

# Developmental Differences in Neural Responding to Threat and Safety: Implications for Treating Youths With Anxiety

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Anxiety disorders are the most prevalent mental health disorders, affecting approximately one in three individuals, and they often onset during development (1). Cognitive-behavioral therapy and selective serotonin reuptake inhibitors can be highly effective for treating anxiety. However, up to 50% of both youths and adults with anxiety do not respond sufficiently to these evidence-based treatments (2), highlighting the critical need to optimize interventions to more effectively reduce the immense burden of anxiety on individuals and society. Given the dynamic course of anxiety across the lifespan (1), as well as marked developmental changes in frontolimbic circuitry implicated in anxiety (3, 4), tailoring interventions based on developmental stage represents a promising approach to maximize efficacy (5).

Difficulty discriminating between cues that predict threat and safety is a core feature of anxiety disorders, leading to fear even in situations and environments that are safe (6). Delineating normative developmental trajectories of threat and safety learning and how such trajectories differ in youths with anxiety may provide critical insight into ways in which mechanisms underlying anxiety vary by age. The ability to distinguish between threat and safety cues improves with age among youths without anxiety disorders (7); however, adolescents without anxiety disorders show diminished extinction (8) and retention of learned safety (9) compared with children and adults without anxiety disorders. Although developmental changes have been less explored in children and adolescents with anxiety disorders, cross-sectional evidence suggests that youths with anxiety exhibit altered neural responses when processing cues that no longer predict threat, compared with both youths without anxiety and adults with anxiety (6, 10). At the same time, findings have been mixed, with some evidence of similar processing in pediatric and adult anxiety disorders (10).

Reconciling inconsistent findings and identifying the conditions under which youths and adults with anxiety may respond similarly versus differently to threat and safety are essential to advance knowledge of the basic mechanisms underlying the development of anxiety and to inform interventions. In this issue of the *Journal*, Gold and colleagues (11) examine neural responses to ambiguous threat and safety cues among youths and adults with and without anxiety

disorders, with the goal of testing for age-related similarities and differences. Threat conditioning and extinction were first assessed via psychophysiological and self-report measures. Three weeks later, participants completed a functional MRI (fMRI) paradigm of extinction recall, during which they rated their own fear (i.e., threat appraisal) and explicit memory of stimuli with varying levels of similarity to the threat cues that had previously been extinguished.

Importantly, diagnostic differences in age-related patterns emerged for both neural activation and functional connectivity. For activation, age-related diagnostic differences varied by task condition, as well as by brain region. When participants attended to their own fear, activation in the ventromedial prefrontal cortex (vmPFC) and inferior temporal cortex (ITC) differed between adults with and without anxiety, such that nonanxious adults exhibited less vmPFC deactivation and greater ITC activation compared with anxious adults. Notably, these differences in vmPFC and ITC activation during threat appraisal did not emerge between youths with and

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without anxiety. By contrast, when participants rated memory for morphed stimuli, ITC activation was higher in youths with anxiety compared with youths without anxiety, but there were no differences in adults. For functional connectivity, as the degree of safety in morphed stimuli increased, diagnostic differences in amygdala-vmPFC functional connectivity depended on age. Whereas adults without anxiety exhibited stronger positive amygdala-vmPFC functional connectivity than adults with anxiety, youths with anxiety exhibited stronger connectivity than youths without anxiety.

Findings from Gold and colleagues of anxiety-related neural alterations during extinction recall may be consistent with evidence that individuals with anxiety disorders have difficulty recognizing safety during laboratory paradigms and in daily life (6, 12). Moreover, the developmental nature of the findings in this study is consistent with previous

cross-species evidence that frontolimbic circuitry implicated in safety learning undergoes distinct changes during childhood and adolescence (3, 4). Gold and colleagues found anxiety-related differences when both youths and adults processed previously extinguished threat cues; however, these findings were identified during engagement of different psychological processes. Anxiety-related differences among adults were observed when appraising one's own fear, whereas anxiety-related differences in youths were observed only when engaging declarative memory. Therefore, in addition to providing strong evidence that age discontinuities exist in anxiety disorders, these findings raise the interesting questions of when and under what conditions such age discontinuities emerge. Although much remains unknown and the nature of age discontinuities likely depends on many factors, findings from the present study suggest that the developmental timing of psychological processes and related neural circuitry may be an important factor to consider. For example, whereas declarative memory requires objective retrieval, threat appraisal requires subjective assessment of internal state. Furthermore, declarative memory follows a different and likely earlier maturational time course than appraisal (13), which may drive the distinct patterns of age-related diagnostic differences observed between these two task conditions.

Neuroimaging has provided critical insight into processes underlying anxiety; however, the field faces many challenges in using fMRI to elucidate mechanisms or meaningfully inform interventions for psychopathology. These challenges include reproducibility of findings and developing paradigms that can adequately capture the complexity of both neural and behavioral processes, as well as psychological processes that are not directly observable. Ethical and practical considerations present further challenges to tackling these questions when studying aversive states using threat and extinction learning in the domain of pediatric anxiety (14). One particularly difficult aspect is identifying an unconditioned stimulus that is aversive enough to elicit a robust response across both youths and adults, but not so upsetting that it contributes to high rates of discomfort and attrition in a pediatric and anxious population.

Gold and colleagues manage to address many of these challenges, maximizing statistical power while balancing practicality with clinical relevance. The authors employed the "screaming lady" paradigm, which has produced robust conditioning effects in youths and adults with anxiety without a physically aversive unconditioned stimulus (15, 16). Importantly, attrition rates improved upon past studies, with <10% of participants who started the study discontinuing during conditioning or extinction and 76% of original participants from the psychophysiology visit returning for the fMRI scan that involved extinction recall. In addition to this evidence of feasibility, the paradigm strengthened clinical implications by obtaining self-reported ratings of fear and memory that allowed for the examination of anxiety-relevant processes. Another major strength of the study is its sample, which was medication-free, spanned a

wide age range (from 8 to 50 years old), and was relatively large (N=200) for the clinical neuroimaging literature. In addition to the increased sample size, the authors leveraged a higher number of stimulus replicates and treated age continuously to maximize statistical power for examining higher-order interactions with task conditions. Finally, the use of relatively conservative statistical thresholds is in keeping with current best practices in neuroimaging to increase the prospect of reproducible findings (17).

The study has several limitations that can continue to be addressed in future research. Given that developmental change is of central importance to this research, longitudinal investigations will be essential to build on the current cross-sectional design and findings. A richer understanding of age discontinuities in anxiety disorders will also require replication of the present findings, particularly because of the demonstrated complex interactions between age, diagnosis, and task conditions. Lastly, the use of social stimuli in this study may enhance external validity but also introduces a potential confound, as neural and psychological responding to emotional faces varies across individuals at different stages of development and with different subtypes of anxiety. Thus, future studies of threat and safety learning could use non-social stimuli (e.g., see reference [14]) to mitigate this confound and potentially enhance generalizability.

Taken together, Gold and colleagues present evidence of age discontinuities in anxiety disorders that could have important implications for understanding how mechanisms of anxiety may vary across development and how treatments may be delivered in a developmentally sensitive manner. These findings underscore the importance of neurodevelopmental frameworks and suggest that the extent to which diagnostic differences in anxiety vary during development is a function of both the psychological process and neural circuitry implicated. Building upon these findings, future research examining the association between neural differences in extinction recall and clinical outcomes will be important for early risk identification. Moreover, applying knowledge of individual or age-related differences in threat and safety learning has the potential to inform tailored treatment recommendations or point to targets for novel interventions. While existing evidence-based treatments for pediatric anxiety have been developmentally adapted, they are largely based on the same learning principles as treatments for adults. Thus, leveraging knowledge of the divergent ways in which anxiety manifests in the developing versus developed brain could provide a powerful approach to optimizing interventions for youths with anxiety.

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