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The Danger of LeDoux and Pine's Two-System Framework for Fear

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Letters to the Editor

The Danger of LeDoux and Pine's Two-System Framework for Fear

TO THE EDITOR: The Review and Overview article by LeDoux and Pine (1), published in the November 2016 issue of the *Journal*, proposes that the subjective emotion of fear and its associated behavioral and physiological responses (e.g., increased freezing and respiration) emerge from distinct neuronal circuits. As a consequence, the authors argue that behavioral and physiological defense responses should not be used to study the subjective emotion of fear. Moreover, they claim that conflation of subjective and behavioral and physiological measures of fear has hampered progress in the treatment of anxiety disorders. However, we feel that this framework would reverse legitimate progress that has been made toward improving interventions for these conditions.

Contrary to LeDoux and Pine's claim that subjective and behavioral and physiological fear responses are orthogonal, there is substantial evidence indicating that they are correlated and represent an integrated response. For example, physiological responses to fear-evoking stimuli covary with subjective ratings of fear across the acquisition, extinction, and re-emergence of a fear memory (2–4), and subjective trait-like assessments of anxiety are correlated with autonomic responses (4, 5). Furthermore, patients with anxiety disorders report both high subjective fear and behavioral and physiological fear responses (6), indicating that these responses track one another across the range of health and disease states, although they may have different thresholds for activation. Lastly, there is no evidence that the subjective emotion of fear can be experienced in the absence of concomitant behavioral and physiological responses, suggesting that these responses are inseparable and emerge from a common neuronal circuit. This is in line with the findings that individuals with bilateral amygdala lesions have both reduced subjective and behavioral and physiological responses to threatening stimuli (7, 8). Although the amygdala is unlikely to be the sole locus of fear genesis, data showing that its perturbation dramatically alters a range of fear responses clearly point to it being a part of a larger hub for coordinating an integrated fear response that includes behavioral, physiological, and cognitive endpoints. As such, we feel it is misguided to argue that behavioral and physiological defense responses cannot be used to make inferences about the subjective experience of fear.

In addition to the two-system framework being based on a biased view of the literature, the adoption of a two-system framework brings with it ominous implications. If it were to be accepted that the subjective experience of fear emerges from orthogonal brain circuits from those responsible for behavioral and physiological defense responses, we would be required to limit ourselves to the study of subjective report. This is because behavioral and physiological indicators of fear would have no ability to predict subjective experience in humans according to the two-system view. Beyond the fact that studies based on physiological and behavioral measures have actually provided us with the ability to predict the efficacy of both behavioral and pharmacological interventions (9), the tremendous insights into the neurobiology of fear gained from animal studies would be lost. Finally, the shift away from subjective report was prompted by issues of reliability and response bias, its semiquantitative nature, and its restriction to populations capable of language. Returning to an emphasis on subjective report therefore turns psychiatry in the direction of a bleak past.

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Elevating the Role of Subjective Experience in the Clinic: Response to Fanselow and Pennington

TO THE EDITOR: It is widely accepted that threat exposure activates the amygdala and elicits behavioral defense reactions, physiological responses, and subjective states of fear in humans. Our central thesis is that the changes in behavior and physiology can be dissociated from the changes in subjective state, with the former depending on the amygdala but the latter depending more heavily on cortical areas. We are pleased to address criticisms of this central idea from Fanselow and Pennington.

Fanselow and Pennington cite evidence that patients with amygdala lesions have both reduced subjective experiences and behavioral and physiological responses to threatening stimuli. However, the same group they referenced later reported opposite findings (1), as did Anderson and Phelps (2). The latter findings are consistent with results from studies using subliminal stimulation in healthy humans and studies of humans with "blindsight." Both sets of studies show that threats that are not consciously reportable and that fail to elicit conscious fear nevertheless elicit amygdala activity and physiological responses (3).

In contrast to Fanselow and Pennington's suggestion, we do think that the study of behavioral and physiological defense responses inform understanding of subjective states. Even though these phenomena are clearly dissociable, changing behavior and physiology can indirectly modulate the subjective states of fear and anxiety because the circuits for these phenomena, though distinct, interact.

Noting that threat exposure leads patients with anxiety disorders to manifest changes in both subjective fear and behavioral physiology, Fanselow and Pennington argue that clinical data contradict our framework. They also note that subjective ratings of fear across the acquisition, extinction, and re-emergence of a fear memory, and subjective trait-like assessments of anxiety, are correlated with autonomic responses. However, contrary to their assertions, a wealth of findings show that subjective reports of fear are poorly correlated with measures of behavior and physiology (4–9). Further, recent studies using a novel, sophisticated approach to brain imaging show successful threat extinction in the absence of the arousal of conscious fear (10).

Fanselow and Pennington argue that physiological and behavioral measures predict the efficacy of both behavioral and pharmacological interventions. This claim not only contradicts our views but also the views of other researchers. For example, Griebel and Holmes (11) summarized the state of efforts to use neuroscience research to develop novel anxiolytic medications and to predict efficacy. In their words, this work has been "disappointing" because rodent research findings have rarely translated into effective treatments for problems related to fear and anxiety. A similar conclusion was reached by pharmaceutical scientists who found that the rodent model did not lead to new treatments (12).

Fanselow and Pennington also suggest that our framework forces insights into the neurobiology of fear gained from animal studies to be lost. In our view, data from animals are important for clinical understanding, especially when their interpretation is restricted to behavioral and physiological responses that can be similarly measured in humans and animals. Adopting this approach would foster more realistic expectations for the translation of basic science work into therapies for anxiety disorders.

Fanselow and Pennington suggest that the unreliability and semiquantitative nature of subjective report led to a shift away from its use. Clearly, subjective reports have limitations (e.g., as an index of motivations underlying behavior or as a fully accurate index of past experiences). However, they have unique strengths, which make them an important indicator of people's immediate experiences (13, 14). Moreover, they are at least as reliable as physiological responses to threats (15). Because of these features, neuroscience is not shifting away from subjective reports; rather, research on consciousness is thriving (16, 17), and subjective report is the gold standard in this field. As a state of consciousness, subjective fear can be explored using subjective report as well as novel quantitative assessment methods (18–20).

Finally, Fanselow and Pennington suggest that an emphasis on subjective experience and self-report turns psychiatry in the direction of a "bleak past." But leading anxiety researchers argue that self-report generates "valid measures of key constructs, some of which cannot be measured in any other way" and that self-report is "sometimes the best measure of the construct of interest" (21). We agree and hold that failure to acknowledge the subjective state as an important, independent area of scientific inquiry ignores vital aspects of patients' clinical experiences. Moreover, focusing on the subjective state frees psychiatry from the bleak legacy of behaviorism and reductionism. At the same time, it elevates patients' experiences to a legitimate focus of both treatment and neuroscience research on novel therapeutics.

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