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Introduction to the special issue on the Neurobiology of Human Fear and Anxiety

A B S T R A C T

Pathological fear and anxiety are a leading cause of human misery and morbidity, afflicting millions of individuals worldwide. Yet existing treatments are inconsistently effective or associated with significant adverse effects, underscoring the urgency of developing a more complete understanding of the neural systems governing fear and anxiety in humans. This emphasis reflects the fact that fear and anxiety disorders are defined and diagnosed based on subjective symptoms, and human studies are essential for understanding the neural mechanisms that underlie the experience of fear and anxiety. Human studies are also crucial for identifying the features of animal models that are conserved and, hence, most relevant to human disease and treatment development ('forward translation'). Finally, human studies afford opportunities for developing objective biomarkers of disease or disease risk, accelerating the development of new diagnostic and treatment strategies, and generating novel hypotheses that can be mechanistically assessed in animal models ('reverse translation'). The present Special Issue—*The Neurobiology of Human Fear and Anxiety*—provides a concise survey of recent progress in this burgeoning area of research. Here we provide an Introduction to the Special Issue, highlighting some of the most significant and exciting advances.

1. Introduction

When fear or anxiety are experienced too intensely or become pervasive—manifesting even in benign contexts—they can be debilitating. Anxiety disorders encompass an extended family of closely related diagnoses, from specific phobias and social anxiety to panic and post-traumatic stress. Collectively, they create enormous suffering for patients and impose an immense burden on public health and the global economy (Dieleman et al., 2020; IHME, 2023). Existing treatments, both psychosocial and pharmacological, were developed decades ago and are limited in their effectiveness and durability, pointing to the need to develop a better understanding of the neural circuits that govern the expression and experience of fear and anxiety (Garakani et al., 2020; Sartori and Singewald, 2019). This special issue of *Neuroscience and Biobehavioral Reviews*—*The Neurobiology of Human Fear and Anxiety*—provides a concise survey of recent advances in this burgeoning area of research. Investigators from North America, Europe, and Australia contributed fifteen original theoretical reviews. This exciting body of work encompasses a range of populations—from rodents and monkeys, to children and psychiatric patients—and showcases a wide variety of paradigms, measures, analytic strategies, and conceptual approaches.

Watson and colleagues focus on the nature and measurement of fear and anxiety in humans (Watson et al., 2022). They examine fear and anxiety from the perspective of structural models of personality and psychopathology and highlight some issues related to their assessment in humans, focusing on distinguishing fear and anxiety from a psychometric perspective.

Four reviews focus on the neurobiology of fear and anxiety. Adopting a more theoretical perspective, Pessoa tries to answer the critical question of how many brain regions we need to understand fear and anxiety

(Pessoa, 2023). He proposes that only multi-region, network-level explanations will provide a satisfying answer to this question. In contrast, Holley and Fox focus their attention squarely on one specific macro-circuit, the central extended amygdala (EAC), drawing heavily on recent work in rodents and monkeys (Holley and Fox, 2022). They propose that the EAC has a critical role as an arbiter of survival and emotion-relevant trade-offs for action selection and describe how this perspective can improve our understanding of anxiety-related disorders. Anxiety and trauma disorders are notoriously heterogeneous (Bryant et al., 2023; Galatzer-Levy and Bryant, 2013), and France and Jovanovic focus on the practical need to identify data-driven brain biotypes that can be used for parsing this heterogeneity and guiding more targeted treatment approaches (France and Jovanovic, 2023). Finally, Abend reviews evidence supporting the utility of adopting an ethologically grounded dimensional perspective on fear and anxiety (Abend, in press). He marshals evidence suggesting that defensive responses are systematically organized around a continuum of threat imminence (i.e., spatial and temporal proximity) and suggests that this framework offers important clues for clarifying the mechanistic underpinnings of fear and anxiety symptoms.

A number of the contributors focused on Pavlovian fear conditioning and related threat-learning paradigms. Hennings and colleagues review the current state of the human neuroimaging literature. They underscore the need to move away from traditional voxel-by-voxel ('mass univariate') approaches and highlight the potential value of more sophisticated multivariate pattern analyses (Hennings et al., 2022). Individuals with anxiety disorders often struggle to learn about and make use of safety cues, leading to a pervasive state of distress (Grupe and Nitschke, 2013; Shackman et al., 2016). Laing and colleagues focus their review on recent efforts to understand the nature and neurobiological substrates of safety learning (Laing et al., 2022). Two reviews focus on threat

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extinction and exposure therapy, the gold-standard cognitive-behavioral treatment for fear and anxiety disorders. Craske and colleagues describe how recent efforts to understand the neurobiology of threat extinction can inform exposure therapy and highlight some behavioral and pharmacological strategies that could enhance the benefits of exposure therapy (Craske et al., 2022). Webler and colleagues focus our attention on emerging transcranial neurostimulation techniques and describe how these tools can be used in combination with threat-extinction paradigms to causally map the relevant circuits, opening the door to developing targeted treatments for pathological fear and anxiety (Webler et al., 2023). Finally, Merz and Wolff review the current state of scientific understanding of how stress and stress hormones influence threat extinction and highlight some potential therapeutic implications (Merz and Wolf, 2022).

Pathological fear and anxiety often first emerge early in development and show a chronic course if left untreated (Ask et al., 2021; Kessler et al., 2007; Lijster et al., 2017; Solmi et al., 2022). Three reviews focus on their development across the lifespan. Poulton and colleagues review findings on fear and anxiety that have emerged from one of the best well-known longitudinal cohort studies on health, the Dunedin study, focusing on implications for nosology and the importance of early-life experiences (Poulton et al., 2023). Caballero et al. review the neural correlates of emotion regulation across development, underscoring the importance of distinguishing individual differences in the capacity to regulate emotion from the tendency to actually deploy regulatory strategies (Caballero et al., 2023). Children and adults with extreme fear and anxiety are often conceptualized as hyper-vigilant for potentially threatening information (Hur et al., 2019). Valadez and colleagues provide a comprehensive mini-review of the state of the attention-bias literature, primarily focusing on potential treatment implications for youth living with extreme fear and anxiety (Valadez et al., 2022).

The special issue also includes two reviews focused on emerging topics of interest. Ehlers and Lonsdorf examine the practice of data sharing in the area of human fear and anxiety research, highlight some of the associated challenges, and propose 10 steps to make data sharing more efficient and scientifically sustainable (Ehlers and Lonsdorf, 2022). Yamamori and Robinson discuss recent efforts to develop computational models of human fear and anxiety, focusing on reinforcement learning strategies in threat and avoidance learning, approach-avoidance conflict paradigms, and negative biases in decision-making when confronted with uncertain aversive outcomes (Yamamori and Robinson, 2023).

The fifteen reviews that make up the bulk of the Special Issue embody the important strides made in our scientific understanding of fear and anxiety. Yet they also make it clear that most of the work necessary to understand the nature and neurobiological bases of human fear and anxiety remains undone. We conclude the special issue with a virtual roundtable discussion. The discussants were an international panel of experts chosen to represent a broad spectrum of disciplines and methodological approaches. The goal was to take stock of what we have already learned and to identify the most urgent next steps (Grogans et al., 2023).

To conclude, we hope this special issue will inspire fear and anxiety researchers—and those working in neighboring areas of the affective sciences—to undertake the next generation of empirical research and conceptual work. Ultimately, we hope that a deeper scientific understanding will accelerate the development of tools to help those who suffer from maladaptive fear and anxiety to find peace and flourish in their lives. *Read and enjoy!*

Declaration of Competing Interest

Authors declare no conflicts of interest.

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