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Commentary

When Uncertainty Is a Certainty: Optimizing Exposure-Based Therapies

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Learning about threat and safety is central to navigating an uncertain world. Adapting to environmental changes requires learning about when something is dangerous, as well as updating those beliefs when cues that once signaled danger are now safe. Difficulty learning about safety via extinction can arise in anxiety disorders and following trauma, and principles of extinction form the basis of exposure-based therapies (1). While therapies focused on exposure, such as cognitive behavioral therapy for anxiety or prolonged exposure for posttraumatic stress disorder, can be highly effective, a substantial portion of individuals do not benefit sufficiently from current treatments or experience relapse after treatment (2). These interventions may be vulnerable to the return of fear in part because extinction involves the formation of a new safety memory but not the erasure of the original fear memory. Previously extinguished fear responses can return via the mere passage of time (spontaneous recovery), exposure to a stressor (reinstatement), or return of a fear-associated context (renewal) (3). A growing body of research focused on strengthening extinction has implications for optimizing the efficacy of exposure-based therapies.

In line with precision medicine approaches, one approach is to examine individual differences that can inform efforts to tailor interventions. In the current issue of *Biological Psychiatry: Global Open Science*, Morriss *et al.* (4) conduct a meta-analysis examining intolerance of uncertainty as it relates to extinction learning. Intolerance of uncertainty, or the tendency to find uncertainty distressing, is heightened across various internalizing disorders. Previous studies have linked intolerance of uncertainty with diminished extinction, but there has been substantial variability in measurement, analysis, and specific findings. While intolerance of uncertainty has been conceptualized as distinct from other related constructs, such as trait anxiety and neuroticism (5), the extent to which intolerance of uncertainty uniquely relates to extinction is unclear. The current meta-analysis examined results from 18 studies (1006 participants) with measures of intolerance of uncertainty and skin conductance response collected during threat extinction training. Skin conductance response was examined as a difference score between the conditioned stimulus and the extinguished cue.

Morriss *et al.* (4) suggest that associations between intolerance of uncertainty and extinction are robust. Intolerance of uncertainty was associated with threat extinction during late extinction and the overall extinction phase, and findings were consistent across all variants of intolerance of uncertainty (i.e., full and abbreviated scales and inhibitory and prospective subfactors). Intolerance of uncertainty did not relate to early extinction. Importantly, intolerance of uncertainty was associated with extinction even when controlling for trait anxiety, highlighting some specificity in the effects.

Given the substantial variability in study design and analytic approaches to studying fear conditioning and extinction in the laboratory (6), it is reassuring to see convergence across studies. Transparency is among the various strengths of the reported meta-analysis, including the fact that Morriss *et al.* (4) have made their materials publicly available. They also tested whether the group conducting the research moderated the effects—particularly since many of the individual studies were conducted by the authors themselves—and did not find that group affected the results. Alongside its strengths, limitations of this meta-analysis include the relatively low number of individual studies and the fact that data were primarily from same-day or next-day threat extinction paradigms, as is typical in the field. It is unknown to what extent the results generalize to the context of treatment, which typically involves multiple sessions across weeks or months.

Individuals with high intolerance of uncertainty may benefit from ongoing efforts to enhance extinction. When the conditioned stimulus is no longer paired with the aversive stimulus during extinction training, the meaning of the conditioned stimulus can be ambiguous. Across species, evidence suggests that replacing the aversive stimulus with a novel (and benign) stimulus during extinction, instead of simply omitting the aversive stimulus, can facilitate extinction (7). While the precise mechanisms supporting novelty-facilitated extinction remain unclear, the strategic incorporation of novelty into extinction may leverage effects of surprise that are central to inhibitory learning (1,3). The meta-analytic findings of Morriss *et al.* (4) suggest that novelty-facilitated extinction may be particularly helpful for individuals who struggle with uncertainty, as the simple omission of threat during extinction may not be sufficient to reduce fear.

Previous research has posited that prolonged opportunities for extinction learning (e.g., via an increased number of extinction trials) may also be helpful for individuals with a high intolerance of uncertainty. A previous study reported preliminary evidence of stronger retention of safety learning among individuals with a higher intolerance of uncertainty following an extended extinction paradigm, relative to standard extinction (8). Whereas higher intolerance of uncertainty was associated with greater skin conductance response during regular extinction, higher intolerance of uncertainty was associated with lower skin conductance response in the extended extinction condition. Of note, the findings were specific to self-reported inhibitory (not prospective) intolerance of uncertainty, and inconsistent findings across level of analysis and same-day versus next-day extinction highlight the

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importance of future work to better understand the impact of the number of trials during extinction.

Importantly, conceptualizations of the mechanisms supporting the effects of exposure therapy have increasingly shifted to emphasize inhibitory learning. While habituation likely plays a role in extinction and while fear often decreases over the course of an exposure, the extent to which fear declines does not predict clinical outcomes (1). Instead, exposure therapy may be best optimized through strategies that enhance inhibitory learning, such as expectancy violation and variability in exposure (1). Paralleling evidence that learning to tolerate fear may be more important than reducing fear during exposure, exposures that provide opportunities to learn that uncertainty itself is not inherently dangerous may be more helpful than reducing or eliminating uncertainty altogether, particularly for individuals with a high intolerance of uncertainty. Cognitive behavioral therapy that specifically targets intolerance of uncertainty, such as by addressing negative beliefs about uncertainty and seeking out experiences with uncertainty, has also shown promise for reducing anxiety (5).

Applying basic research on intolerance of uncertainty and extinction learning to inform interventions highlights several challenges of clinical translation. While exposure therapy relies on principles of extinction learning, scaling up from laboratory-based extinction paradigms to exposure therapy (which takes place across many sessions and often targets responses after traumatic events or intense fears that may be challenging to model in a laboratory paradigm) is a major hurdle. Despite foundational insight gained from studies on fear conditioning and extinction, findings are often inconsistent across levels of analysis (e.g., self-reported expectancy, self-reported fear, skin conductance response, pupil dilation, neural response), and differences in skin conductance response may not track with expectations of threat in the real world or with therapeutic outcomes (3). In addition, much remains unknown at a mechanistic level. Building upon basic research on enhancing extinction will require a better understanding of the mechanisms linking intolerance of uncertainty with extinction and why adaptations such as novelty-facilitated extinction or prolonged extinction may work better than traditional extinction. There is still considerable work to be done before these findings can be used directly to optimize treatments, and testing key hypotheses about intolerance of uncertainty and extinction in clinical populations will be an important next step.

Future developmental research will deepen our understanding of the effects of intolerance of uncertainty and approaches for targeting treatment. Intolerance of uncertainty is thought to be shaped through early environments and learning histories (5). Delineating the developmental origins of intolerance of uncertainty, and the extent to which it may play a causal role in the onset of disorders, will be important for mechanistic insights that can translate to improve treatment. The majority of anxiety-related disorders emerge during childhood and adolescence, and intolerance of uncertainty has been shown to relate to anxiety and worry in youth (9). Moreover, cross-species evidence suggests that extinction is diminished during adolescence relative to childhood and adulthood (10). Adolescents may particularly benefit from efforts to optimize interventions based on knowledge of intolerance of uncertainty and extinction.

Taken together, meta-analytic findings from Morriss *et al.* (4) point to future avenues for optimizing interventions by targeting intolerance of uncertainty. While there are key gaps in knowledge and many uncertainties remain, applying knowledge of individual differences in extinction learning has translational potential to inform exposure-based therapies for anxiety and stress-based disorders.

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Article Information

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