Review

Biological Psychiatry: GOS

Are Fear and Anxiety Truly Distinct?

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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.

https://doi.org/10.1016/j.bpsgos.2021.09.006

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.

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ISSN: 2667-1743

Table 1. Summary of Studies Providing Evidence For or Against the Neurobiological Distinction Between Fear and Anxiety

Study	Evidence For/Against Fear-Anxiety Distinction	Human/Animal	Comments
Davis *et al.* (5)	For	Animal (rodent)	–
Herrmann *et al.* (13)	For	Human	–
Somerville *et al.* (14)	For	Human	–
Alvarez *et al.* (15)	For	Human	–
McMenamin *et al.* (16)	For	Human	–
Buff *et al.* (17)	For	Human	GAD vs. HC subject study
Brinkmann *et al.* (18)	For	Human	PTSD vs. HC subject study
Clauss *et al.* (19)	For	Human	Examining participants across the social anxiety spectrum
Boehme *et al.* (20)	Against	Human	Did not explicitly examine fear vs. anxiety—instead, found no BNST activation difference between SAD and control subjects in anxious anticipation
Choi *et al.* (22)	Against	Human	Did not explicitly examine fear vs. anxiety—found BNST activation in response to immediate threat stimuli
Grupe *et al.* (24)	Against	Human	BNST phasic activation to brief threat
Mobbs *et al.* (25)	Against	Human	Showed decrease in forebrain activation in circa strike vs. postencounter but did not explicitly examine BNST
Andreatta *et al.* (26)	Against	Human	Sustained amygdala activation in uncertain threat context
Lieberman *et al.* (27)	Against	Human	Amygdala activation during unpredictable threat condition in NPU task
Chavanne and Robinson (28)	Against	Human	Meta-analysis showing significant overlap between anxiety inductions and phobic disorders
Naaz *et al.* (29)	Against	Human	Both amygdala and BNST show heightened response to explicit and ambiguous threat
Hur *et al.* (30)	Against	Human	Amygdala and BNST show indistinguishable responses to temporally uncertain and certain threat anticipation
Siminski *et al.* (31)	Against	Human	Both BNST and CM show activation in response to predictable and unpredictable threat

BNST, bed nucleus of the stria terminalis; CM, centromedial amygdala; GAD, generalized anxiety disorder; HC, healthy control; NPU, no-shock, predictable-shock, unpredictable-shock; PTSD, posttraumatic stress disorder; SAD, social anxiety disorder.

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)[1]. 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

[1]This meta-analysis, however, was constrained to full-brain analyses and may have excluded studies examining smaller regions such as the BNST.

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 (38)]. 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 flee. However, if this is impossible, they 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 panicolytic 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

Table 3. Summary of Studies Providing Evidence For or Against the Behavioral Distinction Between Fear and Anxiety

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	BNC210 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 envisages 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

preceding 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 paradigms, the motivation cannot be—the participants are explicitly 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 measurement devices. Limitations in spatial and temporal resolution 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 comparisons between brain activations associated with tasks eliciting anxiety and those eliciting fear, i.e., between tasks entailing sustained levels of anticipation and those entailing brief, phasic manipulations. Such a direct comparison is crucial (66,67) and allows us to avoid what has been referred to as the imager's fallacy (66), wherein separately analyzed patterns of response (e.g., fear compared with neutral and anxiety compared with neutral conditions) are taken to support a fear versus anxiety dissociation in the absence of the necessary direct comparison. Given the inherent timescale differences in phasic versus sustained task manipulations, such a direct comparison is 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 support 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 behaviors, 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 uncertainty of the situation rather than, necessarily, because of differing patterns of fear and anxiety. We consider this limitation 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 subjects actually produces neural activation patterns that more convincingly overlap with those found in phobic (i.e., fear) disorders (28). This raises the possibility that the commonly used anxiety manipulation actually produces feelings more akin to fear.

This 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 behaviors). 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, physiology, 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 translational 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, applicable 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

only manipulation. Contrast this with a clinical situation such as GAD, in which there is continuous worry but no specific threat (69,72), or other typical clinical experiences in which the threat—a feared situation or experience—may be entirely uncertain as well as unpredictable. Moreover, in real life, a person can engage in strenuous avoidance behaviors that may promise to keep the threat at bay entirely. Of course, all models are simplifications and nevertheless remain useful, but their optimal use depends on understanding, and bearing in mind throughout, precisely what our task seeks to model, and, importantly, what it leaves out (73). Acknowledging this may be crucial, furthermore, in helping to understand findings that do not easily accord with expectations, such as those of (28) showing overlap between specific phobias and anxiety-induction experiments.

Ultimately, the convenience and simplicity of the fear-anxiety distinction in basic work should not obscure the fact that many anxiety disorders will involve both acute experiences of fear and more diffuse experiences of anxiety. For example, specific phobia, a primary fear disorder, will also involve experiences of anxiety concerning potentially encountering the feared stimulus. The distinction between the two emotions remains useful, but we should avoid treating models of a single emotion as sufficient models of a psychiatric disorder, especially when differentiating between fear and anxiety, as we should not expect them to occur entirely independently of one another.

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.

ACKNOWLEDGMENTS AND DISCLOSURES

This study was supported by a Wellcome Trust Investigator Award (Grant No. 206368/Z/17/Z [to PCF]) and by the Bernard Wolfe Health Neuroscience fund (to PCF).

PCF has received consultancy fees from GlaxoSmithKline in the past. PCF has received consultancy payments from Ninja Theory Ltd. (video game company). LD-W and PCF have received support for a Ph.D. studentship from Ninja Theory Ltd. LD-W's Ph.D. studies are funded by a donation to the University of Cambridge from Ninja Theory Ltd.

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Received Jun 24, 2021; revised Sep 17, 2021; accepted Sep 24, 2021.

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