In Search of the Behavioral and Neural Basis for Differentiating Fear and Anxiety

To the Editor:

In a recent analysis of the status of a distinction between fear and anxiety, Daniel-Watanabe and Fletcher (1) appear to accept that there are differences in the stimuli and situations (e.g., focus on threat certainty) that elicit these response patterns, and in the behaviors that they involve. However, they also specify mutually exclusive regional brain activity patterns for the two, with fear involving the central nucleus of the amygdala (CeA) and not the bed nucleus of the stria terminalis (BNST), while anxiety involves the opposite: BNST but not CeA activity changes. Thus, behaviors meeting the situational/behavioral criteria for fear without changes in the CeA or those associated with anxiety but not involving the BNST—as well as relevant behaviors involving both brain areas—are taken as evidence against a distinction between the two patterns. In support of this view, their Table 1 ("Summary of Studies Providing Evidence For or Against the Neurobiological Distinction Between Fear and Anxiety") lists 18 articles, of which 8 support and 10 oppose this distinction.

There are several potential problems with this approach. First, all 10 of the against studies listed in Table 1 utilized human subjects and measured CeA and/or BNST responses using functional magnetic resonance imaging (fMRI) based on fluctuations in regional blood flow. Although fMRI resolution has greatly improved in recent years [e.g., (2)] it is unclear whether most, or indeed any, of the studies reported in Table 1 of Daniel-Watanabe and Fletcher (1) have enough resolution to differentiate the CeA: in humans, this structure is very small, representing only a minute percentage of amygdala volume, estimated at about 3% (2). Similarly, the BNST is a small and exceedingly complex structure (3), only representing a small portion of the area measured as BNST in some fMRI studies, e.g., see Figure 3 in Grupe et al. (4). This combination of the very small size of either the CeA or BNST and the relatively low spatial resolution of standard fMRI presents a clear problem in using CeA or BNST activation as a focal criterion in human fMRI studies.

Moreover, in order to provide evidence against a fear/anxiety distinction on the basis of this neurobiological difference, it is necessary that the studies examined involve paradigms that are clearly and specifically related to either fear or anxiety. It is by no means obvious that this is the case in Table 1 (1): specifically, the paradigms used by both Lieberman et al. (5) and Hur et al. (2) are described as involving unpredictable or uncertain threats, although both included 100% shock reinforcement per trial. The element of uncertainty was variability in timing of the shock relative to the conditioned stimulus. Thus, Hur et al. (2) utilized an 18.75-second interval between conditioned stimulus and unconditioned stimulus for the temporally certain group, whereas the temporally uncertain group received shock with a mean conditioned stimulus–unconditioned stimulus latency of 18.75 seconds and a range between 8.75 and 30 seconds. While this does, indeed, represent some degree of temporal uncertainty, it is questionable if it constitutes any real uncertainty of shock on a given trial.

Finally, and perhaps most importantly, there is a problem with the overall strategy of using CeA or BNST involvement as the focal criterion for differentiating fear from anxiety. Specifically, the idea that the CeA is ubiquitously involved in generating fear responses should be viewed with caution. The CeA does appear to participate in fear responses in shock-based fear conditioning, but it does not do so in fear responses to predatory threats (6): in addition, CeA lesions did not affect either innate or contextual responses to predator exposure (7). Therefore, a view of the CeA as being necessary for generating fear responses appears to be simply incorrect.

These caveats, here only briefly elaborated, provide a rationale for disagreement with the conclusion of Daniel-Watanabe and Fletcher (1) that "the current distinction between fear and anxiety is an unreliable one." Viewed in the context of systematic criteria for differentiation of behaviors, such as Tinbergen's four questions (8), the fear–anxiety distinction appears to be holding up pretty well for a hypothesis at the relatively recent stage of development of its current formulation. The relationships of the two behavior patterns to the various situational and threat stimulus characteristics that shape them, the behaviors themselves, and their differential chances of success in these threatening situational/stimulus situations have been repeatedly documented in both laboratory and field studies, clearly outlining different functions for fear and anxiety [e.g., (9)].

The seemingly problematic area in this distinction is the involvement of the CeA in fear and of the BNST in anxiety. Here, several conceptual/analytic/measurement problems emerge. In addition, much animal work concerns evolutionary threats such as exposure to predators, in which the CeA does not appear to be involved (6,7), raising an additional question as to the advisability of using CeA and BNST activation as crucial indices of a fear–anxiety distinction.

Even aside from consideration of these problem areas—some of which, such as the resolution issues in human imaging, are showing steady improvement—we are not suggesting that the fear–anxiety distinction is a done deal. Much remains to be learned about it, its neurobiology, and its involvement in psychopathology. However, to evaluate the distinction as unreliable—substantially on the basis of studies using frequently insufficient measurement techniques and possibly questionable logic—may represent an interesting example of throwing out the baby with the bath water.

D. Caroline Blanchard
Newton S. Canteras

References

1. Daniel-Watanabe L, Fletcher PC (2022): Are fear and anxiety truly distinct? Biol Psychiatry Glob Open Sci 2:341–349.
2. 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 40:7949–7964.
3. Sherman ER, Thomas JJ, Cahill EN (2022): The bed nucleus of the stria terminalis in threat detection: Task choice and rodent experience. Emerg Top Life Sci 6:457–466.
4. Grupe DW, Oathes DJ, Nitschke JB (2013): Dissecting the anticipation of aversion reveals dissociable neural networks. Cereb Cortex 23:1874–1883.
5. Lieberman L, Gorka SM, Shankman SA, Phan KL (2017): Impact of panic on psychophysiological and neural reactivity to unpredictable threat in depression and anxiety. Clin Psychol Sci 5:52–63.
6. Gross CT, Canteras NS (2012): The many paths to fear. Nat Rev Neurosci 13:651–658.
7. Martinez RC, Carvalho-Netto EF, Ribeiro-Barbosa ER, Baldo MV, Canteras NS (2011): Amygdalar roles during exposure to a live predator and to a predator-associated context. Neuroscience 172:314–328.
8. Tinbergen N (1963): On aims and methods of ethology. Z Tierpsychol 20:410–433.
9. Blanchard DC, Griebel G, Pobbe R, Blanchard RJ (2011): Risk assessment as an evolved threat detection and analysis process. Neurosci Biobehav Rev 35:991–998.