Biological Psychiatry: GOS

Correspondence

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

To the Editor:

Blanchard and Canteras (1) express concerns about our recent suggestion (2) that the influential distinction between fear and anxiety, though it has provided a useful and informative framework, is based on unreliable evidence and should be considered an oversimplification. We thank them for raising a number of points and we respond here.

First, as they say, one part of our argument is that fear has been related to the central nucleus of the amygdala (CeA) while anxiety has been related to the bed nucleus of the stria terminalis, and the other part is that if the descriptive distinction is truly upheld at a neurobiological level, then we would expect a dissociation (preferably a double dissociation) between activity in these two regions under conditions deemed to provoke fear compared with those provoking anxiety. Blanchard and Canteras challenge this, suggesting that the small size of these two regions, coupled with the limited spatial resolution of functional magnetic resonance imaging (fMRI), may lead to type II error, i.e., a genuine mapping of fear to the CeA and of anxiety to the bed nucleus of the stria terminalis may be missed. They therefore caution against using such studies as evidence against the distinction. We endorse the need for caution but would qualify it with two observations. First, fMRI studies have often been taken to support the fear/anxiety distinction. Our purpose was to question this. Put simply, just as Blanchard and Canteras counsel that we should be wary of using fMRI to reject the distinction, we argue that its widespread use to support the distinction is not justified. Second, while type II error may account for the inconsistencies that we highlight, this would not explain why some fMRI studies show the opposite of what the standard model would predict, i.e., CeA activity in association with an anxiety-provoking manipulation and bed nucleus of the stria terminalis activity in association with fear. A broader question, of course, is whether functional neuroimaging can ever provide reliable evidence for or against the distinction. We believe that with, for example, optimized sequences for regionally focused studies, it can, but for the present, we believe that statements that it currently supports the fear/anxiety distinction are incorrect.

A second concern raised in their critique is that the association between CeA and fear is not universal and that different types of fear—such as shock-conditioned fear as opposed to predator fear—have different neural underpinnings, with CeA being important for the former but not for the latter. This is an important point, both in helping to explain the unreliability of findings when translating from animals to humans and, importantly, in reaffirming our conclusion that a fear/anxiety distinction is an oversimplification.

Third, Blanchard and Canteras also, very reasonably, raise the point that the experimental manipulations designed to be paradigmatic of fear and anxiety in humans should unequivocally and specifically produce actual fear and anxiety, respectively. They express doubts about whether they successfully do so. Our shared doubts are, we hope, clear in the extensive discussion that we devote to highlighting just how problematic it is to translate such tasks convincingly. We won't rehearse this discussion here but would add that, as with the fMRI research, we view the implications of this observation differently. Our contention in the article was that these very approximate translations of the tasks render dubious claims that they support the fear/anxiety distinction. While we would equally endorse Blanchard and Canteras' position that task limitations prevent us from rejecting the distinction, the prevailing view appears to be that the evidence supports it, and our concern was in challenging this view.

Finally, Blanchard and Canteras make the point that, when we get back to the principles of what constitute and differentiate behaviors by scrutinizing fear and anxiety within the frame of Tinbergen's four questions, the distinction appears to be well supported. We like the idea of re-examining the question in light of these questions. It seems to us that, as Blanchard and Canteras argue, the descriptions of fear and anxiety provide distinct and credible answers to Tinbergen's question of function insofar as anxiety can be seen as shaping behaviors that may assist in avoiding an undesired stimulus or event, while fear can drive responses appropriate to managing contact with this stimulus or event. The success of the distinction in addressing this functionality question is a point that is also well made by Domschke (3) in her thought-provoking commentary, in which she suggests that behavioral studies tend to support the distinction. However, if we examine another of Tinbergen's questions—relating to mechanistic underpinnings—we find it hard to see that a convincing distinction is supported by current evidence. Moreover, we are grateful to Domschke for highlighting an area that we omitted and that also relates to Tinbergen's questions: the genetic underpinnings. As she points out, the growing evidence for a shared genetic basis for the range of anxiety-related disorders does not support a clear distinction across all levels of inquiry.

Importantly, it is not a contradiction to acknowledge behavioral distinctions while finding that underlying mechanisms are shared or overlapping. We have suggested that, when the distinction is translated from animals to humans and from the lab to the clinical domain, and when it is scrutinized in terms of underlying mechanisms, rather than at a behavioral level, it proves to be only partially supported and, furthermore, overly simplistic. We do not reject the distinction captured by the existing model, but rather suggest that, in extending the model to humans and clinical situations, more refined models are needed. The purpose of our article was not to suggest that there is no distinction between fear and anxiety. Our intent was to highlight what we consider a paucity of plausible evidence for a distinction at levels of inquiry that relate more directly to clinical frameworks, such as the Research Domain Criteria. We hope that more careful consideration and experimental work can lead to more conclusive evidence either supporting or rejecting the distinction at the neurobiological level because

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this will have important implications for treatment formulation. We accept that the existing distinction can be useful, but we need to be clear in identifying the limits of where and how it might be used. As we have highlighted previously (4), incorrect models may serve a purpose, but incorrect application of models will ultimately mislead.

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