does not appear that such biological processes map sufficiently clearly and uniformly onto subjective experience, I do not think that a primary or isolated focus on biological markers of psychopathology is likely to greatly advance clinical science. Nevertheless, I view data-driven, multi-method frameworks—such as RDoC and HiTOP—to be very promising in terms of understanding etiology and improving taxonomy. With regard to treatment, the focus should be on improving the efficacy and efficiency of existing treatments, particularly those that are transdiagnostic in nature, as there is a proliferation of closely-related treatments but inadequate understanding of the underlying mechanisms and their interactions with one another. In addition, there is a great need for better personalization of treatments based upon idiographic conceptualizations and individualized application of techniques (Barlow and Eustis, 2022).

**Question 4 Afterword.**

Anxiety and trauma disorders impose a tremendous burden on global public health. Collectively, they represent the 7th leading cause of morbidity worldwide, based on years lived with disability (YLD; IHME, 2023). This reflects the fact that anxiety disorders typically emerge early

in life and are often left untreated or ultimately prove treatment resistant (Craske et al., 2017; Olfson et al., 2019; Solmi et al., 2022). With these unfortunate observations in mind, we asked the discussants to consider what we currently know about the factors that promote and maintain pathological fear and anxiety and to highlight the most fruitful strategies for refining theory and developing new assays and more effective interventions. By and large, the discussants seemed to agree on 3 general conclusions:

1. **Go Beyond Traditional Diagnostic Categories.** There was consensus among the discussants about the need to go beyond traditional Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD) diagnostic categories. Billions of dollars of investment in psychiatric research has largely failed to uncover new assays or cures for pathological fear and anxiety (Shackman and Fox, 2018). Many of the discussants suggested that past underperformance reflects inherent limitations of traditional DSM/ICD categorical diagnoses (e.g., 'PTSD;' Bliss-Moreau, Buss, Clark, Fox, Naragon-Gainey). They emphasized the barriers that categorical diagnoses pose to discovering the nature and biological bases of pathological fear and anxiety, including rampant co-morbidity, low symptom specificity, marked within-diagnosis heterogeneity, and poor inter-rater reliability (Bryant et al., 2023; Hur et al., 2019; Kotov et al., 2022; Kotov et al., 2021; Tiego et al., 2023; Watson et al., 2022). Many discussants highlighted the value of dimensional alternatives to DSM/ICD—including the National Institute of Mental Health Research Domain Criteria (RDoC) and Hierarchical Taxonomy of Psychopathology (HiTOP)—and nearly all of them encouraged a greater emphasis on comparatively narrow behavioral, cognitive, and computational dimensional phenotypes that cut across traditional diagnoses, including attentional biases to threat ('hyper-vigilance'); deficient regulation of threat responses; difficulties recognizing safety; heightened avoidance of threat-related cues, contexts, and feelings; inflated estimates of threat likelihood or harm; and overgeneralization of perceived threat to safe cues and contexts (cf. Grupe and Nitschke, 2013). This 'symptoms-not-syndromes' approach has the added benefit of more naturally aligning with animal models, facilitating the development of coordinated cross-species models (Fried, 2015; Hur et al., 2019). Among the discussants, Fox, MacLeod, and Mobbs all emphasize the complex etiology of pathological fear and anxiety. As Mobbs notes, "Given the complexity of defensive responses, the systems that support them can break down in many different ways."
2. **Skepticism About Clinical Biomarkers.** We also asked the discussants to consider the significance and feasibility of developing biological markers ('biomarkers') of pathological fear and anxiety (FDA-NIH Biomarker Working Group, 2020). Buss and Mobbs appear somewhat indifferent. The remaining discussants were generally skeptical about the short-term prospects for developing conceptually informative or clinically useful biomarkers. Fox tells us that "current efforts to develop fear/anxiety biomarkers have a low chance of success, given the potential for many-to-one mappings between the brain and emotion…I am wary of biomarkers without a clear understanding of mechanism." MacLeod articulates a similar position, and also emphasizes the need for causal clarity. Naragon-Gainey expresses doubts about the feasibility of developing biomarkers that are sufficiently sensitive and specific to fearful and anxious feelings (but see Keltner-Cowen's and Kragel's responses to Question 3). Fox alone expresses guarded confidence in the long-term prospects for biomarker development, telling us that we will eventually "be able to identify biomarkers…that…reflect the underlying pathophysiology and be useful for guiding treatment. I just do not think that this will precede a refined understanding of the [underlying] biology."
3. **Old and New Treatments are Both Useful Scientific Targets.** With respect to the question of clarifying or refining existing treatments versus developing new ones, most of the discussants say that both strategies are potentially useful (Clark, Fox, and MacLeod). MacLeod and Fox, in particular, seem to view the two approaches as complementary paths to the same end. Fox reminds us that, in many cases, we still do not have a detailed understanding of why existing therapies (e.g., benzodiazepines) are clinically effective or why they are more helpful for some individuals than others. He and MacLeod seem to agree that, as MacLeod puts it, "enhanced understanding of the processes that underpin therapeutic improvement …[is] key to improving therapeutic efficacy." They suggest that the resulting knowledge can, in some cases, inform the development of novel treatments. Despite this enthusiasm, Fox cautions us against over-investing in existing treatments (e.g., SSRIs, extinction therapy), telling us that it is unlikely that further 'tweaks' or refinements will yield more than incremental improvements in safety, tolerability, or efficacy. For him, transformative change demands a more detailed understanding of the molecules, cells, and circuits that underlie the subjective experience of threat-related emotions. Like Fox, Clark seems to favor the development of new interventions that build on emerging mechanistic insights, whether biological or psychosocial. Among the discussants, Clark places the greatest emphasis on the development of new evidence-based strategies for preventing or slowing the onset of pathological fear and anxiety, telling us that "it is even more important to develop public-health-focused…prevention programs…Our field has a woeful lack of knowledge regarding how to…reduce the incidence of virtually all types of psychopathology, and there continues to be a dearth of research into prevention." Naragon-Gainey alone seems to favor the refinement of existing treatments, with a particular focus on improving modular cognitive-behavioral strategies (e.g., Unified Protocol) that can be used to efficiently treat a broad spectrum of anxiety, trauma, and mood disorders (Sauer-Zavala and Barlow, 2021). Although their positions on treatment research are quite different, Naragon-Gainey and Fox seem to agree on the importance of developing personalized or stratified treatment strategies that can accommodate marked heterogeneity in clinical presentation and, in all likelihood, etiology (cf. Kragel's response to Question 7).

**Question 5a**. ***Blinders, Barriers, and Local Minima. What are the most important limitations of contemporary approaches to studying fear and anxiety? For example, can we continue to rely on a limited repertoire of generic threats (e.g., shock) to understand the entire family of anxiety and trauma disorders or do we need to adopt precision approaches titrated to the individual or particular diagnoses?***

**Buss:** There are 3 main limitations to the science of fear and anxiety that affect my work specifically, and, I would argue, severely limit the conclusions we can draw from the literature as a whole:

a) Despite dramatic advances in quantitative methods over last 20 years, there are still limitations in our measurement of the complexity of the multifaceted nature of fear and anxiety. Although many of us have moved beyond ANOVAs and simple regressions, we are still often limited by small sample sizes and practical limits on the number of measures that can be included in a single study (e.g., one cannot measure every biomarker in every study).
b) There are important limitations to the generalizability of our knowledge. Consider the study of dispositional fearfulness or behavioral inhibition. Much of what I and others have contributed to the empirical literature likely only applies to a subset of individuals with anxiety. Some individuals with social anxiety disorder were not marked by a fearful temperament as children. Conversely, not all fearful children ultimately develop anxiety disorders.
c) The one key limitation that is perhaps most easily addressed is a lack of diversity in studies of early life emotion. We are still limited by majority *WEIRD* (Western, Educated, Industrialized, Rich, and

Democratic) samples in the field. The paucity of studies examining BIPOC (Black, Indigenous, and People of Color) individuals is noteworthy and severely limits what we know and who stands to benefit from that knowledge.

**Clark:** A major limitation of research on fear and anxiety to date is its limited generalizability to so-called *WEIRD* countries and cultures, including limited generalizability to subcultural differences within North America and Europe. Compared to what we know about college sophomores (who are, further, mostly young women), we know little about fear and anxiety in people of color who regularly experience racial bias; in individuals with low incomes for whom threats to well-being (e.g., food insecurity, substandard housing, health-care disparities) are a daily concern; in immigrants seeking a better standard of living only to find that they are less-than-welcome in their new environments; in refugees fleeing persistent violence who are herded into camps with squalid conditions; and in individuals living in oppressive, totalitarian states. It is unlikely that a fuller understanding of fear and anxiety in these and other un- or understudied populations will develop from using the same kinds of research designs, methods, and measures that are the norm in studies of American college students, so in addition to increasing the diversity and inclusivity of our research samples, our research designs, methods, and measures also will need to become more ecologically valid and more appropriate for use in diverse cultures and environments.

**Fox:** In my earlier responses, I outlined why current fear/anxiety terminology is inadequate, and why translational and reverse translational research will be necessary to develop an adequately complete understanding of fear and anxiety. Here, I will focus on how we can do better.

First, I would like to draw readers' attention to the many neuroimaging studies of threat, fear, and anxiety that do not elicit (or, in some cases, do not even bother to measure) signs or symptoms of distress. For example, it is unclear how a person's response to a fearful or angry facial expression is going to uncover the mechanisms that underlie the experience of anxiety in the real world. This is becoming increasingly clear as some large-scale fMRI studies have failed to find a relationship between the neural responses to these stimuli and clinical disorders (Grogans et al., 2022; Tamm et al., 2022). Although these studies have their place, and can provide useful insights about the perception of socioemotional cues, these approaches dominate the field because of their logistical ease, not because of their relevance to fear and anxiety. I believe that there is much work to be done in decomposing the 'feature space' of potential threats (cf. Holley & Fox, 2022). That is, we need to invest more effort in identifying the precise factors that compete to control the expression and experience of fear and anxiety.

I encourage fear and anxiety researchers to set aside popular 'workhorse' paradigms and instead strive to manipulate a more diverse array of threatening stimuli and situations. These concerns extend to the context in which threat is encountered. For example, the predictability or possibility to escape, and/or the presence of other individuals (which can alter the experience of threat) (Tedeschi et al., 2021). I believe Mobbs and colleagues' efforts to incorporate insights from ecology and computational modeling provides an exemplary illustration (Mobbs et al., 2018, 2020; Silston et al., 2021). The ideal scenario for future research will require a varied approach, as different threats may not be processed by the same neural systems (see my response to Question 3).

It may be especially fruitful to focus on threat anticipation and perceived threat, rather than the response to the threat itself. If you unexpectedly die in your sleep, you would not experience any fear. If instead, you were told that you might die tomorrow, you would have a dramatically different experience. In short, if you do not perceive a threat, you are unlikely to experience fear or anxiety. In fact, many of the things that cause us to feel fearful or anxious are not present in the immediate environment; they are thoughts and worries about what could be. Literature (e.g. *Dracula*) and film (e.g. *Jaws, Godzilla [1956], Alien*) routinely take advantage of the power of suspense on the anxious imagination. Because of the relevance to anxiety-related psychopathology, which is often characterized by excessive worries and inflated perceptions of threat, an increased focus on anticipated and imagined threats is likely to have particular impact on our understanding of emotional illness (Grupe and Nitschke, 2013).

The development of computational models has the power to provide a precise nomenclature (or *lingua franca*) for conceptually integrating the results of diverse paradigms, in humans and across species (cf. Mobbs' responses to Question 2 and Question 5). Computational models offer interpretations of the underlying processes that can extend beyond specific task implementations and experimental contexts. The ideal computational model represents the statistics of the environment, and can be generalized to other experimental stimuli, contexts, and species (see my response to Question 5b).

Finally, I think one of the biggest unknowns in the study of fear and anxiety is why females are more likely to be diagnosed with internalizing disorders than males. These differences are likely to reflect sociocultural influences, life experience, sex-hormone induced changes, as well as sex differences in brain organization at the molecular, cellular, and systems levels. Yet, because there has been a historical bias toward the study of males, most of our understanding is in the context of the male brain. This needs to be rectified.

**Keltner & Cowen:** A key limitation is conceptual, in that the field often seeks to lump a rich variety of behavioral and neurophysiological processes under the monolithic state of 'fear' and the corresponding mood or trait of 'anxiety.' Our work suggests the space of fear is much richer and involves at least 4 distinct kinds of fear: the fear of physical, existential, epistemological, and social threats. To complicate these efforts further, our work has uncovered important variation in each kind of fear, consistent with early claims about within-category heterogeneity (Ekman, 1992; Scherer, 1987). For example, work in social psychology suggests that the fear of separation is likely to vary according to whether that fear is elicited by a lack of connection with attachment figures, by threats to social status, or by social exclusion. Mechanistic work in animals suggests a corresponding complexity of neural circuits (see our response to Question 2).

Developing a deeper understanding of the 4 fears will require more specific elicitors and more precise measures of subjective and behavioral expressions of fear. Relevant stimuli and measures are detailed in Supplementary Note 1.2.

Finally, the field needs to move to new kinds of statistics (e.g., split-half canonical correlation analysis), that allow for the latent dimensions of rich bodies of data to emerge and that can help overcome the field's historical fixation on low-dimensional models of emotion (Cowen and Keltner, 2020; Cowen, Laukka et al., 2019; Cowen and Keltner, 2020a; Demszky et al., 2020; Jolly and Chang, 2019).

**Kragel:** Perhaps the most pressing issue is theoretical. There is little consensus regarding the nature of constructs such as affect, arousal, fear, anxiety, or the relationships between them. Many theories of affective phenomena are rooted in common sense or folk psychology (e.g., notions that emotions are fundamentally 'good' or 'bad' regardless of context or that some construct is inherently more basic than another). Because influential theoretical traditions largely predate methods for probing human brain function, they do not make specific predictions about neural mechanisms. This leads to a focus on issues that cannot easily be resolved through scientific observation. Efforts to develop theories that make explicit predictions about brain function and ontologies that align with biology will be critical for resolving this issue (see also the responses from Bliss-Moreau, Fox, and Mobbs).

A major limitation in understanding fear and anxiety is our limited ability to measure the function of neural ensembles and circuits non-invasively in humans, most notably in cortical-subcortical pathways. Research in animal models clearly shows that projections from deep layers of the prefrontal cortex to the PAG are involved in regulating pain and defensive behavior (Adhikari et al., 2015; Huang et al., 2019).

Different layers of the superior colliculus have different connectivity profiles and play different roles in organizing defensive behavior (Evans et al., 2018). In fact, every subcortical structure implicated in threat processing and defensive behavior has internal structure at fine spatial scales, including subdivisions and neuronal microcircuits in the amygdala nuclei, bed nucleus of the stria terminalis, nucleus accumbens, hypothalamus, and PAG (e.g., Fox and Shackman, 2019). Although developments in ultra-high field MRI hardware, pulse sequences, and analytical approaches are steadily improving anatomical resolution (Chai et al., 2020; Petridou and Siero, 2019; Uğurbil, 2021; Yang et al., 2021), the toolset available to students of the human brain is lacking. Further, even with improved signal quality, fMRI is fundamentally limited in the classes of behaviors it can study as participants are required to lie motionless (see Mobbs' response). If our understanding of emotion is going to improve, e.g., to test theories that make claims about predictive coding (Barrett and Simmons, 2015) and dynamic behavior (e.g., such as active avoidance in complex environments; see Mobbs' response), continued advances in measurement techniques are sorely needed.

A related problem is a reliance on a handful of tightly controlled experimental paradigms that typically manipulate a single construct in a single way that does not capture the complexity of more naturalistic situations (cf. Fox, Mobbs, and Naragon-Gainey's responses). Consider common paradigms that involve fear conditioning, the perception of aversive naturalistic images, and the evaluation of prototypical emotional expressions on the face. These manipulations have become popular because they produce robust activation in the amygdala and connected circuits (but see Fullana et al., 2016; Visser et al., 2021). The overlap in amygdala activity across different tasks has often been interpreted in broad terms, invoking constructs such as arousal, activation, or motivational salience (discussed in Lindquist et al., 2012). This inference assumes that amygdala activation reflects the same neuronal population across paradigms and studies. Given the complex internal structure of the amygdala and other subcortical nuclei, and anatomical variability across individuals, a strong version of this assumption seems implausible, especially when clusters of activation are reduced to peak coordinates, as is typical in meta-analyses of the neuroimaging literature. In short, we need better alignment between theory and methods, and to remain mindful that methodological choices substantially limit our ability to evaluate theories on a level playing field. If one theory predicts that fear is mediated by large-scale networks and another focuses on specific circuits or neural ensembles, they should not be evaluated using a single method unless it is sensitive to brain function on both spatial scales. Furthermore, if theories encompass diverse classes of threats or situations that produce the experience of fear or anxiety, then they should be investigated in similarly diverse conditions, rather than narrowly focusing on the subset of paradigms that most robustly activate a specific brain measure or behavior.

**MacLeod:** Naturally, the most important methodological limitations of contemporary approaches to the study of fear and anxiety will not be equivalent across different research domains. Within my own area, which concerns how individual differences in the selective processing of emotional information contribute to elevated anxiety vulnerability and dysfunction, one of the most significant limitations has certainly been the impoverished nature of the information commonly used as stimulus materials in our studies. Not uncommonly, processing biases have been assessed using single word stimuli. For example, anxiety-linked attentional bias to negative information has been assessed by measuring the degree to which participants preferentially attend to a single negative word (e.g., 'failure') in comparison to a single paired benign word (e.g., 'picture'). In addition to their low informational content, the relevance of such stimuli to participants' current circumstances is likely to be low. Though studies now often use images instead of words, such as faces that show angry and happy expressions, or negative and benign pictures from the International Affective Picture System (IAPS), the informational content of such stimuli remains impoverished, and their personal relevance is extremely limited. A static image of an unknown individual, expressing anger for an unknown reason, conveys little information of direct relevance to participants' current personal circumstances. Hence, I believe that within the domain of cognitive bias research there is scope to greatly enhance both the ecological validity of our studies, and the real-world relevance of the resulting findings, by markedly increasing the informational richness and personal relevance of the stimulus information we employ. For details on our work in this vein, see Supplementary Note 5a.1.

**Mobbs:** Traditional human fear conditioning approaches are limited insofar as they provide little-to-no behavioral data and examine changes over longer periods of time that may not reflect how we interact with real-world dangers. Still, they provide a reliable way to understand threat learning and extinction and provide a platform for cross-species translational work. Aversive images, provide a good tool to measure attention to danger, but again typically lack meaningful behavioral readouts. Creative variants of these approaches have been developed by Joey Dunsmoor, Sonia Bishop, Dominik Bach, and others, but I think the time is ripe to move to paradigms that capitalize on recent advances in virtual reality and gaming. For example, human computational ethology (Mobbs et al., 2021) proposes that we create virtual ecologies that mimic real-world environments. These virtual ecologies can encompass a conditioned threat (CS+) that has the ability to chase, capture, and shock a subject's avatar (e.g., Mobbs et al., 2007). Instead of a static CS+, we can create a stimulus that is dynamic, more closely reflecting how one would interact with a threat in the real world. Such a study produces 2 new data dimensions – spatiotemporal data and movement data that can be used to correlate with other variables, including neural data. This allows one to investigate how the proximity of the threat results in changes in behavior and how threat propagates across different neural population codes.

When we think about the defensive states, we must first have knowledge of the ecological conditions that give rise to them (Mobbs, 2018). Once we understand these conditions, we can ask how the organism (including humans) adaptively responds to the ecology's survival obstacles. This allows us to define ways of measuring contextually appropriate adaptive behaviors and build experiments and computational models characterizing both neural and behavioral responses (Mobbs et al., 2021). Therefore, I believe that when designing an experiment, researchers need to follow a simple heuristic:

*Identify and mirror the natural conditions →*
*Maximize the measurement of defensive behaviors →*
*Determine latent computations →*
*Measure biological responses, including neural populations.*

Studies from my group have shown that as threat moves from distal to proximal, there is a shift in activity from the prefrontal cortex to the midbrain (Mobbs et al., 2007). Later work linked these same switches to fast and slow escape decisions (Qi et al., 2018). Together, these observations provide empirical support for theoretical models focused on defensive distance (McNaughton and Corr, 2004) and threat imminence (Fanselow and Lester, 1988).

Researchers should be encouraged to develop paradigms that maximize:

a) Ecological validity
b) Meaningful behavioral output
c) The opportunity to record whole-brain neural activity
d) Opportunities for meaningful switches in defensive states
e) Opportunities for coordinated cross-species research.

**Naragon-Gainey:** There are some important limitations to popular approaches for assessing and studying subjective fear and anxiety. Trait questionnaires demonstrate strong measurement properties (e.g., retest reliability) and nicely capture broad individual differences, but they typically neglect variation in context, antecedents, and consequents. Self-report measures are also subject to important cognitive and

response biases (Shiffman et al., 2008; Walz et al., 2014). Ratings of fear and anxiety, made in the laboratory, in response to controlled manipulations of fear and anxiety (e.g., threat-of-shock), address many of these concerns, but have questionable generalizability to real-world emotional experience (Walz et al., 2014). Furthermore, neither approach is able to capture brief fluctuations and longer-term trends in emotional experience over an extended duration (e.g., days, weeks or months), limiting knowledge about temporal dynamics, consistency, and clinically relevant patterns.

A second barrier—which lies at the intersection of method and theory—is the tendency to narrowly focus our research on specific fear/anxiety symptoms (e.g., panic) or diagnoses (e.g., PTSD). This is problematic given extensive comorbidity and shared etiology across emotional disorders. A study narrowly focused on GAD, for example, cannot address the degree to which the results are specific to individuals diagnosed with GAD or are broadly relevant to individuals with other, often co-morbid emotional disorders (e.g., MDD). Just as affect has a hierarchical structure, psychopathology is also dimensional and hierarchical. Thus, transdiagnostic approaches are crucial for determining the specificity (or generality) of findings (Kotov et al., 2017; Conway et al., 2019). This is not a semantic or philosophical issue; it has important practical implications for treatment development and clinical implementation. From this perspective, it encouraging to see a growing number of transdiagnostic treatments (Schaeuffele et al., 2021).

**Question 5b**. ***Gaps and Opportunities. What are the most significant conceptual or practical gaps in our current understanding of fear and anxiety? Do new or emerging tools create opportunities to address these gaps?***

**Bliss-Moreau.** The barriers to progress, gaps in our understanding, and opportunities for scientific discovery relative to fear and anxiety are all integrally related and related to the issue the field needs a new theory of emotion that is culturally inclusive (and not Western ethnocentric) and accounts for the significant variation in emotion's biology and psychological experience. Emotion science, including the study of emotion-related psychopathology and neuropathology that affects emotion-related functions, has been using the wrong model of emotion for decades—a model that assumes that emotions are discrete, bounded, context-insensitive categories with discrete biological mechanisms and discrete behavioral/functional outputs (as in Anderson and Adolphs, 2014; Ekman and Cordaro, 2011; Keltner et al., 2019). This Western-ethnocentric model of emotion leads to searching for the biological underpinnings of Western concepts of emotion and pathology (which are not culturally universal) and in the context of pathology, trying to explain the biology of symptoms that people find problematic. An alternative approach is to start with understanding the biological systems (for starters, the domain-general survival systems highlighted in my earlier responses) and how variation in their function within and across individuals and within and across contexts leads to variation in behavior and experience, including variation deemed 'pathological' by clinicians. This is, in essence, how constructivist approaches to emotion, and to psychopathology, flip the script in terms of the phenomena of study and will hopefully hasten discovery (Shaffer et al., 2022).

**Clark:** As I noted earlier, the most significant conceptual and practical gaps are in our limited ability to generalize current knowledge, which is based on a relatively thin slice of humanity, to the broader human population. Another concern, of more limited scope but fundamentally important, has surfaced recently; specifically, "existing assessment approaches [to attentional bias]… do not exhibit the internal consistency or test-retest reliability necessary to classify individuals in terms of their characteristic pattern of attentional responding to threat. [That is, existing measures can characterize groups as having] "average, elevated attention to threat," [but cannot] "classify individuals in terms of their characteristic pattern of attentional responding to threat" (MacLeod, Grafton, and Notebaert, 2019, p. 529). This problem needs to be addressed and solved before any other further research on attentional bias is conducted.

The extent to which similar issues plague other laboratory-based measures of fear and/or anxiety is unknown, but it will be critical to determine this and, as with the measurement of attentional bias, to take all necessary action needed to develop reliable methods, without which further understanding is not possible. All science ultimately depends on reliable and valid measurement but, unfortunately, this axiom is routinely ignored in psychology and biomedicine, a grave mistake that we cannot allow to continue if we aspire to become a mature science.

**Fox:** We have a reasonable idea of what brain regions might contribute to the experience of fear and anxiety. Yet we have almost no idea what computations are being performed in these regions or how they interact. Scientists are beginning to uncover distinct cell-types within fear- and anxiety-relevant regions. Researchers who work with rodent models are undertaking mechanistic manipulations that can uncover the contribution of specific cell-types to the expression of defensive behavior (See Supplementary Note 3.1). Although a great deal of progress is being made in this area, there is an increasingly large gap between our understanding of rodent freezing and human anxiety. To close this gap, researchers need to test hypotheses derived from rodent models in humans. There are a few approaches that currently stand out as particularly relevant for the translation of these findings to humans, including pharmacological manipulations, multi-voxel pattern analysis (MVPA), computational modeling, and genetic studies (for details, see Supplementary Note 5b.1).

**Keltner & Cowen:** Alongside the need for a richer conceptual approach to fear and anxiety, another key gap is the need to chart nuanced behavioral indicators of fear and anxiety. Work animated by Semantic Space Theory demonstrates that the 4 fears are signaled in distinct patterns of facial, body, vocal behavior, and language (Cowen and Keltner, 2021; Keltner et al., in press).

Of the 4 traditional approaches to measuring fear and other emotions—self-report, physiological measures, task-based measures, and behavioral indicators—only behavioral indicators are non-intrusive. Behavioral indicators have inherent ecological validity and have the potential to reveal the dynamics of the actual instances of emotion that underpin healthy and pathological functioning. However, their potential is largely untapped in science because measures of meaningful real-world behavior—language, facial expression, speech prosody, vocal bursts—have been lacking, reflecting the laborious nature of traditional manual scoring techniques and the artificial limitations imposed by popular neuroimaging techniques.

Recent advances in machine learning have the potential to allow for accurate and nuanced measurement of emotion-related behaviors at scale, enabling new advances in the science of fear and anxiety. Grounded in Semantic Space Theory, we have developed machine-learning methods to identify nearly 30 distinct emotions in the face, vocal bursts, speech prosody, and language, including signals associated with the 4 fears (Baird, Tzirakis, Brooks et al., 2022; Baird, Tzirakis, Gidel et al., 2022; Brooks et al., in press; Christ et al., 2022; Cowen et al., 2021; Demszky et al., 2020; Sun et al., 2020). This approach opens the door to studying the 4 fears and other emotions objectively, as they naturally exist in the lab, clinic, and everyday life at millisecond resolution. This approach may be particularly useful for studying developmental and neurological populations. Cross-cultural studies can bypass population differences in emotional language and emotion concepts, and directly measure the behavioral expression of emotion.

**Mobbs:** I think 4 main innovations are needed. *Innovations in experimental design.* We need to build on classic Pavlovian fear paradigms through innovations in experimental design and the use of new technology. This can be accomplished by embracing virtual reality and human computational ethology. *Innovations in neural measurement and manipulation.* We can leverage advances in multiple cell recordings in humans to investigate how populations of neurons integrate information. New technologies (e.g., focused ultrasound) may provide non-invasive approaches to causal manipulation of neural circuits in

humans. *Innovations in statistical inference.* The use of machine learning has not only been critical to the evolution of artificial intelligence, but also in the measurement of behavior (computational ethology) and ways to parse neural data. This approach also allows us to examine high-dimensional population codes and their geometry. Therefore, the increased use of machine learning will provide new ways to study the nature and brain bases of defensive states. *Theoretical innovations.* We need to continue to develop theories of emotion and find better ways to test them. Recent examples include Barrett's constructivist theory (Barrett, 2017) and LeDoux and Pine's two-systems theory (LeDoux and Pine, 2016); both encourage us to look differently at the functional and biological basis of defensive states.

**Naragon-Gainey:** At present, we know far too little about the factors that govern the momentary dynamics of fear and anxiety in the real world. Smartphone digital phenotyping, actigraphy, and other 'wearable' technologies are poised to address this gap. Multi-method assessments can be obtained by integrating real-time reports of subjective emotional experience with objective measures of physiology (e.g., heart rate variability, electrodermal activity), behavior (e.g., actigraphy, texting, internet use), and environmental information (e.g., ambient light/sound, geolocation) (Carpenter et al., 2016). This approach can also be applied to treatment contexts: for example, just-in-time interventions can nudge patients to deploy skills cultivated in therapy in moments of need (Nahum-Shani et al., 2018).

A key advantage of intensive longitudinal designs is the focus on within-person processes, meaning how variables vary and co-vary over time for a given individual. Not only does within-person assessment provide important idiographic information about the nature of an individual's unique risk and resilience factors, but it is aligned with the broad aim of psychological intervention: to alter *a specific person's trajectory,* relative to their own current baseline (Barlow and Eustis, 2022). Despite treatment being an inherently within-person process, the vast majority of our knowledge of processes associated with anxiety and fear (and many other psychological constructs) comes from between-person analyses focused on between-person differences (Fisher et al., 2018). There is often an implicit assumption that such findings provide insight into the mechanisms operating within individuals. Yet there is a growing appreciation that this assumption is generally not founded (Fisher et al., 2018; Molenaar, 2004). In short, a greater emphasis on intensive within-person designs is likely to have substantial benefits for our understanding of the person-specific factors that promote, maintain, and reduce fear and anxiety (Barlow and Eustis, 2022).

**Question 5 Afterword.**

> *"Scientific progress is incremental in nature…Time, effort, and funding are most likely to be squandered when scientists fail to determine adequately the best next step to take."*
>
> —Colin MacLeod, response to Question 7.

The past half-century has witnessed remarkable advances in our ability to manipulate and measure fear and anxiety in the laboratory, clinic, and field; and a concerted effort to develop more sophisticated conceptual models that can better accommodate these new observations. The responses to Questions 1–3 reflect these important advances. Yet it is clear that our understanding remains far from complete. In Questions 5a and 5b, we asked the discussants to identify the most significant limitations of contemporary approaches to the scientific study of threat-related emotions, and to provide their recommendations for addressing these gaps and challenges, with a special focus on new and emerging tools.

1. **Beyond Fear: *Embrace the Complexity of Threat-Elicited Emotion.*** In response to Question 1, there was a strong consensus among the discussants that there are multiple threat-elicited states—*not* just fear—and many noted that these states can be influenced in important ways by experience, learning, context, and culture. They emphasized that the context in which a threat is encountered can transform emotional experience (e.g., fear vs. anxiety), behavior (e.g., freezing vs. flight vs. defensive attack), and the balance of neural circuits engaged. Here, the discussants indicate that empirical studies of fear and anxiety have simply not kept pace with the growing complexity and precision of theory (Keltner-Cowen, Kragel, Fox, Naragon-Gainey, MacLeod, and Mobbs). Instead they remind us that the field has continued to rely on comparatively simple paradigms, stimuli, assays, and assessments. As Kragel puts it, "[a] key problem is the field's heavy reliance on a handful of tightly controlled experimental paradigms that typically manipulate a single construct in a single way [and do]…not capture the complexity of more naturalistic situations." MacLeod and Fox stake out overlapping positions, emphasizing the limited utility of static photographs of 'threat-related' emotional facial expressions for probing fear and anxiety. As Fox notes, "although these studies have their place…[they] dominate the field because of their logistical ease, not because of their relevance" or validity. Naragon-Gainey focuses her critique on the neglect of "variation in context, antecedents, and consequents" in popular self-report measures.

   The discussants emphasized that the time is ripe to rectify this mismatch between theoretical complexity and experimental simplicity. Kragel, for instance, tells us that "if [our] theories encompass diverse classes of threats…then they should be investigated in similarly diverse conditions." Fox underscores the importance of context, including manipulations focused on the prospects of evading or escaping threat and the presence or absence of allies. MacLeod and Mobbs highlight the value of adopting more personally relevant and immersive paradigms, such as virtual reality, video game-type tasks, and semi-structured social-evaluative stressors (e.g., public speaking, mock interviews).
2. **Beyond Narrative Models: *Embrace Computational Modeling of Brain and Behavior***. Drawing on ethological studies of fear and anxiety, Mobbs offers what is perhaps the most comprehensive recommendation for embracing the complexity of threat-elicited emotion in the laboratory. He tells us that,

   > *"Once we understand…[the] conditions [that elicit defense states], we can ask how the organism…adaptively responds to the ecology's survival obstacles. This allows us to define ways of measuring contextually appropriate adaptive behaviors and build experiments and computational models…[In sum] when designing an experiment, researchers need to follow a simple heuristic: Identify and mirror the natural conditions → Maximize the measurement of defensive behaviors → Determine latent computations → Measure biological responses."*

   Fox echoes Mobbs' call for focusing on computational models, suggesting that while we have made important strides in identifying the brain regions most relevant to fear and anxiety, "we have almost no idea what computations are being performed in these regions" (cf. Supplementary Note 5b.1). He tells us that formal computational models can "provide a precise nomenclature (or *lingua franca)* for conceptually integrating the results of diverse paradigms, in humans and across species." Or, as Mobbs notes elsewhere, "computational ethological approaches to human neuroscience are critical in reducing the behavioral [and biological] gap between animal and human research" (Question 2).
3. **Beyond the Laboratory: *Embrace the Complexity of Threat-Elicited Emotion in the Real World***. Clark, Keltner-Cowen, and Naragon-Gainey stress the importance of studying fear and anxiety in the real world, outside the artificial confines of the laboratory (e.g., Anderson et al., 2018; Tashjian et al., 2020). The emergence of commercial software for automated analyses of facial expressions, the development of mobile eye-trackers, and the widespread dissemination of smartphones, fitness trackers, and other kinds of

'wearable' technology afford unprecedented opportunities for objectively, efficiently, and unobtrusively quantifying context, emotion, and motivated behavior in vivo. Keltner-Cowen and Naragon-Gainey tell us that these digital tools have the potential to provide valuable new clues about the temporal dynamics of fear, anxiety, and other emotions in daily life (e.g., spillover of mood across sequential contexts and assessments) and the social factors and coping behaviors that help govern and regulate them. Because they make it increasingly easily to track momentary fluctuations in activity (e.g., actigraphy, food intake, sleep) and context—including annotated geolocation data, digital photographs, and audio recordings—they also provide as-yet under-explored opportunities for understanding the intra- and inter-individual factors that trigger, maintain, and dampen fear and anxiety in the real world, and an opportunity to identify potentially modifiable targets for treatment development. Clark and Keltner-Cowen remind us that these new kinds of behavioral assays can also facilitate the comparison of diverse cultures and demographic groups.

4. **Beyond the Voxel: *Embrace Cross-Species Research*.** Here and in their responses to Question 2, Fox, Kragel, and Mobbs emphasize the importance of going beyond *The Voxel*. Fox reminds us that "[t]he tools commonly available for studying the human brain are largely constrained to studying aggregate brain responses across hundreds of thousands of neurons" (cf. Logothetis, 2008). Kragel makes a related point, telling us that "…every subcortical structure implicated in threat processing and defensive behavior has internal structure at fine spatial scales, including subdivisions and neuronal microcircuits." They and Mobbs agree that that the coarse resolution afforded by conventional whole-brain human neuroimaging techniques, while valuable, is not sufficient to decipher the molecular and cellular complexity of the neural systems underlying threat-related emotions. All of them emphasize the the importance of coordinated cross-species research for bridging this gap. In addition, Kragel recommends increased investment in neuroimaging techniques with improved anatomical resolution. Fox underscores the need for "an open dialogue between clinicians and basic scientists working with different species" and highlights the utility of several other specific approaches, including acute pharmacological challenges, multi-voxel pattern analyses, and molecular genetics (Supplementary Note 5b.1).
5. **Beyond ANOVA: *Embrace Data-Driven Frameworks for Making Sense of Complex Data*.** Buss, Fox, Keltner & Cowen, and Mobbs encourage the adoption of more sophisticated statistical and computational tools. Buss stresses the need for Big Data, telling us that, "[w]hile many of us have moved beyond ANOVAs and simple regressions, we are still often limited by small sample sizes and practical limits on the number of measures that can be included in a single study." Fox, Keltner-Cowen, and Mobbs highlight the utility of machine learning and related data-driven computational approaches (see also Kragel's response to Question 3; Yarkoni and Westfall, 2017). Keltner and Cowen argue that such approaches are critical for "overcome[ing] the field's historical fixation on low-dimensional models of emotion" (e.g., Ekman's Big 6).
6. **Beyond Case-Control Studies: *Embrace the Complex Structure of Pathological Fear and Anxiety*.** Building on the discussants' critique of DSM/ICD diagnoses in Question 4, Naragon-Gainey underscores the utility of going beyond case-control studies and more fully embracing the hierarchical-dimensional structure of fear and anxiety symptoms in clinical research (Conway et al., 2019; Kotov et al., 2021, 2022; Forbes et al., 2023). As one example, she reminds us that "a study narrowly focused on GAD, for example, cannot address the degree to which the results are specific to individuals diagnosed with GAD or are broadly relevant to individuals with other, often co-morbid emotional disorders (e.g., MDD)." Naragon-Gainey stresses that "this is not a semantic or philosophical issue; it has important practical implications" for the development and dissemination of more efficient and scalable interventions for pathological fear and anxiety.
7. **Beyond 'Measurement Schmeasurement': *Embrace the Empirical Structure of Pathological Fear and Anxiety*.** Clark encourages us to let go of what all-too-often amounts to a laissez faire attitude toward measurement (*'measurement schmeasurement'*), emphasizing the importance of developing and deploying psychometrically sound measures of fear- and anxiety-related experience, behavior, and biology (Flake and Fried, 2020; Fox et al., 2018). She cautions that the reliability of most laboratory-based measures—from response-time measures and computational modeling parameters to eye-tracking and fMRI metrics—remains under-explored and poorly understood (cf. Elliott et al., 2021; Kragel et al., 2021; Spisak et al., 2023). Clark ends with a sober reminder: "All science ultimately depends on reliable and valid measurement but, unfortunately, this axiom is routinely ignored in psychology and biomedicine, a grave mistake that we cannot allow to continue if we aspire to become a mature science."
8. **Beyond WEIRD Science: *Embrace Diversity to Ensure Generalizability and Equity*.** Fear- and anxiety-related states, traits, and disorders vary in potentially important ways across genders, demographic groups, and cultures (cf. Bliss-Moreau's response to Question 1). Yet scientists often make fundamental claims about the nature of emotion on the basis of data drawn from a narrow slice of this diversity. The vast majority of human studies rely on individuals drawn from WEIRD societies—who represent perhaps as much as 80% of the participants in biopsychosocial research, but only ~12% of the world's population (Henrich, Heine, and Norenzayan, 2010). Likewise, until very recently, biomedical research in animals relied almost exclusively on male rats and mice (Institute of Medicine, 2001). Whether the fruits of this work translate to 'everyone else' remains unclear. There was a resounding chorus of consensus among our discussants regarding the need for samples that better mirror the diversity of our society, subcultures within our societies, and the human species as a whole (Bliss-Moreau, Buss, Clark, and Fox). As Clark notes, "the most significant conceptual and practical gaps [in the scientific study of fear and anxiety] are in our limited ability to generalize current knowledge, which is based on a relatively thin slice of humanity." She reminds that, when "[c]ompared to what we know about college sophomores (who are, further, mostly young women), we know little about fear and anxiety in people of color…; in individuals with low incomes for whom threats to well-being…are a daily concern;…and in individuals living in oppressive, totalitarian states." In short, an increased focus on diversity and inclusion is essential to avoid perpetuating existing scientific and health inequities, and to ensure that the fruits of fear and anxiety research—including clinical research (Forbes et al., 2023)—benefit everyone equally.

**Question 6.** ***Resources and Infrastructure: What kinds of funding mechanisms, incentives, focused meetings, or grassroots efforts (e.g., formal or informal consortia) would have the greatest positive impact on our ability to explain, predict, and treat fear and anxiety?***

**Buss:** I believe the answer lies in bringing researchers and clinicians together. While funding is important, what drives innovation and transformative research are the scholars that push their work through interdisciplinary lenses and address research questions that have translational implications. I have been fortunate in my career to engage in collaboration and discussion with a wide-range of scholars. Even exposure to other sub-disciplines of psychology is valuable for pushing our science forward. Exposure to emotion scholars from a wide range of theoretical and methodological expertise, has shaped my thinking and challenged me to think in new and creative ways.

**Clark:** First, targeted funding for the development of reliable and valid measures must be a top priority. Study groups that review grant

applications should be directed to require sound documentation of the internal consistency reliability of all measures and evidence that their level of temporal stability is consistent with their conceptualization (i.e., that 'trait-like' measures are sufficiently stable across time, whereas measures of momentary states show changes commensurate with the expectations for interventions and changing conditions). Tests of the reliability and validity of measures should be conducted in a multiplicity of populations, including diverse cultures and subcultures, a wide range of socioeconomic statuses, and so on, as I noted earlier. This will require the development of cross-cultural (or subcultural) collaborations and measure development in multiple languages, including ensuring equivalence across translated measures. Second, assuming an improved measurement landscape, current knowledge that is based on research with relatively homogeneous samples should be tested in a diversity of samples to examine the generalizability of findings. This may go hand-in-hand with measure development with the same (or same type of) cross-cultural collaborations mentioned above to ensure the broad applicability of research paradigms. Third, (but of equal importance with the second) is the need to deepen our understanding of prevention. It is extremely telling that Question 6 does not include the term *prevent*, but jumps directly from *predict* to *treat*, whereas *prevent* routinely should be placed between those terms. It is ultimately better—and potentially easier—to prevent psychopathology from developing in the first place—or at least to inhibit its development—than to treat it after it has gotten to the point that individuals' suffering leads them to seek treatment. Finally, increased funding should be targeted to developing evidence-based ways to decrease the stigma of mental health problems, which is an important factor that inhibits individuals from seeking help for their psychological suffering.

**Fox:** Understanding the neurobiology of fear and anxiety mandates coordinated cross-species research. I would encourage funders to develop targeted mechanisms to incentivize and facilitate such research, and to equip the next generation of scientists with the knowledge, skills, and experience necessary to lead multidisciplinary, multi-species projects.

Work in other brain-related disorders (e.g., Parkinson's) suggests that focused efforts aimed at breaking down the traditional barriers ('silos') between scientific disciplines and approaches could really move the needle. Over the past decade, advances in the tools and approaches available for use in mice have revolutionized our understanding of the brain circuits underlying freezing, flight, and other defensive responses to threat. Yet the relevance of these tantalizing discoveries to human fear and anxiety remains little explored and largely unknown. Conversely, the majority of mouse studies continue to focus on a small subset of threat-relevant paradigms (e.g., Pavlovian conditioned threat, elevated-plus maze) of questionable relevance to human anxiety and trauma disorders. In part, this state of affairs simply reflects the lack of engagement across scientific silos, including journals, grant review panels, conferences, societies, and even graduate training. An investigator focused on understanding the neural underpinnings of threat-elicited freezing in the mouse, for example, could have a long and successful career, while remaining blissfully ignorant of current trends in psychiatric nosology and human neuroimaging. Topic-focused research centers, consortia, and conferences provide a powerful means of breaking down the barriers typically associated with research species and approach, and facilitating the bi-directional flow of expertise from bench to bedside and back again.

**MacLeod:** In my view, one of the most important contributors to research progress is collaboration. This is especially so in my own field, as progress in our understanding is likely to depend upon the constructive synthesis of prior research approaches previously developed by different teams of investigators to assess quite different types of cognitive bias. Consequently, I think initiatives that successfully stimulate and support research collaboration will have the greatest positive impact on such progress. If there has been an upside to the disruptions inflicted by the global COVID-19 pandemic on traditional scientific conferences (which have hitherto been a major driver of collaboration), it is the increased capacity to engage effectively in virtual research meetings. Within my own field of cognitive bias research, this has led to more frequent, smaller scale, on-line meetings that bring together international researchers with overlapping interests, motivated by the goal of sharing not only their recent findings, but also their respective expertise. Although I warmly welcome the return of conventional conferences, I greatly hope that we will continue to collectively capitalize on our new capacity to complement these events with the types of focused virtual meetings we have recently come to rely upon. The resulting increase in the frequency and quality of direct communication and discussion, between research teams that each contribute different skills and experience but pursue the same shared objective of explaining, predicting, and treating fear and anxiety, will nurture the development of productive collaborations that contribute both to the advancement of understanding and to the enhancement of therapeutic efficacy.

**Mobbs:** In the case of human neuroscience, I think we need to develop better theoretical models of defensive states. These models should then guide how we approach paradigm development. Funders, therefore, need to be open to alternative approaches to measuring fear and anxiety in humans. For example, we need to develop experiments that allow us to investigate the role of regions beyond the amygdala and link these to behaviors and computation. There is an alarming lack of research on these brain areas in humans. The amygdala has been well characterized in humans but there is no paradigm that targets other important regions. I would love to see targeted funding mechanisms focused on less-explored brain regions in humans. Other targeted funding mechanisms might focus on fundamental question, such as:

- How does the brain switch between defensive states?
- How does the brain use representations to elicit defensive responses across threat stimuli?
- How do internal states influence our perceptions of danger?
- How does the brain represent safety?

Adequately understanding how the human brain distinguishes between different threats is a prerequisite to determining what goes awry in anxiety and trauma disorders.

**Question 6 Afterword.**

In Question 6 we asked the discussants to broadly consider the role of research funding and infrastructure in the scientific study of fear and anxiety, and to make concrete recommendations for enhancing the speed and reliability of the discovery process.

Building on their responses to Questions 5a and 5b, the discussants highlighted several key priorities, including efforts to incentivize and support:

1. The development of reliable and valid measures of fear- and anxiety-related states, traits, and disorders (Clark).
2. The acquisition of diverse, equitable, and unbiased human research samples (Clark).
3. The development and dissemination of evidence-based strategies for preventing or slowing the development of pathological fear and anxiety, and to reduce stigma and other barriers to care (Clark). As Clark notes, "It is ultimately better—and potentially easier—to prevent psychopathology from developing in the first place—or at least to inhibit its development—than to treat it after it has gotten to the point that individuals' suffering leads them to seek treatment."
4. Coordinated cross-species research (Fox).
5. Work aimed at addressing the fundamental questions that cut across fear and anxiety research in animals and humans (e.g., *How does the brain switch between defensive states? How does the brain represent the absence of threat?*) (Mobbs).
6. In addition, Buss, Fox, and MacLeod all underscore the importance of problem-focused multidisciplinary research collaborations. As Fox writes, "Work in other brain-related disorders (e.g., Parkinson's)

suggests that focused efforts aimed at breaking down the traditional barriers ('silos') between scientific disciplines and approaches could really move the needle…Topic-focused research centers, consortia, and conferences [can help dissolve] the barriers typically associated with research species and approach, and facilitate[*e*]…the bi-directional flow of expertise from bench to bedside and back again." Fox goes a step further than the other discussants, emphasizing the importance of creating training opportunities for the next-generation of fear and anxiety researchers to cultivate the knowledge, skills, and experience necessary to lead multidisciplinary research projects (cf. Gee et al., 2022; Fox, Lapate et al., 2018).

**Question 7.** ***The Ultimate Goal. Science is often incremental and focused on the most immediate next step. What would an adequately complete understanding of fear and anxiety look like? What is the ultimate goal of the scientific study of human fear and anxiety?***

**Bliss-Moreau:** For me, the ultimate goal of the scientific study of fear and anxiety is not to explain them specifically, but rather to understand the neurobiology and psychological experience of emotions and moods generally. In this view, fear and anxiety are examples of the phenomena we seek to explain, but the theories and models we build must account for the rest of our emotional life. These theories and models need to be grounded in a systems and evolutionary understanding of how the brain works, accounting for both domain general functions and degeneracy, and both accommodate and predict the incredible variation in emotions evident within and across individuals. It is also critical that we move away from the ethnocentric approaches that have long dominated the psychological and neurobiological sciences to ensure their relevance globally and ultimately build a nomothetic understanding of how emotions and moods come to be in all people.

**Clark:** From our current vantage point, I do not think is possible to specify what "an adequately complete understanding of fear and anxiety would look like," any more than someone living in the year 1800 CE could specify what an adequately complete understanding of atomic structure would look like. That is, we don't know what we don't know, although I think we can say with confidence that the ultimate goal of scientific study of human fear and anxiety is to understand emotions sufficiently to be able to prevent fear, anxiety, and other negative emotions from becoming maladaptive. Just as physical pain is an indicator that something is wrong with our bodies, psychological pain is an indicator that something is wrong with our psyches.

Relatedly, it is to be hoped that increased scientific understanding of human fear and anxiety would be accompanied by its destigmatization, which would help pave the way toward prevention and early intervention. There was a time when cancer was stigmatized and people avoiding talking about it for the same reasons that we avoid talking about mental health problems today. It is only when we understand phenomena that we can address them from a problem-solving rather than judgmental perspective.

**Fox:** From my perspective, the ultimate goal is the development of tools that would allow individuals to choose the extent to which they experience fear and anxiety. If a person is experiencing unwanted or impairing levels of distress, we should be able to help them diminish this experience. It is likely that this will need to be addressed on a case-by-case basis, as a single strategy is unlikely to be effective for all individuals—there are many underlying biological alterations that may result in similar symptomatology, and the optimal approach may require that the intervention be tailored to the specific alteration. Ultimately, this will be most tractable in the context of a full biological understanding, and will require moving toward a knowledge-based engineering of the mind.

**Keltner & Cowen:** One trajectory in the progress of emotion science, as in other scientific disciplines, is that toward greater precision of the phenomena that are of interest, the causal claims, and the search for specific neurophysiological patterns or behavioral profiles of psychological states. For 25 years, canonical studies in emotion science focused on one positive state—'happiness' or 'joy.' Intuition alone suggests that this singular concept does not do justice to the richness of positive emotional states. The robust field of positive emotions has sought greater precision in mapping this space of emotion (Shiota et al., 2021), and now it is increasingly clear that there are upwards of 8 to 10 distinct positive emotions, with their own behavioral profiles, influences upon cognition, and functions (e.g., Fredrickson, 2013; Keltner and Cowen, 2021; Keltner et al., in press; Manokara et al., in press; Shiota et al., 2017).

We suggest the same sort of trajectory toward greater precision is needed in the study of fear and anxiety, to begin to map the varieties of fear in terms of behavior, function, and underlying neurophysiology. A central next step in such work is to move beyond the concepts of the past—'fear' and 'anxiety'—to a richer characterization of the states that have been lumped under these labels.

**Kragel:** A complete understanding of fear and anxiety would provide an explicit account of (a) the situations in which humans experience fear and anxiety and (b) the operations performed by the brain that give rise to emotional responses, including (but not limited to) subjective experience. Importantly, this level of understanding will not only require characterizing the nature of representations that underlie emotional behavior (e.g., what are the types of sensory inputs and internal states that give rise to behaviors indicative of fear and anxiety, however they are defined), but also the order and kinds of transformations that satisfy constraints on information processing (cf. Fox and Mobbs' emphasis on computational approaches). Such an account should be able to both predict human behavior and also brain activity, along with differences between individuals, including psychiatric disease. I am optimistic that computational approaches, including artificial neural networks (Hasson et al., 2020; Saxe et al., 2021; Yamins and DiCarlo, 2016) and Bayesian modeling approaches (Saxe and Houlihan, 2017), will accelerate progress to this goal. Having more computationally and neurally explicit models of emotional phenomena would not only enable us to better explain the processes that give rise to fear and anxiety—either over evolutionary timescales or over the lifetime of an individual—it should provide more precise ways of predicting the effect of interventions in cases of dysfunction.

**MacLeod:** Scientific progress is incremental in nature, and I do not consider it inherently problematic when anxiety researchers focus principally on planning their best immediate next step, without considering what a complete understanding of fear and anxiety might look like. Time, effort, and funding are most likely to be squandered when scientists fail to determine adequately the best next step to take, as the common consequence of such failure is the execution of studies that make suboptimal contributions to the advancement of understanding. The purpose of fear and anxiety research is to advance our understanding of the processes that underpin the development, maintenance and alteration of these emotions, not to reach a point where such understanding is complete. Like the end of the rainbow, although we might experience the illusion of moving towards such a point, no such place exists. As scientists, we work at the perimeter that borders the established body of knowledge within our field and separates this existing knowledge from the many uncertainties that lie beyond. Our specific studies are designed to resolve particular uncertainties that lie just outside this perimeter, and when our studies are well-designed and carefully executed they can serve to convert such uncertainties into new knowledge. In consequence, our knowledge expands, but so too does the size of the perimeter that now separates this larger body of knowledge from the uncertainties beyond. For this reason, we can be confident that each question we successfully answer as we advance our understanding of the processes that underpin anxiety and fear will leave us with a greater number of new questions to ask. Thus, although our understanding will undoubtedly grow, it will never be complete.

Although the journey may have no ending, the most important decision faced by every scientist will always concern what next step they

should take. I believe the best step will always be the one that serves to reduce the uncertainties faced at that particular juncture most greatly. For this reason, I advise making each such decision by moving through the following 3 stages. First, we should seek to identify a key distinction that can be drawn between alternative families of candidate explanations, each of which is capable of accounting for what we presently know concerning the phenomenon of interest. Second, we should then discriminate the differing predictions that are respectively generated by these alternative families of explanations, concerning the outcome of a potential study that has not yet been conducted. Third, we should then execute this specific study, as our next step. The results will serve to refute one or more families of potential explanation. Following each such study, we can continue progress by now identifying a new key distinction between candidate subtypes of account within the surviving family of explanations, each of which generates differing predictions concerning a new potential study that has not yet been conducted, and this study should be executed as our next step. In this way, the wheel of science will roll ever forward, with each turn serving to reduce uncertainty and to advance understanding.

Within our own field, I anticipate that such research progress will, in time, come to illuminate the range of anomalies in cognitive processes that contribute to fear and anxiety (which will likely be substantially greater than the range of cognitive factors implicated in contemporary theories), and also will increase understanding concerning which such cognitive biases operate independently to drive fear and anxiety, and which moderate or mediate the impact of others. However, this growth in understanding will also serve to generate new questions, perhaps concerning how these cognitive anomalies develop, and answering these questions will in turn lead to further questions, for example concerning the factors that moderate such development, and in this way the process of advancing understanding will continue unchecked. Likewise, a fuller grasp of the cognitive biases that characterize elevated fear and anxiety also will lead to new questions concerning how best to modify newly identified biases, the factors that moderate the efficacy of differing bias modification approaches, the best ways to maximize the duration of resulting bias change, and so forth. Though I anticipate that the advent of more effective cognitive bias modification techniques will result in clearer delineation of the types of cognitive change that serve to reduce fear and anxiety, this too will lead to new questions concerning how to combine such therapeutic elements most effectively with other types of treatment. It seems likely that future advances will shed light on the neural structures and pathways that underpin such cognitive anomalies, again leading to new questions, perhaps concerning neural development or the molecular underpinning of the neural factors implicated in these biased patterns of cognitive processing. We cannot anticipate the many future questions that await us, as these will depend upon the future findings that precede them and guide their formulation. Instead, we must always focus on identifying which new questions we should address as our immediate next step. Scientific progress will be optimized by consistently choosing to address those questions that promise to deliver the greatest advance to understanding within our chosen area of study.

**Mobbs:** Basic affective science has 2 core aims:

a) Understand the conditions that elicit distinct defensive states.
b) Understand the biological mechanisms underlying them.

Once these 2 fundamental questions have been sufficiently addressed, tools can then be developed to causally alter these defensive states. This knowledge can then be applied to clinical populations to understand how the relevant neural systems go awry and the factors that cause them to do so. From there, we can begin to develop targeted interventions aimed at ameliorating clinical symptoms.

**Naragon-Gainey:** This is a complicated question, but as a clinical psychologist, I will focus more narrowly on pathological fear and anxiety. From this perspective, the ultimate goal is to (a) understand the range of risk and protective factors, distal and proximal antecedents, and distal and proximal consequents of pathological fear and anxiety, (b) identify the factors—including individual and situational variables—that influence the strength of risk and resilience pathways (which would provide a framework for developing personalized interventions), and (c) determine which of these factors is most potent and amenable to treatment, and the optimal means of cultivating durable change. Such a goal is admittedly aspirational in nature, but I do think we have already made meaningful steps in this direction.

**Question 7 Afterword.**

Questions 1–4 were squarely focused on the state of the science. Questions 5–6 asked discussants to look to the horizon and identify the most important challenges and next steps. Here we asked them to take an even broader perspective and consider the ultimate goals of the scientific study of fear and anxiety.

The Nobel laureate physicist, Richard Feynman, described *science* as consisting of 3 things: a set of procedures for rigorously observing nature, the body of understanding that emerges from attempts to make sense of those data, and the practical application of that hard-won knowledge (Feynman, 2005). Different groups of discussants emphasized each of these distinct facets of science.

Many focused on theory and basic scientific understanding (Bliss-Moreau, Keltner & Cowen, Kragel, MacLeod, and Mobbs). Kragel and Mobbs emphasize the importance of identifying the precise conditions that evoke distinct threat-related states, and the biological and computational mechanisms that transform threat into the signs and symptoms of fear, anxiety, and related states. Bliss-Moreau sets her sights even higher, telling us that "the ultimate goal of the scientific study of fear and anxiety is not to explain them specifically, but rather to understand…emotion" more generally. For her, the long-term goal is to develop a general theory of affect and emotion that applies equally well to *all* humans, regardless of demography, language, and culture.

All the discussants underscore the practical significance of reducing the suffering associated with pathological fear and anxiety. As Fox notes, "the ultimate goal is the development of tools that would allow individuals to choose the extent to which they experience fear and anxiety." Clark highlights the importance of developing interventions that can be deployed early, before fear and anxiety become debilitating. Kragel, Fox, and Naragon-Gainey all emphasize the importance of developing tools that can predict and optimally ameliorate maladaptive fear and anxiety, independent of variation in clinical presentation and etiology.

While agreeing with these long-term goals, MacLeod emphasizes the first part of Feynman's threefold definition, the process of gathering empirical data. Adopting a more philosophical perspective, he writes that, "Like the end of the rainbow, although we might experience the illusion of moving towards such a point, no such place exists. As scientists, we work at the perimeter that borders the established body of knowledge within our field and separates this existing knowledge from the many uncertainties that lie beyond. Our specific studies are designed to resolve particular uncertainties that lie just outside this perimeter, and when our studies are well-designed and carefully executed they can serve to convert such uncertainties into new knowledge. In [sum]…our knowledge expands, but so too does the size of the perimeter that now separates this larger body of knowledge from the uncertainties beyond… [T]he wheel of science will roll ever forward, with each turn serving to reduce uncertainty and to advance understanding."

## 2. Conclusions

The present discussion makes it abundantly clear that most of the work—both empirical and conceptual—necessary to understand the nature and the neurobiology of threat-related related emotions remains undone. A central goal of the roundtable, and the parent Special Issue, is

to motivate the scientists to do the thinking and the research that will be required to address these outstanding questions, to develop new questions, and to generate more complete and useful conceptual frameworks (Fullana and Shackman, in press).

Work to understand fear and anxiety is a matter of the utmost practical importance. When extreme or pervasive, fear and anxiety can be debilitating (Vos et al., 2020). Anxiety and trauma disorders are among the leading cause of years lived with disability, afflicting ~300 million individuals annually, and contribute to the etiology and course of depression, substance misuse, and psychosis (Freeman, 2016; Volkow, Koob, and McLellan, 2016; Vos et al., 2020). In the United States alone, nearly 1 in 3 individuals will experience an anxiety disorder in their lifetime, diagnoses and service utilization are surging among young people, and direct health care costs exceed $40 billion annually (Binkley and Fenn, 2019; Dieleman et al., 2020; NCS-R, 2007; Vos et al., 2016). Yet existing treatments are inconsistently effective, underscoring the urgency of developing a clearer understanding of the nature and biological bases of threat-related emotions, and the myriad ways in which they influence the way we think, feel, and behave (Craske et al., 2017; Garakani et al., 2020; Sartori and Singewald, 2019).

Addressing this urgent challenge will require an increased investment in fear and anxiety research—one commensurate with the staggering burden that anxiety and trauma disorders impose on global public health—and greater collaboration among researchers drawn from a range of disciplines, from anthropologists and ethologists to social and cognitive psychologists; from economists to data scientists. Affective science is, by its very nature, interdisciplinary, and if we are to address these fundamental questions, we will have to work together. A major challenge for the future will be to adopt training models that fully embrace this kind of multi-disciplinary research (Gee et al., 2022; Fox, Lapate et al., 2018).

We hope that readers of this roundtable make a lasting impression on our scientific understanding of fear and anxiety, that they work to address the fundamental questions that we have considered, and that they play a role in developing new ones. Ultimately, we hope that a deeper understanding of threat-related emotions will hasten the development and dissemination of tools to help those suffering from maladaptive fear and anxiety to find peace and flourish in their lives.

## Author contributions

A.J.S. envisioned the virtual panel discussion. A.J.S. formulated the discussion prompts with guidance from M.A.F. and A.S.F. E.B.-M., K.A.B., L.A.C., A.S.F., D.K., A.S.C., J.J.K., P.A.K., C.M, D.M., and K.N.-G. responded to the discussion prompts. A.J.S. and L.A.C. reviewed and edited the responses. S.E.G. and A.J.S. wrote the remaining sections of the paper. M.A.F. and A.J.S. coordinated editorial communications. All authors contributed to reviewing and revising the paper and approved the final version.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105237.

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M., Meitei, W.B., Memiah, P.T.N., Mendoza, W., Menezes, R.G., Mengesha, E.W., Mengesha, M.B., Mereke, A., Meretoja, A., Meretoja, T.J., Mestrovic, T., Miazgowski, B., Miazgowski, T., Michalek, I.M., Mihretie, K.M., Miller, T.R., Mills, E. J., Mirica, A., Mirrakhimov, E.M., Mirzaei, H., Mirzaei, M., Mirzaei-Alavijeh, M., Misganaw, A.T., Mithra, P., Moazen, B., Moghadaszadeh, M., Mohamadi, E., Mohammad, D.K., Mohammad, Y., Mohammad Gholi Mezerji, N., Mohammadian-Hafshejani, A., Mohammadifard, N., Mohammadpourhodki, R., Mohammed, S., Mokdad, A.H., Molokhia, M., Momen, N.C., Monasta, L., Mondello, S., Mooney, M. 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# Supplementary Materials

Shannon E. Grogans[1]

Eliza Bliss-Moreau[4,5]

Kristin A. Buss[6]

Lee Anna Clark[7]

Andrew S. Fox[4,5]

Dacher Keltner[8]

Alan S. Cowen[9]

Jeansok J. Kim[10]

Philip A. Kragel[11]

Colin MacLeod[12]

Dean Mobbs[13,14]

Kristin Naragon-Gainey[15]

Miquel A. Fullana[16,17]

Alexander J. Shackman[1,2,3]

[1]Department of Psychology, [2]Neuroscience and Cognitive Science Program, and [3]Maryland Neuroimaging Center, University of Maryland, College Park, MD 20742 USA. [4]Department of Psychology and [5]California National Primate Research Center, University of California, Davis, CA 95616, USA. [6]Department of Psychology, The Pennsylvania State University, University Park, PA 16802 USA. [7]Department of Psychology, University of Notre Dame, Notre Dame, IN 46556 USA. [8]Department of Psychology, University of California, Berkeley, Berkeley, CA 94720 USA. [9]Hume AI, New York, NY 10010 USA. [10]Department of Psychology, University of Washington, Seattle, WA 98195 USA. [11]Department of Psychology, Emory University, Atlanta, Georgia 30322 USA. [12]Centre for the Advancement of Research on Emotion, School of Psychological Science, The University of Western Australia, Perth, WA 6009, Australia. [13]Department of Humanities and Social Sciences and [14]Computation and Neural Systems Program, California Institute of Technology, Pasadena, California 91125 USA. [15]School of Psychological Science, University of Western Australia, Perth, WA 6009, Australia. [16]Adult Psychiatry and Psychology Department, Institute of Neurosciences, Hospital Clinic, Barcelona, Spain. [17]Imaging of Mood- and Anxiety-Related Disorders Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer, CIBERSAM, Barcelona, Spain

**Please Address Manuscript Correspondence to**

Alexander J. Shackman (shackman@umd.edu)

**Cowen & Keltner Supplementary Note 1.1.** Capturing semantic spaces of emotional response requires new kinds of data and statistical approaches of a more inductive variety. The prevalent focus on a limited number of emotions and prototypical stimuli (Barrett et al., 2019; Elfenbein & Ambady, 2002; Lindquist et al., 2012) captures approximately 30% of the information conveyed in self-report and expressive behavior (Cowen, Sauter, et al., 2019). Characterizing a semantic space of emotion (or other subjective realms) requires vast arrays of evocative stimuli and participants' responses in terms of widely varying emotion terms and questions that capture feelings, appraisal processes, or nonverbal behaviors (Cowen & Keltner, 2021). It requires moving beyond univariate measures (Lench et al., 2011), recognition accuracy (Elfenbein & Ambady, 2002), and factor analysis (Russell, 2003), approaches that presuppose universal one-to-one mappings between emotion-related behaviors and discrete labels (e.g., anger) or position along a few broad dimensions of response.

What insights has Semantic Space Theory yielded with respect to fear, anxiety, and related emotional phenomena? Consider the results of a first study of the subjective experience of emotion. In this study, participants rated 2185 short, evocative videos in terms of 34 distinct emotions and a full array of 14 appraisal dimensions, including valence and arousal (Cowen & Keltner, 2017). New statistical techniques revealed a semantic space of subjective emotion we visualize in **Figure 1**.1.

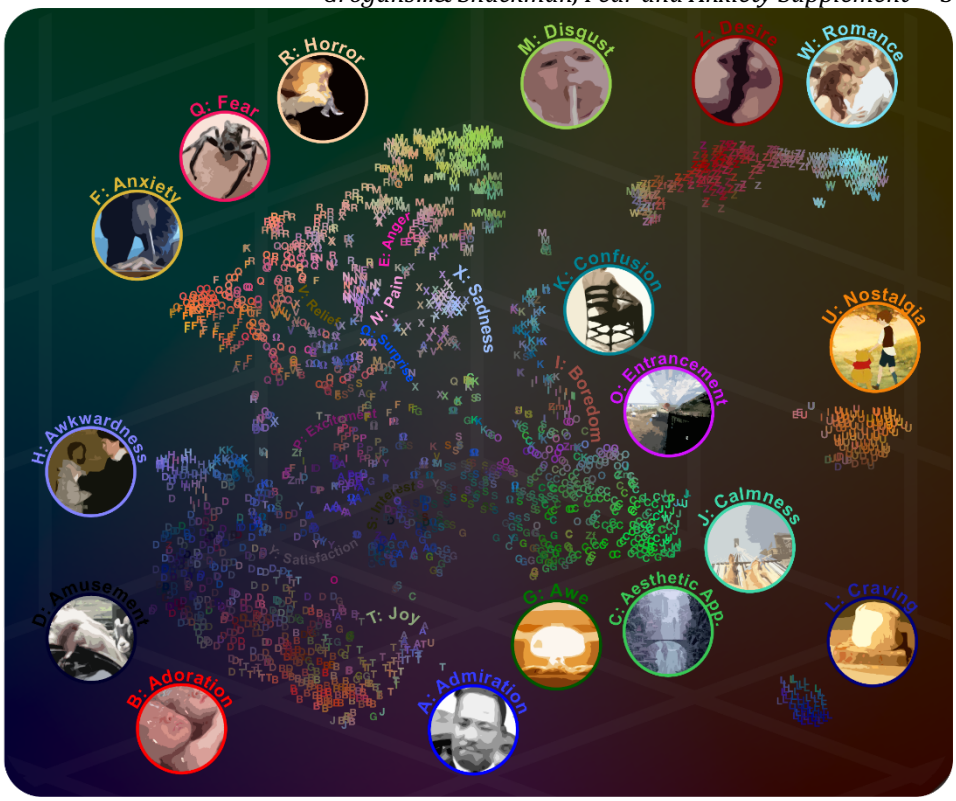


**Figure 1.1.** ***Semantic space of emotion evoked by 2185 brief videos.*** At least 27 distinct affective states are reliably captured in reports of emotional experience evoked by video, best conceptualized in terms of nuanced emotion concepts such as fear, horror, anxiety, empathic pain, and disgust. Gradients bridge emotion concepts traditionally thought of as discrete, such as fear and surprise. Interactive map: https://s3-us-west-1.amazonaws.com/emogifs/map.html

This study, and others like it, have revealed that emotion is high dimensional (in this study, 27 states emerged as distinct); in terms of the distribution of emotion, the boundaries between emotion categories are not discrete, but bridged by gradients of meaning (and many experiences are systematic blends of states); and people more reliably conceptualize emotional experience in terms of discrete emotion concepts rather than higher-order dimensions such as valence or arousal (for a summary of convergent findings in the study of emotion recognition in the face and voice, music, and visual art, see (Cowen & Keltner, 2021).

**Cowen & Keltner Supplementary Note 1.2.** A careful examination of the space in which "fear" is located makes the case for distinguishing at least four kinds of experience commonly conflated in studies of "fear" and "anxiety" (**Supplementary Note 1.2**). "Fear" is mostly evoked by physical threat (e.g., spiders, heights). "Horror" is elicited by depictions of gore, death, and destruction. "Anxiety" is associated with

epistemological uncertainty, and is elicited by stimuli that upset, challenge, or subvert the individual's stable understanding of the world. "Awkwardness" is associated with social separation and rejection concerns and is elicited by scenes of people violating social conventions or not fitting in with social standards. Studies of emotional expression demonstrate that fear, anxiety, horror, and awkwardness are reliably communicated by distinct vocal and facial signals (Brooks et al., n.d.; Cowen & Keltner, 2020b). In short, recent work fractionates fear into at least four kinds. They are evoked by distinct threats: physical, existential, epistemological, and social. They appear to trigger qualitatively different experiences and are likely subserved by distinct neurophysiological processes. In the **Table 1.2**, we provide self-report labels, eliciting stimuli, and associated expressions for the four kinds of fear.

**Supplementary Table 1.2**

| **Fear Subtype** | **Physical** | **Existential** | **Epistemological** | **Social** |
|---|---|---|---|---|
| **Self-Report Labels** | Physical Danger | Horror, Dread | Anxiety, Worry | Awkwardness, Social Anxiety |
| **Induction Stimuli** | https://emogifs.s3.us-west-1.amazonaws.com/mp4_noname/0564.mp4 | https://emogifs.s3.us-west-1.amazonaws.com/mp4_noname/0744.mp4 | https://emogifs.s3.us-west-1.amazonaws.com/mp4_noname/0724.mp4 | https://emogifs.s3.us-west-1.amazonaws.com/mp4_noname/1729.mp4 |
| **Expression** | https://mturkrecord.s3.amazonaws.com/targaudio/Katherine_088.mp3 | https://mturkrecord.s3.amazonaws.com/targaudio/Ana_018.mp3 | https://mturkrecord.s3.amazonaws.com/targaudio/Francine_066.mp3 | https://mturkrecord.s3.amazonaws.com/targaudio/VENEC_0220.mp3 |

**Bliss-Moreau Supplementary Note 2.1.** While there is ample evidence that many animals have the capacity for generating and using concepts, the capacity for abstract concepts is likely much more limited in the animal kingdom, making the existence of emotions likely limited to a small number of species. As a result, the likelihood of finding an animal homolog of human fear is low (particularly in the species most typically used as models in biomedical and psychological science) which makes the popular practice of trying to find evidence of fear homologs in humans and our model species (e.g., freezing) unlikely to be successful.

This approach is tenuous at best as it often relies on measuring single behaviors or suites of behaviors that are thought to be related to fear but for which no external validity exists. These approaches largely rely on inferences grounded in anthropomorphism and/or investigators' folk beliefs about emotions. Further, evidence exists suggesting that some of the behaviors typically used to index "fear" in animals are specifically related to evolutionary demands (e.g., freezing is related to predation) rather than emotionality or even arousal (Suarez & Gallup, 1981).

***Question 3: The Brain: How are fear, anxiety, and related constructs organized in the brain? For example, are some regions central? Is there an "anxious brain"? Are there distinct kinds of fear embodied in dissociable (or overlapping) neural circuits? How does the brain dynamically choose the most adaptive response to threats that vary across multiple dimensions (e.g. nature, intensity, probability, imminence, certainty, opportunity for avoidance)? Do different specialized circuits compete for control over behavior ('biased competition')?***

**Fox Supplementary Note 3.1.** As outlined in my responses to Questions 2 and 3, we can reasonably hypothesize that there exist brain systems that are specific to detecting and responding to specific kinds of threat (e.g., looming aerial predators), as well as systems that are well-suited to provide a broader, generalized, framework for detecting and responding to threat. If a system is useful for avoiding death in both fruit flies and humans, it seems likely that it was useful for our common ancestor and that the biology that underlies this system is likely to be conserved, to a greater or lesser extent. In contrast, if there is a particular set of threats that are uniquely applicable to particular species, or rely on a capacity that is unique to some species, it is less likely that the biological substrates that enable processing of these threats are evolutionarily conserved. In addition, because evolution necessarily builds on what has come before, it is likely that these systems work in concert to enable adaptive threat responses. Below are a few examples of how these circuits are organized in human and non-human animal brains, highlighting a number of critical take-home messages that emerge. These considerations should be incorporated when attempting to elucidate the brain systems that contribute to fear and anxiety.

*There are specific circuits that elicit threat-responses to specific stimuli.* In the mouse, there are neurons in the medial superior colliculus (mSC) that can detect a looming shadow, and directly excite neurons in the dorsal periaqueductal gray (dPAG) to elicit escape behavior (Evans et al., 2018). These neurons are necessary and sufficient for an animal to avoid the area with the looming shadow, presumably enabling escape from a potential threat coming from above, such as a swooping hawk. This is an example of a very specific process. Because flying predators have been a constant throughout human evolution (Hart et al., 2005), I would hypothesize that these circuits remain intact in humans (though, to my knowledge, this remains to be tested).

*Not all threats are processed in quite the same way, and specific circuits are involved in initiating specific responses to specific threats.* Although rodents' responses to a looming shadow rely on mSC and dPAG neurons, learned associations between a tone and shock rely on the amygdala and ventral lateral PAG (vlPAG). This learning is thought to occur in amygdala neurons across the basolateral of the amygdala (BLA) and the lateral part of the central nucleus of the amygdala (CeL). These regions induce freezing via projections to the medial part of the central nucleus (CeM). CeM, in turn, inhibits local interneurons in the ventrolateral PAG (vlPAG), which through feed-forward inhibition, can result in excitation of neurons in the medulla that initiate freezing through spinal cord and forelimb muscles (Tovote et al., 2016). This represents another specific circuit that can initiate threat responses. Together, these findings outline how midbrain PAG systems are integrated into a broader circuit, which likely evolved later in evolutionary history.

*The circuits responsible for specific responses to threat interact.* Not all behaviors can be implemented at the same time—an animal cannot flee while it is freezing. Thus, there must be competition between systems to determine the desired response. In the PAG, dPAG "escape" circuits can excite local interneurons in vlPAG "freezing" circuits to inhibit freezing and facilitate escape. Similarly, distinct sets of mutually inhibitory cells in the CeL can compete to help determine the adaptive response (Moscarello & Penzo, 2022). For example, stimulation of somatostatin and corticotropin releasing hormone positive cells during a shock-predicting tone can initiate freezing and escape, respectively (Fadok et al., 2017). Because these cells are mutually inhibitory, this provides a potential biological mechanism for competition between competing defensive responses. This competition is not likely to be confined to CeL and PAG (though it remains to be determined the extent to which other systems instantiate this competition, or simply provide Ce/PAG with relevant information and leverage their computations). In addition, it is worth noting that this competition is likely to encompass both aversive and appetitively motivated behaviors. After all, one cannot simultaneously freeze and forage (Holley & Fox, 2022).

*The neural circuits involved in threat processing extend far beyond a specific subcortical circuit.* Throughout the course of evolution, it is reasonable to hypothesize that humans have incorporated these threat-relevant systems into the distributed circuits that underlie fear and anxiety (Fox, 2018). As more general cortical information-processing systems emerged, these systems have likely provided utility for detecting and responding to threat. As such, the brain has incorporated or repurposed midbrain systems, including PAG, to enable cortically initiated freezing and escape behaviors in response to a more complex stimulus. Although the methods for projection-specific manipulation of primate brain circuits is still in its infancy, the mere existence of projections from the primate subgenual anterior cingulate cortex (sgACC; which receives information from many prefrontal regions) to the PAG suggests additional brain circuits that could be involved in the initiation of threat responding (Hardy & Leichnetz, 1981). These data are consistent with human neuroimaging work implicating cortical (e.g., sgAGG) and midbrain (PAG) BOLD activity during fear- and anxiety-relevant tasks (Chavanne & Robinson, 2020). Together, these highlight how some "evolutionarily-old" circuits can function in concert with more recently evolved circuits during threat processing. In short, in humans, the function of evolutionarily conserved midbrain circuits is likely to be best understood within the broader context of human or primate-specific brain circuits.

*Primate evolution has endowed numerous brain regions with new cell-types.* Evolution is not necessarily linear or additive. Studies in animals cannot be assumed to apply to humans. Even within putatively evolutionarily conserved brain regions, there is compelling evidence that there is not a one-to-one correspondence between the same region in a mouse and a human. For example, recent studies have identified primate-specific cell-types in parts of the midbrain (e.g., substantia nigra) (Kamath et al., 2022). This is also true for portions of the striatum (Krienen et al., 2020) and cortex (Schmitz et al., 2022), where primate specific cell-types have been discovered. This highlights the fact that a full understanding of mouse

circuits will not translate to a full understanding of primate circuits. Thus, rodent studies implicating a specific cell-type or projection in threat processing are most useful when they can provide testable hypotheses about the experience of fear and anxiety in humans.

*Finally, the neural substrates that contribute to threat responding are not limited to a "fear circuit."* Across species, perceiving and responding to a threat requires adaptive coordination between perceptual, motor, and peripheral physiological systems (Fox & Shackman, 2018). As such, the involvement of these brain systems in affect should not be discounted. It is important to consider the possibility that these systems are actively participating in the processing of affect-related information, as opposed to simply relaying information. In some cases, we know that sensory systems are actively participating in the processing of fear- and anxiety-relevant information. For example, in mice exposed to tone-shock conditioning, cholinergic activation of layer 1 interneurons inhibits layer 2/3 parvalbumin+ interneurons (Letzkus et al., 2011). This results in a disinhibition of pyramidal neurons in auditory cortex, which is *required* for the well-established increase in freezing to the conditioned tone in Pavlovian tone-shock conditioning. Thus, even sensory systems like auditory cortex do not seem to be simply passively passing on sensory information, but, instead are critically involved in the learning process that can make these circuits sensitive to threat-relevant information. Adapting sensory systems to be increasingly sensitive to learned threat-relevant information is likely to provide an additional benefit for threat detection and increase our likelihood of staying safe.

To summarize—

a) Specific circuits assemble responses to specific kinds of threat.
b) There are multiple brain circuit capable of initiating the same threat-related behavior.
c) These circuits are interconnected, with multiple points for competitive interactions.

d) Throughout evolution, these systems have been incorporated into increasingly distributed networks.

e) Primate evolution has also endowed many (if not most) brain regions with cell types that are not present in rodents.

f) The brain regions that contribute to threat processing are not limited to a "fear circuit" and include sensory and motor regions.

**Kragel Supplementary Note 3.2.** The accompanying figure depicts the minimum conjunction (Logical 'AND') of 4 independent multivoxel signatures of fear at 3 arbitrary thresholds (75$^{th}$, 90$^{th}$, and 95$^{th}$ percentiles).

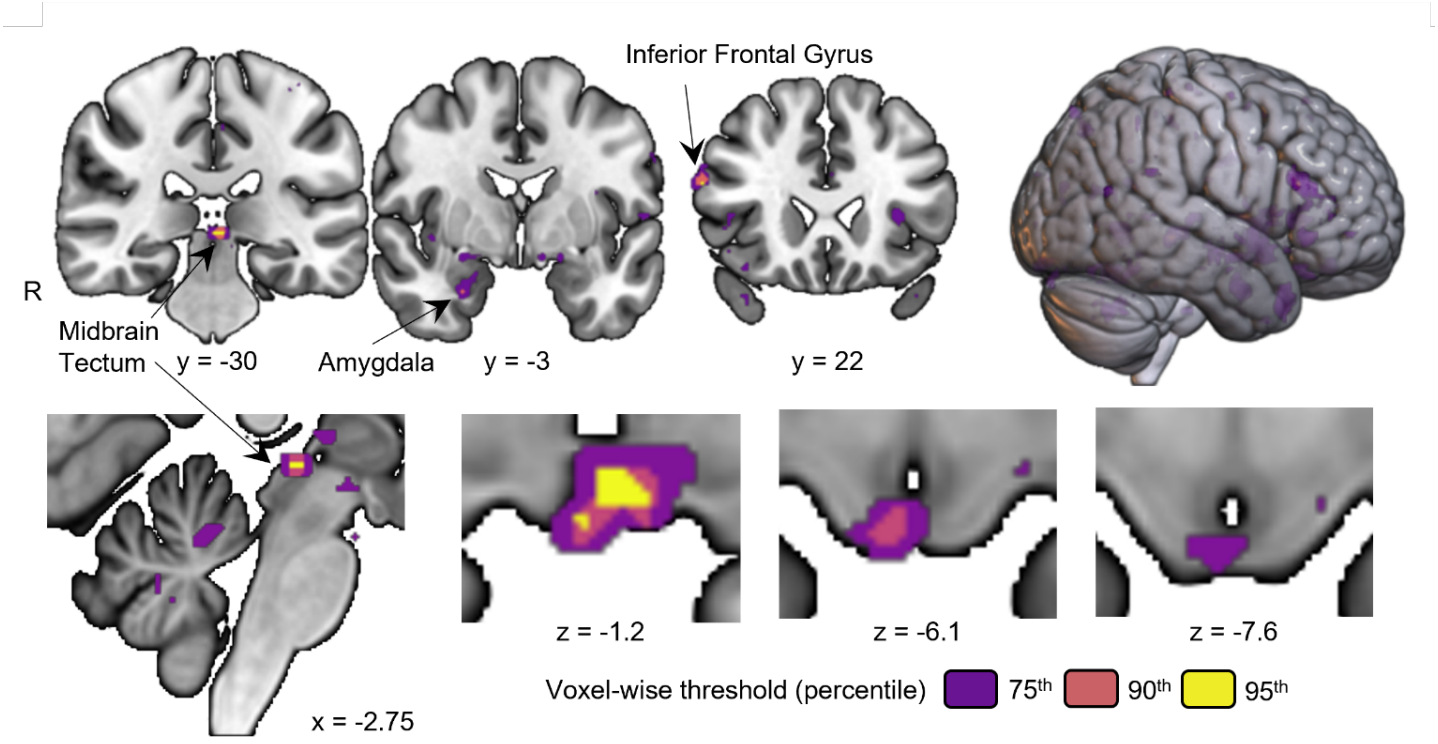


**Figure 3.2.** ***Anatomical overlap of multivoxel signatures of fear-related constructs.*** Figure depicts the minimum conjunction (Logical 'AND') of 4 independent multivoxel signatures of fear at 3 arbitrary thresholds (75th, 90th, and 95th percentiles). The signatures included models that predict Pavlovian auditory threat cues (Reddan et al., 2018), the phenomenologically distinct states of fear evoked by film and instrumental music (Kragel & LaBar, 2015), and variation in subjective feelings of fear evoked by photographs of predators and other naturalistic threats (Čeko et al., 2022, Zhou et al., 2021).

**MacLeod Supplementary Note 5a.1.** Within the domain of cognitive bias research there is scope to greatly enhance both the ecological validity of our studies, and the real-world relevance of the resulting findings, by markedly increasing the informational richness and personal relevance of the stimulus information we employ. In the pursuit of this objective, we are endeavoring in our own current research to assess individual differences in selective attention to simultaneously presented video clips, that each present richly detailed information concerning events of direct personal relevance to participants. For example, using participants who know they will undertake a stressful interview task at the end of the experimental session, we have assessed selective attention to videos of prior participants respectively describing either negative or positive aspects of this specific interview experience. Not only do we find that participants with elevated levels of anxiety vulnerability display heightened selective attention to the videos that present negative information about the stressful event they are approaching, but their emotional response to this event is predicted by their negative attentional bias. In addition to addressing prior limitations associated with impoverished stimulus information, it is to be hoped that future research using richer forms of personally relevant stimulus information will now proceed to more systematically test hypotheses concerning the independence or interdependence of differing types of cognitive bias in the determination of anxiety vulnerability. With this objective in mind, we have recently conducted variants of the above-described study in which we also assess participants' negative expectancy bias concerning the upcoming interview stressor, which demonstrate that variation in this expectancy bias fully mediates the association between participants' negative attentional bias and their heightened experience of anxiety. While firm conclusions would be premature at this stage, I am optimistic that we can anticipate the expansion of research studies that incorporate measures of multiple cognitive bias, with the aim of testing hypotheses concerning their independence or interdependence in the determination of anxiety vulnerability. I am also optimistic that such studies will significantly enhance understanding concerning the cognitive basis of anxiety vulnerability and dysfunction.

**Fox Supplementary Note 5b.1.** *Pharmacological Manipulations*. To test hypotheses about the involvement of specific neurotransmitter systems in humans, human researchers can leverage pharmacological manipulations alongside brain imaging, behavioral assessments, and self-report. Specifically, when rodent modelers have identified a specific neurotransmitter system that acts in an anxiety-related brain region, human researchers can examine the extent to which a drug that binds this neurotransmitter receptor will have the predicted effect on brain function, fear- and anxiety-relevant behaviors, and self-reported fear and anxiety (Holley & Fox, 2022). For example, despite extensive research on somatostatin expressing cells in rodent freezing, little work has examined the somatostatin system in humans (Abelson et al., 1990). Importantly, as with somatostatin drugs, many neurotransmitter-targeting drugs will have substantial side-effects, due to the broad distribution of neurotransmitter systems in the brain and body. Thus, these drugs are unlikely to be useful as treatments. Nevertheless, studies of specific neurotransmitter systems in humans can go a long way toward bridging the gap between rodent and human studies of fear and anxiety by shedding light on what neurotransmitter systems are important for the phenomenological experience of fear and anxiety in humans. Even small-scale studies in patients receiving potentially-relevant drugs for unrelated treatments have the potential to dramatically increase our understanding of these neurotransmitter systems in relation to the experience of fear and anxiety. Similarly, the strength of these hypotheses derived from the animal literature can also be supported by further examination of human genetic studies to provide further support for the involvement of a specific neurotransmitter system.

*Multi-Voxel Pattern Analysis (MVPA)*. The heterogeneity of cell types within specific fear/anxiety-relevant brain regions can also motivate hypotheses that can be tested using MVPA. Many subcortical regions contain mixtures of various cell-types within the space occupied by a single fMRI voxel. Importantly, the relative concentration of these cell-types is unlikely to be uniform across voxels, making it possible to identify changes in patterns of BOLD activation hypothesized to result from activation of specific cell-types. Researchers should leverage MVPA to test hypotheses about the contribution of specific cell-types to

different stimuli/responses to move beyond simple one-to-one mappings between brain regions and specific affective phenomena (Holley & Fox, *this issue*). For example, based on findings from mice, we might hypothesize that the voxels of the basal and lateral regions of the amygdala contain a mixture of reward and threat sensitive cells (Beyeler et al., 2018; Namburi et al., 2015). With this hypothesis in mind, we might not expect to see reliable differences in whole-amygdala activation in a straight forward test of reward vs. threat. In contrast, we might expect dissociable *patterns* of activation across these voxels to be associated with reward as compared to threat. Testing this hypothesis would lend support to a conserved organization of reward- and threat- sensitive cells across species. As researchers continue to develop translationally-informed MVPA findings, these approaches can inform hypotheses about cell-type distribution as they relate to individual differences. For example, are there patterns of BOLD activation that are associated with individual differences in threat sensitivity, such as the spatial extent of threat-predictive voxels? As outlined above, animal studies have convincingly implicated multiple cell types within the same brain region as differentially related to fear- and anxiety-relevant behavior. MVPA and other emerging analytic approaches may provide a powerful tool for linking these animal studies to our understanding of human threat processing.

*Computational Modeling*. We need to move beyond general descriptions of anxiety-related brain regions and develop a more refined nomenclature to describe the computations that give rise to the experience of fear and anxiety. A few groups are beginning to explore these issues , but most of the work remains undone (Bach & Dayan, 2017, 2017; Bishop & Gagne, 2018; Browning et al., 2015; Lawrance et al., 2022; Mobbs et al., 2018, 2020; Silston et al., 2021)). For example, while computationally tractable concepts such as threat “uncertainty” and "proximity" are undoubtedly useful, they are also underspecified. Uncertainty can refer to variance in the likelihood of a threat (i.e., how certain we are in a potential outcome), the amount of information available (i.e., the extent to which the likelihood of a threat is unknowable), the nature of the threat (e.g., intensity, modality, etc.), as well as various features of threat-space that might change the

probability of threat at a given moment (e.g., temporal uncertainty). Similarly, "proximity" may be a proxy for the likelihood of danger, and/or the extent to which the threat can be avoided (i.e., escapability). Each of these might or might not reflect differences in the underlying computational processes that link threats to behavioral, physiological, and phenomenological outcomes. Computational models have already been impactful in studies of reward (Dabney et al., 2020; O'Doherty et al., 2007; Wang et al., 2016), navigation (Doeller et al., 2010; Moser et al., 2008), and many more, allowing for insights into concept formation (Baram et al., 2021; Constantinescu et al., 2016; Park et al., 2021). A major strength of this approach lies in the ability to extrapolate and test hypotheses that extend beyond the original paradigms and tools used. More specifically, computational models can enable complementary cross-species investigations that do not rely exclusively on face-validity. Instead, researchers can focus on testing hypotheses about the specific computations performed within a given brain region using the paradigms and techniques that are most amenable to the species and research question (i.e., the probability of threat, as opposed to using the identical threat stimulus, which may mean something very different when presented to a human, monkey, or mouse).

*Genetic Studies to Guide Reverse Translation.* There is a need for insights from humans that can help prioritize specific molecules and cell types for mechanistic studies in animal models. To this end, there is still much to be learned from genetic studies. There are a number of large-scale efforts to perform genome-wide association studies that may help to identify specific molecules that could motivate reverse translation. Unfortunately, because of the multi-faceted biology of fear and anxiety (see my responses to Questions 1 and 3 and **Supplemental Note 3.1**), the associations between specific genetic polymorphisms and fear and anxiety are likely to be variable and account for a small portion of the variance in emotional traits and disorders. To overcome this limitation, I propose family-based whole-genome-sequencing studies that might identify specific genes that co-vary with anxiety in families enriched for disorder. This approach is well-suited to identify a small set of highly-penetrant polymorphisms and may be our best bet

for identifying a few genes that, when disrupted, can impact human anxiety. Critically, this approach has provided insights into other neurological disorders, as highly penetrant polymorphisms with large effect sizes are sufficient to provide a foothold into the related molecular processes that contribute to distributed neural alterations (Glahn et al., 2019; Polymeropoulos et al., 1997). For example, implicating a specific part of a CRH receptor in anxiety disorders, anxiety, and anxiety-like behavior (Levey et al., 2020; Nagel et al., 2018; Rogers et al., 2012), can implicate the cells that release CRH, and the internal cellular cascades initiated by receptor activation in anxiety. These studies can play an important role in guiding nonhuman animal research toward the molecules and cell-types most relevant to the experience of fear and anxiety in humans, and inform the development of more effective interventions.

*Developing New Tools for Nonhuman Primate Studies*. In addition to the kinds of studies that can be performed in humans right now, cross-species studies in nonhuman primates can help bridge the gap between rodent and human neuroscience (see my response to Questions 2 and 3). Tools for cell-type and projection-specific recording and manipulations in rodents have greatly added to our understanding of the brain. It will be critical to develop an analogous toolkit for studying the primate brain, including neurotransmitter sensors (e.g., GCaMP & DLight) and effectors (e.g., opsins & DREADDs) (Campos et al., n.d.) . These tools will enable measurement and manipulation of specific projections and cell-types within specific brain regions. Studies using these tools have the potential to elucidate the contribution of specific projections and cell-types in nonhuman primates that are most likely to be conserved in humans. A critical first-step in developing these tools for use in primates will be the further development of viral vectors that can be used to deliver these genetic cargos to the primate brain (Campos et al., n.d.; Challis et al., 2022; Chen et al., 2022; Chuapoco et al., 2022; Lawler et al., 2022). Ultimately, these tools will necessary to develop a refined understanding of the link between cell-type-specific functions and the complex expression of fear and anxiety.

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