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RESEARCH HIGHLIGHT

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The paradoxical effects of chronic stress on avoidance: a role for amygdala-dorsomedial prefrontal cortex dialogue

Itamar S. Grunfeld[1] and Ekaterina Likhtik[2,3] ✉

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Chronic stress has been a pervasive factor during the new-normal of the COVID era. Notably, although moderate stress is critical for adaptation in a changing world, prolonged stress exposure can lead to an array of mental health conditions, often associated with structural changes in brain regions that affect emotional learning, such as the amygdala, the frontal cortices, and the hippocampus. To better target treatments, it is critical that we improve our understanding of the physiological and behavioral consequences of increased exposure to chronic stress. To this end, rodent behavioral tasks have been instrumental for probing symptoms of stress-induced behavioral change, including the social interaction test, the sucrose preference test, and the forced swim test to study increased social avoidance, anhedonia, and decreased motivation, respectively. However, one notable behavior that has received less attention thus far, is avoidance of aversive stimuli. Given that periods of increased chronic stress are also often coupled with frequent occurrences of aversive cues and events, this poses an important question for the field. In this issue of Neuropsychopharmacology, Shukla and Chattarji [1] tackle this question by tapping into the rodent behavioral repertoire in response to different frequencies of ultrasonic vocalizations (USVs), which rats use to communicate their affective states.

In this study, the authors take advantage of untrained rodent responses to USVs to develop a robust paradigm for assessing the effects of chronic stress on approach-avoidance behavior in relation to naturalistic stimuli. The authors used a speaker located at one end of a several meter long track to play either 22-kHz USVs, representative of rat alarm calls that are avoided by non-stressed rats, or 50-kHz USV appetitive signals that are associated with approach behaviors for play and mating. The authors expected the chronically stressed rats to avoid the aversive 22-kHz USVs even more than the non-stressed controls, but to their surprise, found the opposite. Whereas controls spent significantly more time on the distal part of the track, avoiding the 22-kHz USVs, chronically stressed rats did not avoid the aversive calls, instead spending equal time on the proximal and distal parts of the arena (Fig. 1). This appears to be a robust behavioral phenotype, as the authors show that stressed animals didn't avoid a range of cues, including an auditory aversive conditioned stimulus, a zone on the track that was previously paired with shock, and a white noise, all stimuli that control animals consistently found aversive enough to avoid. Notably, the authors demonstrate that decreased avoidance occurs in conjunction with elevating defensive freezing during retrieval of an auditory fear-conditioned cue, supporting previous data showing that stress leads to a stronger fear memory [2]. In the case of a fear-conditioned cue, the effects of stress on these two behavioral responses can be seen as complementary, and indeed the authors show that decreased avoidance of the conditioned tone is paired with less movement on the track. However, in the case of decreased avoidance of unconditioned stimuli, there is no change in total movement on the track, suggesting that a different mechanism is involved. Taken together, these data indicate that exposure to chronic stress leads to a panoply of changes in the behavioral response to conditioned and unconditioned aversive cues, including a decrease in active avoidance, and an enhancement of fear memories. As always, interpreting these results poses an interesting and enticing challenge.

One interpretation comes from an emerging field in rodent research that focuses on the role of prior experiences in developing pro-social tendencies. This work shows that prior experience determines whether a rat is likely to help another rat in distress. A lack of familiarity with the distressed rat or situation can result in a decreased likelihood to behave pro-socially and a reduced tendency to help conspecifics [3]. It is therefore possible that stressed rats display a form of empathic-like behavior as manifest via decreased avoidance, wherein their previous exposure to stress makes them more likely to approach distressing USVs than their stress-naïve counterparts. This behavior may rely on partially overlapping neural circuits and communication patterns with those of fear learning.

In line with the above, an additional interpretation is that chronically stressed animals lose their ability to effectively discriminate the aversive valence of the unconditioned USVs. The authors find that the basolateral amygdala (BLA) has increased cFos activity and theta-range (2–12 Hz) field potential responses to the USVs in controls, whereas these responses are absent in stressed animals (Fig. 1). Given that BLA theta activation is a signature of threat processing, the absence of USV-evoked theta suggests that these calls are not perceived as threatening. Moreover, in control animals, USVs evoke theta-range responses in the dorsal medial prefrontal cortex (dmPFC), and synchrony between the BLA and dmPFC, but this communication is absent in stressed rats (Fig. 1). Previous work shows that dmPFC projections to the BLA mediate avoidance [4]. We can therefore speculate that increased theta synchrony seen in controls in this study, may be the means for dmPFC inputs to engage amygdala activity during avoidance. Interestingly, theta communication along this route is also important

[1]Psychology Program, The Graduate Center, CUNY, New York, NY, USA. [2]Biological Sciences Dept., Hunter College, CUNY, New York, NY, USA. [3]Biology Program, The Graduate Center, CUNY, New York, NY, USA. ✉email: elikhtik@genectr.hunter.cuny.edu

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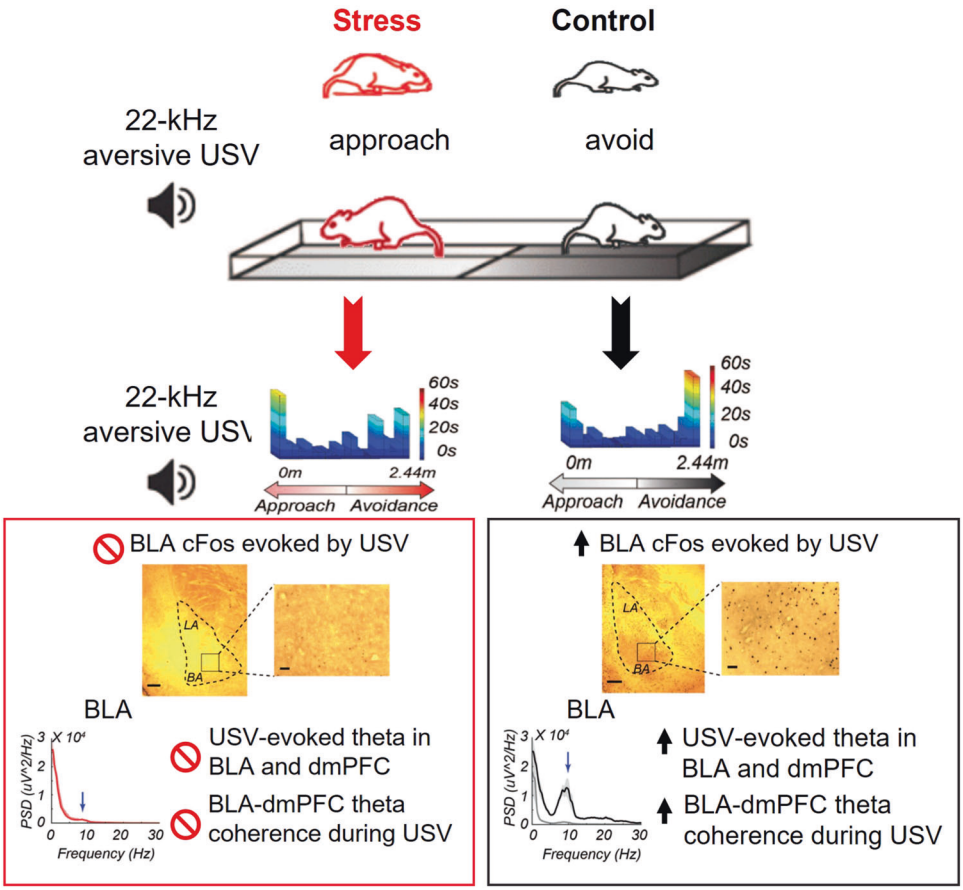

Fig. 1 Aversive social calls don't evoke avoidance behavior, or amygdala and dorsomedial prefrontal cortex theta responses in chronically stressed rats. Rats were subjected to 10 days of chronic immobilization stress (2 h/day) or control conditions. Both groups were then placed in a long track with a speaker at one end emitting innately aversive (22-kHz) ultrasonic vocalizations (USV). Whereas control rats consistently avoided the calls, spending time on the distal half of the track, stressed rats failed to avoid, and approached the speaker. Whereas control rats showed USV- evoked increases in cFos activity in the Basolateral Amygdala (BLA), theta power in the BLA and dorsomedial prefrontal cortex (dmPFC) and BLA-dmPFC theta synchrony, stressed rats did not display any USV-evoked theta responses or theta synchrony communication in these regions.

for discrimination of a conditioned non-threat. Thus, if stress breaks down oscillatory communication in this circuit, it will alter several different responses, including worsen discrimination of conditioned non-threat and impair avoidance of unconditioned threat.

The study by Shukla and Chattarji paves a way forward for a better understanding of how stress impacts physiology and behavior through compelling evidence that theta-range dmPFC-BLA communication underlies avoidance. Further work is necessary to uncover how stress-induced physiological changes that impact avoidance also tie into social behavior. There is much evidence that both types of behavior involve encoding at the level of the BLA and dmPFC, as well as active communication between them [5]. By utilizing inherently aversive USVs to assess approach/avoidance behavior, the authors bridge this gap in a way that is simple and ethologically relevant, creating a clear path for unpacking an important mechanism poised to mediate a range of stress-induced outcomes.

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AUTHOR CONTRIBUTIONS

ISG wrote the initial draft and created the figure. EL wrote and edited the finalized manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Ekaterina Likhtik.