COMMENTARY

Extending Fear Extinction Beyond Anxiety Disorders

Karen G. Martínez and Gregory J. Quirk

"Nothing in life is to be feared, it is only to be understood." This encouraging statement by Marie Curie in the early 1900s holds new meaning given the current interest in extinction of conditioned fear in psychiatry. Decades of experimental psychology in both animals and humans have shown that stimuli paired with an aversive outcome such as electric shock induce conditioned fear responses, both behavioral and physiological. Learned fear responses can be extinguished by presenting the stimulus in the absence of shock. Rather than eliminate the original fear memory, extinction represents a type of "safety" learning that we now know depends on a network of structures including the amygdala, medial prefrontal cortex, and hippocampus (1). Fear extinction has obvious relevance for the etiology and treatment of anxiety disorders such as post-traumatic stress disorder, in which both fear extinction and prefrontal-hippocampal circuits are compromised. Indeed, much recent progress has been made in identifying areas in the human brain involved in extinction memory and in testing new pharmacological adjuncts for extinction-based therapies for anxiety disorders (2). However, the prefrontal–amygdala–hippocampal circuit is also implicated in mood and thought disorders, suggesting the interesting possibility that deficits in fear extinction might extend beyond anxiety disorders. In this issue of *Biological Psychiatry*, Holt *et al.* (3) test this hypothesis for schizophrenia, a thought disorder characterized by prefrontal deficits as well as fear-inducing perceptual disturbances and delusions.

Holt *et al.* compared patients with schizophrenia with normal matched subjects in a fear learning protocol that has been used to study anxiety disorders (4). Subjects are shown visual stimuli consisting of a photo of a lighted lamp in a specific room. The color of the light (red or blue) is the conditioned stimulus (CS) and indicates whether or not a shock to the fingers will occur. Subjects rapidly learn to associate the lamp color with shock and show conditioned fear responses as indicated by an increase in the skin conductance response (SCR). Immediately after conditioning, fear responses are extinguished by repeatedly presenting the light in the absence of the shock. Conditioning takes place in one environmental context (room), and the extinction takes place in another. The following day, subjects are brought back and tested for their memory of extinction by re-exposing them to the extinguished CS in both contexts. Patients with schizophrenia showed normal conditioning and extinction on day 1 but were unable to recall extinction memory on Day 2, as evidenced by abnormally high SCR responses to the extinguished stimulus presented in the safe context. Thus, there was no general deficit in associative learning but a specific deficit in safety learning. In further support of this, patients with schizophrenia also showed increased SCR responses to the light that was never paired with shock (CS−).

Extinction recall is a complex process requiring the integration of contextual information with conditioning history, to determine the most appropriate behavioral response (1). If extinguished stimuli are presented in the context in which conditioning occurred, fear responses are renewed. During the recall test, patients with schizophrenia responded with high fear, as if the stimulus was presented in the conditioning context. Interestingly, when asked about the relationship between context and shock, patients were unable to state that one context was safe relative to the other. This difficulty with contextual learning supports the findings of hippocampal deficits in schizophrenia (5) and raises the possibility of an interaction between the consolidation of declarative memory and fear processing in schizophrenia. Furthermore, a deficit in safety signaling could explain why patients with schizophrenia consistently attribute fear to neutral stimuli, such as nonthreatening facial expressions (6), and suffer from hallucinations and delusions accompanied by perceptions of imminent danger and threat. Indeed, Holt *et al.* reported a positive correlation between the prevalence of delusions and baseline SCR, suggesting that patients with schizophrenia were overly suspicious or mistrustful of the experimental situation.

One potential caveat concerns the antipsychotic medication used by the majority of subjects in the Holt *et al.* study. Of 16 patients, 13 were receiving atypical or typical antipsychotic drugs, which are known to have anti-dopaminergic action as well as varying effects on serotonin and other neurotransmitter systems. One wonders whether the deficit in extinction recall was due to presence of schizophrenia or the medication used to treat the condition. Holt *et al.* cite previous rodent studies suggesting that dopamine antagonists do not impair extinction, but more recent rodent work challenges this view, showing that specific antagonists of D2 or D4 receptors given before extinction learning impair extinction recall (7,8). One way to dissociate the effects of medication from the pathology in schizophrenia would be to evaluate fear extinction in non-schizophrenic patients treated with dopamine antagonists, such as patients with tics or Tourette's disorder. Other possibilities would be to repeat the experiment with a greater number of patients who are not taking any medications or study first-degree relatives of patients without active psychopathology.

It is becoming well-established that recall of fear extinction depends on the integrity of the ventromedial prefrontal and cingulate cortices. Deficient activity in these areas is found throughout the anxiety disorders (post-traumatic stress disorder, panic, specific phobia, obsessive-compulsive disorder) (2) and also in depression, schizophrenia, bipolar disorder, and even addictive disorders (9,10). Furthermore, the short allele of the serotonin transporter, a risk factor for depression and anxiety, is associated with decreased coupling of the ventromedial prefrontal cortex with the amygdala (11). These findings are consistent with a lack of top-down control of the amygdala, possibly resulting in extinction deficits in multiple disorders. Extinction-based techniques of cognitive behavioral therapy, in which a patient is repeatedly exposed to feared stimuli, are dependent on the capacity to recall extinction. Enhancing extinction-based therapies with pharmacological or brain stimulation techniques could allow more patients to benefit from cognitive behavioral therapy and potentially ameliorate a wide range of disorders. At the very least, Holt *et al.*'s findings suggest that safety processing

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should be integrated into the treatment plan of schizophrenia and other disorders.

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