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Fear, anxiety and the functional architecture of the human central extended amygdala

Fear, anxiety and other threat-elicited states help to protect organisms from harm; but when expressed too intensely or pervasively, they can be crippling[1]. Fear and anxiety disorders are common, and existing treatments are inconsistently effective, underscoring the urgency of clarifying the underlying neurobiology[1]. We were excited to read Tseng and colleagues' Review, which highlights evidence that fear and anxiety reflect bi-directional interactions between threat-sensitive brain circuits and the endocrine, immune, gastrointestinal and reproductive systems (Tseng, Y.-T., Schaefke, B., Wei, P. & Wang, L. Defensive responses: behaviour, the brain and the body. *Nat. Rev. Neurosci.* https://doi.org/10.1038/s41583-023-00736-3; 2023)[2].

Although there is much to like about their Review, it mischaracterizes our current understanding of the functional architecture of the central extended amygdala (EAc) — a macrocircuit encompassing the central nucleus of the amygdala (Ce) and bed nucleus of the stria terminalis (BST) — and omits key evidence from human research. This omission is important. Fear and anxiety disorders are largely diagnosed on the basis of subjective symptoms, and human studies are essential for understanding the neural systems that support fearful and anxious feelings and for identifying the features of animal models that are most relevant to human disease[1].

There is consensus that the EAc plays a critical role in assembling fear and anxiety in response to a broad spectrum of threats and contributes to the development of emotional illness[2–6]. Yet confusion persists about the respective contributions of its major subdivisions[7,8], exacerbated by inconsistent and imprecise terminology[1,9]. Drawing on rodent perturbation studies, Tseng and colleagues articulate a 'single-dissociation' model,

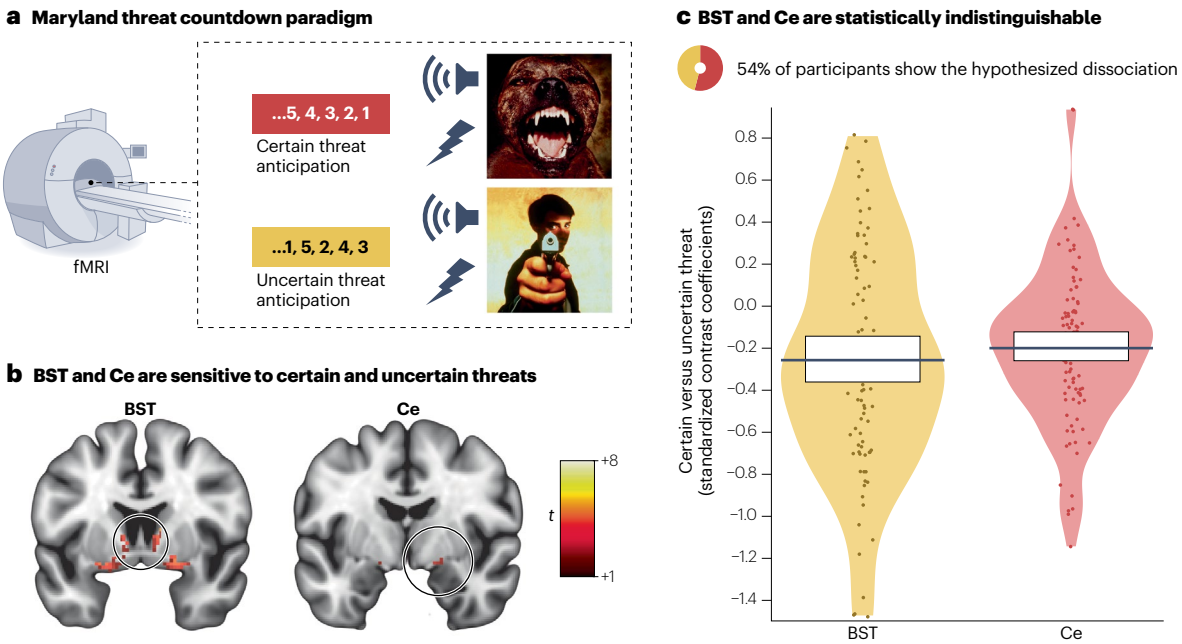

Fig. 1 | BST and Ce show similar responses to certain- and uncertain-threat anticipation in humans. a, The Maryland Threat Countdown is an fMRI-optimized threat-anticipation paradigm adapted from assays previously validated in rodents and humans[8]. On certain-threat trials, participants saw a descending stream of integers ('countdown') for 18.75 s. To ensure robust fear and anxiety, this anticipatory epoch terminated with a noxious electric shock, unpleasant photograph and thematically related audio clip. Uncertain-threat trials were similar, but the integer stream was randomized and presented for an unsignalled and variable duration (8.75–30.00 s; mean, 18.75 s). Here, participants knew that something aversive was going to occur, but had no way of knowing precisely when. **b**, A minimum-conjunction test was used to identify regions that were significantly activated by both certain- and uncertain-threat anticipation. The results reveal co-localization in the BST and Ce[8]. **c**, In a head-to-head comparison, regional differences in reactivity to certain- versus uncertain-threat anticipation were numerically small and nonsignificant, contrary to single- and double-dissociation models. While it is impossible to demonstrate that the true difference is zero, a formal test of statistical equivalence (TOST) was significant[8]. The ring plot depicts the percentage of participants showing the single dissociation anticipated by Tseng and colleagues' conceptual model (BST: certain < uncertain; Ce: certain ≈ uncertain threat). BST, bed nucleus of the stria terminalis; Ce, central nucleus of the amygdala; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; *t*, Student's *t*-test; TOST, two one-sided tests. Panels **b** and **c** adapted from ref. 8, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

positing that the Ce and BST are both involved in orchestrating defensive responses to uncertain, distal threats (which some equate with 'anxiety') (claim 1), whereas the Ce alone triggers responses to more certain and immediate dangers (which some equate with 'fear') (claim 2).

We concur with claim 1, which dovetails with human and animal evidence, and represents an important advance over earlier 'double-dissociation' models, which implied that the amygdala mediates 'fear', whereas the BST mediates 'anxiety'[3,5].

We take issue with claim 2. In fact, rodent research demonstrates that the BST strengthens responses to Pavlovian threat cues (the prototypical laboratory probe of certain and immediate threat or 'fear'), mediates fluoxetine-induced enhancement of cued fear recall, and has a critical role in Pavlovian threat discrimination and overgeneralization[3,10]. Large-scale monkey neuroimaging studies (n = 592) show that BST (and Ce) metabolism co-varies with defensive responses elicited by uncertain naturalistic threats[5]. Human neuroimaging studies demonstrate that the BST responds to both Pavlovian and naturalistic threats (such as an approaching tarantula or horror films)[4,5]. Leveraging new fMRI assays and bigger samples, recent work has made it plain that the BST and Ce are engaged by both certain and uncertain threat, with statistically indistinguishable responses to the two kinds of anticipated threat (Fig. 1). While this most assuredly does not mean that the BST and Ce are identical or interchangeable, it does license rejection of strict single- and double-dissociation models of human EAc function.

As Tseng and colleagues remind us, discovering the brain and bodily bases of fear and anxiety is important. Addressing this challenge will require an increased investment in coordinated cross-species research and the extension of semantically slippery narrative models of fear and anxiety to encompass parametric variation in dimensional constructs (such as threat probability) and computational modelling. Doing this promises to accelerate our understanding of the mechanisms that govern threat-related states, traits and disorders in humans[1].

There is a reply to this letter by Wang, L., Tseng, Y. T., Schaefke, B., Wei, P. & Sheng, H. *Nat. Rev. Neurosci*. https://doi.org/10.1038/s41583-024-00834-w (2024).

Data availability

Relevant de-identified raw data are available at the NIMH Data Archive (https://nda.nih.gov/edit_collection.html?id=2447). Key neuroimaging maps are available at NeuroVault (https://neurovault.org/collections/8583/).

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Author contributions

A.J.S. and A.S.F. envisioned the present project. A.J.S., A.S.F., and S.E.G. wrote the paper. S.E.G. and A.J.S. created figures. A.J.S. funded and supervised all aspects of the study. All authors contributed to reviewing and revising the paper and approved the final version.

Competing interests

The authors declare no competing interests.