Are fear and anxiety distinct phenomena? Clinical differentiation between disorders involving fear (phobic disorders), anxiety (generalized anxiety disorder [GAD]), or a combination (panic disorder, social anxiety) (1) reflects a prevailing view that they are indeed distinct. Moreover, factor analyses of so-called internalizing disorders, most notably anxiety and mood disorders, suggest that they can be divided into those characterized by fear and those characterized by anxious-misery (2,3), which themselves appear to be associated with different patterns of physiological reactivity (4) and distinct underlying neurobiology (5). Furthermore, it shapes research, insofar as Research Domain Criteria framework uses constructs of acute threat and potential threat, corresponding to fear and anxiety, respectively (6).

Widespread acceptance of the distinction carries implications for research, diagnosis, and treatment, but its validity has been contested based on isolated findings inconsistent with a distinction. We review the field more to clarify how well this distinction is supported overall. We consider evidence from clinical and nonclinical studies of neurocircuitry, psychophysiology, and behavior. We focus on studies and paradigms explicitly focusing on the distinction and, as such, do not seek to provide a comprehensive account of the literature more generally. We refer to studies of fear and anxiety in rats but acknowledge that this application of the terms is contentious (7), and we consider this contention later.

NEUROBIOLOGICAL EVIDENCE FOR THE FEAR-ANXIETY DISTINCTION

Psychiatric approaches have been informed by findings from rodent models, which have inspired therapies (8) and elucidated causal factors and mechanisms [e.g., biological preparedness (9,10)] (Table 1). Our understanding of fear and anxiety is heavily influenced by paradigms, such as fear conditioning, that are feasible in animal research. In rodent models of fear, a typical approach is to pair a stimulus (conditioned stimulus) with an aversive event (unconditioned stimulus, e.g., a foot shock). Animals develop a conditioned response—fear—to presentation of the conditioned stimulus. In comparable rodent models of anxiety, the aversive stimulus can be presented either unpredictably or in a context that predicts that it is more likely to occur but not precisely when (5). The difference is that fear is related to the presence, or imminent presence, of the aversive stimulus, while anxiety is considered the more protracted state produced by a sustained expectation that the aversive event is likely to occur. Using this distinction, studies in rodents suggest that fear and anxiety are mediated by separate brain areas (5,11,12). Specifically, phasic (fear) responses are blocked by lesions or pharmacological blockade of the central nucleus of the amygdala, whereas sustained (anxiety) responses are blocked by interference with the bed nucleus of the stria terminalis (BNST) (5).

The translatability of this approach is a major advantage because it allows us to develop convincingly similar paradigms for humans, where neuroimaging has drawn on the same model: that fear arises from the imminence of an unpleasant event, while anxiety comes from being in a context when an unpleasant event will occur but with uncertain timing and perhaps not imminently. Findings have been consistent with the animal work, showing amygdala activation in immediate threat conditions and BNST activation in a threatening context (13–16). This apparently clear distinction supports models in which the amygdala (specifically the central nucleus; central nucleus of the amygdala) is singularly responsible for generating fear responses, and the BNST for anxious responses (5), with corresponding implications for potential pharmacological treatments.

ABSTRACT

Fear and anxiety are largely seen as separate entities, a distinction that inspires and shapes basic and clinical research. Evidence for this distinction has a rich translational base and comes from physiological, behavioral, and neurobiological studies. However, there is a high degree of inconsistency and a number of fundamental limitations that lead us to question the validity of the distinction. We consider a range of studies examining specifically whether and how the distinction may manifest at the neural, physiological, and behavioral levels, and we highlight a number of inconsistencies that call the distinction into question. We go on to critically examine assumptions in approaches to the fear-anxiety distinction and consider the implications that these assumptions may have in weighing evidence for and against the distinction. Acknowledging the contention over whether emotion research in animals is easily translatable to subjective experience in humans, we conclude that although the distinction between fear and anxiety has proved useful and informative, there are a number of reasons for recognizing that it is an oversimplification and that future progress may be guided, but should not be limited, by it.

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Additional support has emerged from clinical studies in which patients with fear/anxiety disorders demonstrate altered BNST and amygdala responses to threat. For example, patients with posttraumatic stress disorder (PTSD) and GAD, compared with healthy control subjects, demonstrate increased amygdala activity at the onset of threat anticipation and sustained BNST activation afterward (17,18). In addition, social anxiety is associated with lower BNST-amygdala connectivity during unpredictable threat cues (19) as well as amygdala hyperactivation during the initial stages of an anxiety-provoking event (20). Notably, though, BNST activity is unaffected by social anxiety (20), contradicting a direct mapping from an amygdala-BNST dissociation to the fear-anxiety distinction. Apart from concerns, discussed below, over how well clinical states of fear/anxiety are modeled by acute stress inductions in healthy participants, support at the neural level for the distinction has been questioned (21). Several human studies show BNST activation in response to immediate threat stimuli (22–25), while others report amygdala activation in response to uncertain threat anticipation (25–27), and a recent meta-analysis did not support the amygdala-BNST dissociation (28). Indeed, the robustness of the distinction in rodents has also recently been questioned (21).

Additional evidence that both amygdala and BNST are responsive to both predictable and unpredictable threats (28–31), as well as the fact that one well-powered (n = 99) study elicited no regional activation differences (30), further calls into question this overall claim for a neural distinction between fear and anxiety.

### PHYSIOLOGY

Cardiac, respiratory, and other physiological changes have long been recognized as markers for emotional states—both...
as causes and consequences, with growing research into the subjective experiences of these phenomena and how they may be modified therapeutically (32,33) (Table 2). However, use of these markers to identify specific emotional states [e.g., (34)] is greatly limited, even in differentiating basic emotions, let alone closely related states such as fear and anxiety. Here, we focus on research examining whether patterns of physiological response differ across disorders characterized by fear from those characterized by anxiety.

One experimental approach to examining physiological reactivity to manipulations of fear and/or anxiety is the no-shock, predictable-shock, unpredictable-shock (NPU) task, which has been applied in anxiety disorders (35). Participants’ physiological responses are measured in three different conditions: 1) no aversive stimulus, 2) predictable aversive stimulus (fear), and 3) unpredictable aversive stimulus (anxiety). Using eyeblink response to startle probes (such as short blasts of white noise) presented during each phase (35), it is possible to measure the fear-potentiated startle (i.e., eyeblink magnitude in condition 2) and the anxiety-potentiated startle (eyeblink in condition 3).

When applied in differing clinical groups, this task enables us indirectly to examine anxiety-specific and fear-specific reactivity. A clear prediction would be that disorders characterized predominantly by fear (e.g., phobias; PTSD) should be distinct from those characterized by anxiety (e.g., GAD). While some distinctions do indeed emerge, the patterns are not straightforward. For example, patients with PTSD and GAD show similar fear-potentiated startle, but those with PTSD show elevated anxiety-potentiated startle compared with both patients with GAD and control subjects (36). Patients with panic disorder also show elevated anxiety-potentiated startle (37), while social anxiety is associated with elevated fear-potentiated startle (38). Overall, therefore, although these studies present intriguing findings, they do not support any simple idea that disorders can be divided, on the basis of physiological responses, into those characterized by anxious-misery and those characterized by fear. GAD, a disorder of anxiety as opposed to fear, does not show anxiety-potentiated startle in either study [although it is near significance in (36)]. Panic disorder, which has been categorized as a disorder of fear (2,3), shows increased anxiety-potentiated but not fear-potentiated startle.

Lang et al. (4) comprehensively studied physiological fear responses across anxiety disorders. Participants were asked to imagine various threatening scenarios to induce feelings of fear. Building on their previous work demonstrating differential physiological response profiles (39,40), they divided participants into quintiles representing a continuum from physiological hyperreactivity to hyporeactivity in terms of a composite of heart rate and startle reflex. Most patients in the hyporeactor quintile were those with principal anxious-misery disorders, and most patients in the hyperreactivity quintile were diagnosed with circumscribed fear disorders. Overall, therefore, and in contrast to the NPU paradigm, these imagery-based studies do demonstrate different physiological reactivity across fear and anxiety disorders. However, the picture remains very complex. While Lang et al. (4) show elevated fear-based responses in disorders predominantly characterized by fear, there was no formal comparison of differences between fear and anxiety, and, moreover, comparable work using anxiety probes is not associated with elevated responses in patients with anxiety conditions (37,38). It may be, as Lang et al. suggest, that at the physiological level, fear and anxiety dissociate not according to their responses to fear- and anxiety-inducing manipulations, respectively, but rather in terms of relative hypo-(anxiety) and hyper-(fear) reactivity. However, this observation was based on those small subsets of patients who showed a predominance of fear or anxiety while the majority of patients occupied a middle ground, showing mixtures of fear and anxiety and intermediate levels of reactivity. Even for the extremes, 20% of patients within the first and fifth quintiles showed different patterns of fear/anxiety symptoms from the prevailing ones. Therefore, one cannot conclude that patients with fear disorders can be

Table 2. Summary of Studies Providing Evidence For or Against the Physiological Distinction Between Fear and Anxiety

| Study            | Evidence For/Against Fear-Anxiety Distinction | Human/Animal | Comments                                                                                                                      |
|------------------|----------------------------------------------|--------------|------------------------------------------------------------------------------------------------------------------------------|
| Lang et al. (4)  | For                                          | Human        | Difference in physiological reactivity across fear and anxiety disorders (although on a spectrum)                           |
| Grillon et al. (36) | For                                      | Human        | Difference in physiological reactivity in GAD and PTSD in predictable/unpredictable-threat conditions compared with healthy control subjects |
| Grillon et al. (37) | For                                      | Human        | Patients with panic disorder show greater anxiety-potentiated startle but not fear-potentiated startle compared with control subjects |
| Grillon et al. (38) | For                                      | Human        | History of panic attacks associated with hypersensitivity to unpredictable threat (anxiety); SAD associated with hypersensitivity to predictable threat (fear) |
| McTeague and Lang (40) | For                                      | Human        | Difference in physiological reactivity across anxiety disorders (although spectrum)                                           |

GAD, generalized anxiety disorder; PTSD, posttraumatic stress disorder; SAD, social anxiety disorder.
clearly differentiated from those with anxiety disorders based on their physiological responses.

**BEHAVIOR**

Observable behaviors offer clues to underlying emotional states and have formed a key component of rodent research (41) (Table 3). The Mouse Defence Test Battery (MDTB) examines behavioral responses to threat, identifying five different defensive responses: defensive threat and attack, flight, freezing, and risk assessment (42), with these behaviors depending on the context, proximity, and ambiguity of the threat. In unambiguous threat, animals preferentially freeze or (at sufficiently close proximity) use defensive threat or attack. Risk assessment behavior is observed when the threat is ambiguous or unlocalized, perhaps reflecting information gathering by the threatened animal (42,43). Risk assessment behaviors were thus proposed to model anxiety, whereas other defensive behaviors, particularly flight, may model fear (42). This distinction was supported by selective modulation by different pharmacological agents—benzodiazepines and serotonin receptor ligands led to reductions in risk assessment behaviors, whereas known panicogenic agents (yohimbine) selectively increased flight activity, and chronic administration of anxiolytic drugs (alprazolam, imipramine, fluoxetine) reduced flight (42,44). These findings suggest that in rodent models, fear and anxiety may be characterized by different observable behaviors that demonstrate distinct responses to pharmacological interventions.

Attempts have been made to translate the findings from the MDTB into human behavioral studies. One method involves the use of mental imagery, in which participants are asked to imagine various threat scenarios and indicate from a list of possibilities how they would respond. The scenarios are designed to vary on the same dimensions as the MDTB—namely, the magnitude, ambiguity, and distance of the threat, as well as the option for escape and ability to hide (45). Initial studies demonstrated that ambiguous situations clearly led to more risk assessment behavior in both men and women (45), which, as described above, has been hypothesized as a core behavioral feature of anxiety (43). Other responses to the threatening scenarios indicated differences in behavioral responses between men and women, with women tending to assess the scenarios as more dangerous and endorse fewer defensive attack responses (45). These findings have been replicated (46,47) and linked to measures of state and trait anxiety (48). Interestingly, responses of males with social anxiety disorder in this task were much closer to those of females with social anxiety disorder than those of males in the control group were to those of females in the control group—indicating that social anxiety disorder involves heightened levels of defense responses (43,49).

These studies demonstrate the role of ambiguity in dictating the behavioral reaction to threatening situations, with risk assessment behavior being preferred in ambiguously threatening situations and other defensive behaviors taking the fore in explicitly threatening situations (42,45). It highlights that a comprehensive conceptualization of fear and anxiety should relate not just to the contexts and stimuli but to the information available to the agent and, critically, to their ability to process it and to compute levels of uncertainty to guide decision making (50).

The Joystick Operated Runway Task (JORT)—a simplified equivalent of MDTB—aims to disentangle fear and anxiety behaviors in humans (51). Participants (represented by a green dot) either use a joystick to move away from a threatening agent (a red dot) presented on a virtual runway or must oscillate between two threatening agents (two red dots with the participant’s green dot located in between). The pressure

| Study                  | Evidence For/Against Fear-Anxiety Distinction | Human/Animal | Comments                                                                 |
|------------------------|-----------------------------------------------|--------------|---------------------------------------------------------------------------|
| Blanchard et al. (42)  | For                                           | Animal (rodent) | Different observable behaviors depending on proximity of predator, sensitive to pharmacological agents |
| Blanchard et al. (44)  | For                                           | Animal (rodent) | –                                                                         |
| Blanchard et al. (45)  | For                                           | Human         | Imagery study                                                            |
| Perkins et al. (46)    | For                                           | Human         | –                                                                         |
| Perkins and Corr (48)  | For                                           | Human         | –                                                                         |
| Mesquita et al. (49)   | For                                           | Human         | Patients with SAD report different behavioral responses to threat scenarios |
| Perkins et al. (51)    | For                                           | Human         | Lorazepam reduced defensive behavior during anxiety-related approach but not departure from threat (fear); citalopram did not affect either |
| Perkins et al. (52)    | Against                                      | Human         | Lorazepam has a dose-dependent effect on threat avoidance behavior, not always in line with rodent research |
| Lippold et al. (53)    | For                                           | Human         | Lorazepam has dose-dependent effect on risk assessment but no effect on fear |
| Perkins et al. (54)    | For                                           | Human         | BNC2210 reduces flight intensity but not risk-assessment intensity          |

SAD, social anxiety disorder.
placed on the joystick in the former condition is assumed to be an index of fear—the equivalent of a mouse’s flight velocity away from a predator—whereas the oscillations between the two threatening agents in the latter condition are used as an index of anxiety—the equivalent to rodent approach-withdrawal oscillations when presented with a predator in an inescapable situation (44,51). The JORT has been used to examine the effects of pharmacological agents on human behavioral responses, with complex results. For example, an initial study found a main effect of lorazepam on anxiety but not on fear (51), while a follow-up study found no main effect of lorazepam on anxiety, but a main effect on fear (52). Subsequently, the same group found an effect of lorazepam on anxiety but at a lower dose (0.5 mg), while the previously effective dose (1 mg) did not differ from placebo (52). Moreover, there was conflicting evidence for the influence of personality traits on fear/anxiety behaviors, as measured by the JORT (53,54), making it, overall, difficult to draw any conclusions with respect to the fear-anxiety distinction.

Notwithstanding the inconsistencies, theories that frame the fear-anxiety spectrum as a range of ways in which the agent attempts to avoid, mitigate, or escape an aversive situation are conceptually important. One framework that shows promise in addressing the distinction categorizes responses according to whether they occur at the pre-encounter, postencounter, or circa-strike stages of confrontation with predatory danger. This predatory imminence theory (55,56) offers operationally defined constructs that can more formally be related to the antecedent or precipitating events and to the ensuing behavioral responses.

TREATMENT

Despite the ambiguities above, modeling fear and anxiety as separate experiences has proven useful in exploring potential treatments. Cued fear paradigms have clearly been useful in developing treatments for psychiatric disorders characterized by fear disorders (57) and have helped formulate mechanistic understandings of treatments effects. For example, considerations of how to counteract fear renewal can form the basis for optimizing the use of pharmacological intervention (57). Fear conditioning models may apply best where there is a clear conditioning event, however, such as in PTSD or some cases of social phobia.

Translational models are also integral in pharmacological treatment development. For example, citalopram has an effect on anxiety-potentiated but not on fear-potentiated startle in healthy control subjects using the NPU task (58), enabling informed speculation on the mechanisms of action of citalopram and related pharmacological agents.

MODELING FEAR AND ANXIETY: UNDERLYING ASSUMPTIONS AND LIMITATIONS

In summary, while neurobiological, physiological, and behavioral evidence has been invoked to support the distinctions between fear and anxiety, the data are inconsistent and sometimes contradictory. We now consider more deeply the assumptions underlying the varying approaches and highlight certain practical and conceptual limitations. We consider these both in relation to the particular experimental designs and more broadly in terms of the difficulties of translating emotion research from rodents to humans.

Limitations of Tasks and Measures

Rodent work distinguishing fear-like and anxiety-like responses has driven much of the human research, but how well do the commonly used tasks translate across species? Here, we identify a number of challenges relating to how well tasks map across rodents and humans (face validity) and how similar the underlying constructs are in their application across species (construct validity). While the predictive validity, or how well the task is able to make predictions about future outcomes, such as response to treatment (59,60), may prove useful in establishing the success of these models, we focus primarily on the two former criteria.

In neuroimaging experiments, because of the setting and technical demands, some lack of face validity is almost always inevitable. For example, rodent studies examining anxiety-like responses have used relatively long time periods in their experimental design—e.g., BNST lesions do not affect conditioned fear responses unless they are of a very long duration (>8 minutes) (61). Yet studies in humans tend to use much shorter timescales (of the order of 30 seconds). Even virtual reality contextual fear conditioning paradigms, where it is plausible to have participants in the sustained fear condition for longer, may involve less than a minute of exposure (14,26). Some human studies have defined phasic and sustained fear as different time periods in the same anticipatory anxiety condition. These studies define phasic fear as the neural response on initial exposure (i.e., the first second) to the stimulus indicating that aversive experience will occur unpredictably. Sustained fear is then defined as the neural response over the entire course of viewing this stimulus (13,17,18,62). The stimulus presentation in this design appears to be treated as akin to a conditioned stimulus, although this is clearly dissimilar to fear conditioning paradigms. Such experimental nuances reflect creative attempts to surmount some of the restrictions imposed by the functional magnetic resonance imaging technique. However, inevitably, changes in task structure render them less comparable to animal work.

Task adaptations in physiological and behavioral studies impose comparable limitations. For example, imagery tasks (4,45), although they may arguably tap into similar underlying processes, should be mapped to animal work with caution. Such studies (45) rely on participants’ imagining how they would respond in a given situation (63) and are thus prone to biases that vary across individuals. Perhaps this could account for why males and females exhibit differing responses, with many males opting to predict that they would engage in fight behaviors. In addition, imagery studies lack the emotional immediacy that one envisions would be core to tasks used in rodent models to induce fear and anxiety.

While the JORT, as a human version of the rodent MDTB, has relatively high face validity (albeit the JORT uses virtual avatars), it is doubtful whether the underlying constructs are recapitulated. The MDTB indexes anxiety in terms of movement of a rodent toward and away from a predator (42). The JORT translates this by asking a participant to move their avatar (a green dot) between two hostile avatars (two red dots).
Are Fear and Anxiety Distinct?

precipitating and proceeding the participant’s avatar) and uses
the oscillations between the two as an index of anxiety (48).
While the movement is perhaps comparable in these para-
digms, the motivation cannot be—the participants are explicit-
ily instructed to do this, it is not a naturalistic, information-
seeking behavior and, consequently, the degree to which it
translates the animal task is questionable.

We must also acknowledge the constraints of our mea-
surement devices. Limitations in spatial and temporal resolu-
tion of functional magnetic resonance imaging are well known.
It is difficult to localize activation definitively to the BNST and,
although this can be mitigated [e.g., 64,65], we must remain
cautious about claims of BNST localization for standard
magnetic resonance field strength. Furthermore, conceptual
limitations should be borne in mind. Statements about such
fear-anxiety dissociations require evidence from direct com-
parisons between brain activations associated with tasks
eliciting anxiety and those eliciting fear, i.e., between tasks
tailing sustained levels of anticipation and those entailing
brief, phasic manipulations. Such a direct comparison is

It is not particularly difficult to interpret, calling into question how
useful functional magnetic resonance imaging alone is in
supporting a true double dissociation. Solutions have been
proposed (68), but we face a profound problem because a
direct comparison of phasic (fear) and context (anxiety) effects
is far from straightforward [though see (14)]. This ultimately
limits support for assertions of a fear-anxiety distinction based
on observations, say, that central nucleus of the amygdala is
involved in the phasic fear response but the BNST is not.

Whether examining emotional responses to tasks at the
neural, physiological, or behavioral levels, our assumption is
that comparable responses across rodents and humans sup-
port the comparability of the tasks. This is perhaps most
tenuous in terms of overt behavior. For example, in comparing
JORT and MDTB, we may observe superficially similar be-
haviors, but it is difficult, as we have discussed, to be confident
that these reflect similar underlying patterns of fear or anxiety.
While, for example, in rodent behavioral tests of anxiety,
certain behaviors are thought to map onto particular emotions,
such as risk assessment behaviors mapping onto anxiety, we
must be mindful that these behaviors are underpinned by
complex information processing and decision making (69).
As such, two agents may occupy different states (e.g., risk
assessment and defensive attack) because of differences in
the ways in which they have processed and used the uncer-
tainty of the situation rather than, necessarily, because of
differing patterns of fear and anxiety. We consider this limita-
tion in translatability below.

How Well Do Emotional Responses Translate?

Leaving aside the frequently inevitable discrepancies in task
design across species, a more fundamental question relates to
the degree to which the chosen task can elicit, reliably and
specifically, the targeted emotion. Even with near-identical
tasks, we must consider whether a particular task or context
 will have comparable effects in rodents and humans. In this
respect, it is noteworthy that physiological studies examining
fear and anxiety manipulations in healthy control subjects
produce no discernible differences (37,38), suggesting that
seemingly distinct task manipulations inspired by rodent work
do not necessarily produce distinct emotional responses when
applied in humans. A recent meta-analysis (28) comparing
neural responses in an unpredictable-threat condition with
responses found in patients with anxiety disorder suggests
that a task assumed to induce anxiety in healthy control sub-
jects actually produces neural activation patterns that more
convincingly overlap with those found in phobic (i.e., fear)

The central concern about the translatability of emotional
experiences across species has been carefully explored in
relation to fear (70,71), with the suggestion that the term, as
commonly used to imply a psychological state, is problematic
when applied to animals (although it remains reasonable to
refer to fear as a physiological construct or intervening variable
that conveniently links threat to an array of defensive behav-
iors). While it is possible and useful to identify neural circuitry
involved in detecting and reacting to threat, this circuitry will
only partially overlap with that giving rise to the conscious
experience that we typically refer to as fear. As such, for animal
work at least, a term such as fear conditioning should be
replaced, one possible replacement being threat conditioning
(70).

This argument for caution in translating such subjective
experiences from animals to humans also raises questions
about the value of work examining the fear-anxiety distinction
in animals. However, such work can be helpful if it can be
shown that clear distinctions emerge (in neurocircuitry, physi-
ology, and behavior) when rodents are exposed to particular
experimental manipulations, and that these manipulations can
be related to fear and anxiety, and dissociations therein, in
humans. While the distinctions, as we have shown, are by no
means clear, the fundamental transatlational value of the work is
by no means undermined if we restrict terms such as fear and
anxiety for use solely in humans. However, the concerns are
important and motivate an emphasis on human research in
analyzing the distinction. We return to this in our concluding
section.

Challenges in Applying Experimental Insights to the
Clinic

A further concern relates to how well a laboratory experience
translates to real clinical symptoms. This is, of course, appli-
cable to all experimental models but is perhaps especially
salient in the fear/anxiety literature, given the use of artificial
laboratory conditions and manipulations applied in rodents as
models for complex emotions and responses in humans. For
example, distinguishing fear and anxiety in rodents relies on
dissociating predictable and unpredictable threat. Generally,
the threat is definite in both conditions—the predictability is the
CONCLUSIONS AND FUTURE DIRECTIONS

It is difficult to escape the conclusion that the current distinction between fear and anxiety is an unreliable one. While it has been useful in guiding research and clinical work, the inconsistencies suggest that there is a need to reexamine the distinction and consider the importance of other aspects of the experience of anxiety, such as uncertainty and avoidance. Through a more comprehensive program of research taking into account the relevant but neglected aspects of the experiences, it may be possible to provide firmer foundations for enhancing our understanding of whether, and how well, these measures translate across species. In doing so, we may be in a better position to exploit technical advances such as a capacity to use high-field neuroimaging to elucidate functional roles of the subdivisions of BNST (12,74). Such technological advances are inherently limited by the validity of the models that underpin them, and while the fear-anxiety distinction has provided a powerful framework in their use so far, it seems that further progress will be hampered by an over-reliance on what is clearly an oversimplification. This is inevitable: models lay the foundations for basic understanding but must be tested, expanded, and where necessary, rejected and replaced. It seems inevitable that future research, particularly given the concerns about translational limitations described above (73), will require human studies that more directly address the rich subjective experience of these states. While work in rodents has inspired experimental manipulations (namely, certain vs. uncertain threat) to engender the different states, the actual conscious experiences, which are the sine qua non for the use of such terms, have been neglected. Given the current sophistication of neuroimaging techniques and the development of technology that allows us to present highly realistic and emotive experiences (75) with a high degree of experimental control over relatively sustained periods, a key part of developing our understanding of this question will surely lie in human studies involving extensive subjective assessments to complement the standard measures.

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ARTICLE INFORMATION

From the Department of Psychiatry (LD-W, PCF), University of Cambridge, Addenbrooke’s Hospital; Wellcome Trust MRC Institute of Metabolic Science (PCF) Cambridge Biomedical Campus, University of Cambridge; and Cambridgeshire and Peterborough NHS Foundation Trust (PCF), Cambridge, United Kingdom.

Address correspondence to Lucie Daniel-Watanabe, M.Sc., at ld589@cam.ac.uk.

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REFERENCES

1. Grillon C (2008): Models and mechanisms of anxiety: Evidence from startle studies. Psychopharmacology 199:421–437.
2. Krueger RF (1999): The structure of common mental disorders. Arch Gen Psychiatry 56:921–926.
3. Clark LA, Watson D (2006): Distress and fear disorders: An alternative empirically based taxonomy of the ‘mood’ and ‘anxiety’ disorders. Br J Psychiatry 189:481–483.
4. Lang PJ, McTeague LM, Bradley MM (2016): RDoC, DSM, and the reflex physiology of fear: A biodimensional analysis of the anxiety disorders spectrum. Psychophysiology 53:336–347.
5. Davis M, Walker DL, Miles L, Grillon C (2010): Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. Neuropsychopharmacology 35:105–135.
6. Insell T, Cuthbert B, Garvey M, Heinissen R, Pine DS, Quinn K, et al. (2010): Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. Am J Psychiatry 167:748–751.
7. LeDoux JE, Hofmann SG (2018): The subjective experience of emotion: A fearful view. Curr Opin Behav Sci 19:67–72.
8. Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B (2014): Maximizing exposure therapy: An inhibitory learning approach. Behav Res Ther 58:10–23.
9. Seligman ME (1970): On the generality of the laws of learning. Psychol Rev 77:406–418.
10. Seligman MEP (1971): Phobias and preparedness. Behav Ther 2:307–320.
11. Walker DL, Miles LA, Davis M (2009): Selective participation of the bed nucleus of the stria terminalis and CRF in sustained anxiety-like versus phasic fear-like responses. Prog Neuropsychopharmacol Biol Psychiatry 33:1291–1308.
12. Lebow MA, Chen A (2016): Overshadowed by the amygdala: The bed nucleus of the stria terminalis emerges as key to psychiatric disorders. Mol Psychiatry 21:450–463.
13. Herrmann MJ, Boehme S, Becker MPI, Tupak SV, Guhn A, Schmidt B, et al. (2016): Phasic and sustained brain responses in the amygdala
and the bed nucleus of the stria terminals during threat anticipation. Hum Brain Mapp 37:1091–1102.

14. Somerville LH, Wagner DD, Wig GS, Moran JM, Whalen PJ, Kelley WM (2013): Interactions between transient and sustained neural signals support the generation and regulation of anxious emotion. Cereb Cortex 23:49–60.

15. Alvarez RP, Chen G, Bodurka J, Kaplan R, Grillon C (2011): Phasic and sustained fear in humans elicits distinct patterns of brain activity. Neuroimage 55:389–400.

16. McMenamin BW, Langeslag SJE, Sirbu M, Padmola S, Pessaio L (2014): Network organization unfolds over time during periods of anticipatory anxiety. J Neurosci 34:11261–11273.

17. Buff C, Brinkmann L, Bruchmann M, Becker MPI, Tupak SV, Hermann MJ, Straube T (2017): Activity alterations in the bed nucleus of the stria terminals and amygdala during threat anticipation in generalized anxiety disorder. Soc Cogn Affect Neurosci 12:1766–1774.

18. Brinkmann L, Buff C, Neumeister P, Tupak SV, Becker MPI, Hermann MJ, Straube T (2017): Dissociation between amygdala and bed nucleus of the stria terminals during threat anticipation in female post-traumatic stress disorder patients. Hum Brain Mapp 38:2190–2205.

19. Clauss JA, Avery SN, Benning K, et al. (2019): From threat to fear: The neural organization of defensive fear. Neuron 99:1912–1924.

20. McTeague LM, Nitschke JB, Rabin S, Bonne O, Vythilingam M (2009): Increased anxiety during anticipation of unpredictable aversive stimuli in posttraumatic stress disorder but not in generalized anxiety disorder. Biol Psychiatry 66:47–53.

21. Choi JM, Padmola S, Pessoa L (2012): Impact of state anxiety on the processing: Functionally dissociable roles of the amygdala and bed nucleus of the stria terminals. J Cogn Neurosci 31:543–554.

22. Fox AS, Shackman AJ (2019): The central extended amygdala in fear and anxiety: Closing the gap between mechanistic and neuroimaging research. Neurosci Lett 693:58–67.

23. Choi JM, Padmola S, Pessoa L (2012): Impact of state anxiety on the interaction between threat monitoring and cognition. Neuroimage 59:1912–1923.

24. Grupe DW, Oathes DJ, Chang CM, et al. (2013): Social anxiety is associated with BNST response to unpredictability. Depress Anxiety 36:666–675.

25. Boehrme S, Ritter V, Telikow S, Stanger U, Strauss B, Milther WHR, Straube T (2014): Brain activation during anticipatory anxiety in social anxiety disorder. Soc Cogn Affect Neurosci 9:1413–1418.

26. Blanchard JJ, Vythilingam M (2009): From threat to fear: The neural organization of defensive fear. Neuron 59:1912–1924.

27. Brinkmann L, Buff C, Neumeister P, Tupak SV, Becker MPI, Hermann MJ, Straube T (2017): Dissociation between amygdala and bed nucleus of the stria terminals during threat anticipation in female post-traumatic stress disorder patients. Hum Brain Mapp 38:2190–2205.

28. Clauss JA, Avery SN, Benning K, et al. (2019): From threat to fear: The neural organization of defensive fear. Neuron 99:1912–1924.

29. Naaz F, Knight LK, Depue BE (2019): Explicit and ambiguous threat processing: Functionally dissociable roles of the amygdala and bed nucleus of the stria terminals. J Cogn Neurosci 31:543–554.

30. Hur J, Smith JF, DeYoung KA, Anderson AS, Kuang J, Kim HC, et al. (2020): Anxiety and the neurobiology of temporally uncertain threat anticipation. J Neurosci 40:7964–7984.

31. Siminski N, Böhme S, Zeller JBM, Becker MPI, Bruchmann M, Hofmann D, et al. (2021): BNST and amygdala activation to threat: Effects of temporal predictability and threat mode. Behav Brain Res 396:112883.

32. Paulus MP, Stein MB (2010): Interception in anxiety and depression. Brain Struct Funct 214:451–463.

33. Goessl VC, Curtiss JE, Hofmann SG (2017): The effect of heart rate variability biofeedback training on stress and anxiety: A meta-analysis. Psychol Med 47:2578–2586.

34. Levenson RW (2003): Autonomic specificity and emotion. In: Davidson KR, Scherer KR, Goldsmith HH, editors. Series in Affective Science. Handbook of Affective Sciences. Oxford: Oxford University Press, 212–224.

35. Schmitz A, Grillon C (2012): Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). Nat Protoc 7:527–532.

36. Grillon C, Pine DS, Lissek S, Rabin S, Bonne O, Vythilingam M (2009): Increased anxiety during anticipation of unpredictable aversive stimuli in posttraumatic stress disorder but not in generalized anxiety disorder. Biol Psychiatry 66:47–53.

37. Grillon C, Lissek S, Rabin S, McDowell D, Dvir S, Pine DS (2008): Increased anxiety during anticipation of unpredictable but not predictable aversive stimuli as a psychophysiological marker of panic disorder. Am J Psychiatry 165:898–904.

38. Grillon C, O’Connell K, Lieberman L, Alvarez G, Geraci M, Pine DS, Ernst M (2017): Distinct responses to predictable and unpredictable threat in anxiety pathologies: Effect of panic attack. Biol Psychiatry Cogn Neurosci Neuroimaging 2:575–581.

39. Lang PJ, McTeague LM, Bradley MM (2014): Pathological anxiety and function/dysfunction in the brain’s fear/defense circuitry. Restor Neurol Neurosci 32:63–77.

40. McTeague LM, Lang PJ (2012): The anxiety spectrum and the reflex physiology of defense: From circumscribed fear to broad distress. Depress Anxiety 29:264–281.

41. Harro J (2018): Animals, anxiety, and anxiety disorders: How to measure anxiety in rodents and why. Behav Brain Res 352:81–93.

42. Blanchard DD, Griebel G, Blanchard RJ (2003): The Mouse Defense Test Battery: Pharmacological and behavioral assays for anxiety and panic. Eur J Pharmacol 463:97–116.

43. Blanchard CD (2017): Translating dynamic defense patterns from rodents to people. Neurosci Biobehav Rev 76:22–28.

44. Blanchard RJ, Griebel G, Henrie JA, Blanchard DD (1997): Differentiation of anxiolytic and anxiogenic drugs by effects on rat and mouse defense test batteries. Neurosci Biobehav Rev 21:783–789.

45. Blanchard CD, Hynd AL, Minke KA, Minemoto T, Blanchard RJ (2001): Human defensive behaviors to threat scenarios show parallels to fear- and anxiety-related defense patterns of non-human mammals. Neurosci Biobehav Rev 25:761–770.

46. Perkins AM, Cooper A, Abdelali M, Smillie LD, Corr PJ (2010): Personality and defensive reactions: Fear, trait anxiety, and threat magnification. J Pers 78:1071–1080.

47. Shuhama R, Del-Ben CM, Loureiro SR, Graeff FG (2007): Animal defense strategies and anxiety disorders. An Acad Bras Cienc 79:97–109.

48. Perkins AM, Corr PJ (2006): Reactions to threat and personality: Psychometric differentiation of intensity and direction dimensions of human defensive behaviour. Behav Brain Res 169:21–28.

49. Mesquita SCV, Shuhama R, Osorio FL, Croppa JAS, Loureiro SR, Landeira-Fernandez J, et al. (2011): The response of social anxiety disorder patients to threat scenarios differs from that of healthy controls. Braz J Med Biol Res 44:1261–1268.

50. Huang H, Thompson W, Paulus MP (2017): Computational dysfunctions in anxiety: Failure to differentiate signal from noise. Biol Psychiatry 82:440–446.

51. Perkins AM, Ettinger U, Davis R, Foster R, Williams SCR, Corr PJ (2010): Effects of lorazepam and citalopram on human defensive reactions: Ethopharmacological differentiation of fear and anxiety. J Pers 78:1071–1080.

52. Perkins AM, Ettinger U, Davis R, Foster R, Williams SCR, Corr PJ (2010): Effects of lorazepam and citalopram on human defensive reactions: Ethopharmacological differentiation of fear and anxiety. J Pers 78:1071–1080.

53. Lippold JV, Ettinger U, Hurlemann R, Corr PJ, Reuter M, Perkins AM (2020): Differentiating anxiety from fear: An experimental-pharmacological approach. Personal Neurosci 3:e246.

54. Lippold JV, Ettinger U, Hurlemann R, Corr PJ, Reuter M, Perkins AM (2020): Differentiating anxiety from fear: An experimental-pharmacological approach. Personal Neurosci 3:e246.

55. Perkins AM, Ettinger U, Wolfe K, Schmechter A, Schraette A, Morrison PD, et al. (2013): Advancing the defensive explanation for anxiety disorders: Lorazepam effects on human defense are systematically modulated by personality and threat-type. Transl Psychiatry 3:e246.

56. Persun A, Faselov S (2015): Neurobehavioral perspectives on the distinction between fear and anxiety. Learn Mem 22:417–425.
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56. Mobbs D, Headley DB, Ding W, Dayan P (2020): Space, time, and fear: Survival computations along defensive circuits. Trends Cogn Sci 24:228–241.

57. Carpenter JK, Pinaire M, Hofmann SG (2019): From extinction learning to anxiety treatment: Mind the gap. Brain Sci 9:164.

58. Grillon C, Chavis C, Covington MF, Pine DS (2009): Two-week treatment with the selective serotonin reuptake inhibitor citalopram reduces contextual anxiety but not cued fear in healthy volunteers: A fear-potentiated startle study. Neuropsychopharmacology 34:964–971.

59. Pike AC, Lowther M, Robinson OJ (2021): The importance of common currency tasks in translational psychiatry. Curr Behav Neurosci Rep 8:1–10.

60. Grillon C, Ernst M (2020): A way forward for anxiolytic drug development: Testing candidate anxiolytics with anxiety-potentiated startle in healthy humans. Neurosci Biobehav Rev 119:348–354.

61. Gungor NZ, Paré D (2016): Functional heterogeneity in the bed nucleus of the stria terminalis. J Neurosci 36:8038–8049.

62. Brinkmann L, Buff C, Feldker K, Tupak SV, Becker MPI, Hermann MJ, Straube T (2017): Distinct phasic and sustained brain responses and connectivity of amygdala and bed nucleus of the stria terminals during threat anticipation in panic disorder. Psychol Med 47:2675–2688.

63. Sharot T (2011): The optimism bias. Curr Biol 21:R941–R945.

64. Miller MI, Beg MF, Cenfloglu C, Stark C (2005): Increasing the power of functional maps of the medial temporal lobe by using large deformation diffeomorphic metric mapping. Proc Natl Acad Sci U S A 102:9685–9690.

65. Tyszka JM, Pauli WM (2016): In vivo delineation of subdivisions of the human amygdaloid complex in a high-resolution group template. Hum Brain Mapp 37:3979–3998.

66. Henson R (2005): What can functional neuroimaging tell the experimental psychologist? Q J Exp Psychol A 58:193–233.

67. Nieuwenhuis S, Forstmann BU, Wagenmakers EJ (2011): Erroneous analyses of interactions in neuroscience: A problem of significance. Nat Neurosci 14:1105–1107.

68. de Hollander G, Wagenmakers EJ, Waldorp L, Forstmann B (2014): An antidote to the imager’s fallacy, or how to identify brain areas that are in limbo. PLoS One 9:e115700.

69. Raymond JG, Steele JD, Seriès P (2017): Modeling trait anxiety: From computational processes to personality. Front Psychiatry 8:1.

70. LeDoux JE (2014): Coming to terms with fear. Proc Natl Acad Sci U S A 111:2871–2878.

71. LeDoux JE, Pine DS (2016): Using neuroscience to help understand fear and anxiety: A two-system framework. Am J Psychiatry 173:1083–1093.

72. Tyrer P, Baldwin D (2006): Generalised anxiety disorder. Lancet 368:2156–2166.

73. Teufel C, Fletcher PC (2016): The promises and pitfalls of applying computational models to neurological and psychiatric disorders. Brain 139:2600–2608.

74. Robinson OJ, Pike AC, Cornwell B, Grillon C (2019): The translational neural circuitry of anxiety. J Neurol Neurosurg Psychiatry 90:1353–1360.

75. Yilmaz Balban M, Cafaro E, Saue-Fletcher L, Washington MJ, Bijanzadeh M, Lee AM, et al. (2021): Human responses to visually evoked threat. Curr Biol 31:601–612.e3.