Extinction: New Excitement for an Old Phenomenon

Extinction of Pavlovian conditioning is deceptively simple: repeated presentation of the conditioned stimulus in the absence of the unconditioned stimulus causes conditioned responding to diminish. In his influential 1927 book that formalized the study of conditioning, Pavlov (1927) observed that extinction did not erase the memory of conditioning but was a form of inhibitory learning. In the decades that followed, psychologists extended our knowledge of extinction (Bouton 1993; reviewed in Delamater 2004; Konorski 1948; Rescorla 2004; Rescorla and Heth 1975) but little was learned about how the brain mediates extinction. In the past 6 years, however, there has been explosive growth in our understanding of the neural mechanisms of extinction, particularly for extinction of conditioned fear. Understanding fear extinction could revolutionize treatment of anxiety disorders such as phobias and posttraumatic stress, which employ extinction-based cognitive and exposure therapies.

This special issue of *Biological Psychiatry* reviews these recent advances, which were presented at the first international conference ever held on the topic of extinction in February, 2005, over 30 basic and clinical researchers from 11 countries spent 4 days in Puerto Rico at the Ponce School of Medicine in a National Institute of Mental Health (NIMH)-sponsored conference entitled "Extinction: The Neural Mechanisms of Behavior Change." Student and postdoctoral trainees from an additional seven countries were brought in, to make this a truly global event. The goal was to bring together the entire field to build consensus and set a translational trajectory for future work on extinction. The result is this series of unique reviews, each co-authored by three or more different groups working on a related theme within extinction. Rather than offering a single point of view, these reviews integrate across laboratories and highlight controversial aspects within the field.

While extinction is applicable to all types of appetitive and aversive conditioning, the resurgence of interest in extinction comes largely from the field of fear conditioning. The past 20 years have seen dramatic advances in our understanding of the neural mechanisms of fear learning. Experimental approaches as diverse as anatomical tract-tracing, behavioral neurophysiology, behavioral pharmacology, transgenic mice, human lesion analysis, and human brain imaging converge on the central role of the amygdala in acquiring and expressing fear associations (reviewed in Davis and Whalen 2001; Maren and Quirk 2004; Phelps and LeDoux 2005). This body of knowledge, which did not exist in Pavlov's day, was a necessary prerequisite for understanding extinction-induced modifications of previously acquired fear memory.

Animal Studies of Extinction

Given the central role of the amygdala in fear learning and expression, it is expected that extinction would involve changes in this structure. Barad et al (2006, in this issue) describe the physiological and molecular "footprints" of extinction in the amygdala. Following early observations that amygdala *N*-methyl-D-aspartate (NMDA) receptors were involved, they review recent evidence that voltage-gated calcium channels and cannabinoid receptors in the amygdala are also necessary for extinction, perhaps by modulating inhibitory intra-amygdala inhibitory circuits. Extinction may even involve erasure of conditioning memory in the amygdala, as suggested by the involvement of extinction-associated kinases and phosphatases in depotentiation. While this contradicts the prevalent view that extinction is not erasure, it raises the interesting possibility that extinction might partially erase recently acquired traumatic memories, under certain conditions. As shown for the cerebellum (Medina et al 2002), extinction may erase conditioning in some structures, while leaving it intact in others.

Another controversial question raised by Lattal et al (2006, in this issue) is whether long-term memory for extinction requires gene transcription and protein synthesis. Because these processes are involved in acquisition of fear conditioning, they may also be involved in the "new learning" of extinction. While there is substantial experimental support for this idea from rodents as well as invertebrates, there are also recent reports of intact extinction in the presence of protein synthesis blockers. This suggests that extinction learning may involve more subtle mechanisms of synaptic modification in the amygdala, such as cytoskeletal rearrangement.

The role of the hippocampus and prefrontal cortex in modulating amygdala-dependent fear memories is becoming increasingly central to models of extinction. Unlike conditioning, the expression of extinction is exquisitely controlled by contextual and temporal factors. Bouton et al (2006, in this issue) describe the behavioral and neural mechanisms involved in modulation of extinction, focusing on hippocampal and gamma-aminobutyric acid (GABA)ergic processes. Data such as these are directly applicable to the practice of therapeutic exposure, in which the context and timing of exposure sessions can be optimized for maximum benefit.

Interest in the prefrontal cortex as a site of extinction originated from studies in the 1960s showing that monkeys with lesions of the ventromedial prefrontal cortex (vmPFC) perseverated following changes in reward contingencies. Sotres-Bayon et al (2006, in this issue) review this work and describe how rats with lesions of the vmPFC show "emotional perseveration" in their responses to conditioned fear stimuli. The authors propose that vmPFC modulates fear via its projections to the lateral nucleus of the amygdala, while the hippocampus modulates fear via its projections to the vmPFC, as well as the basal nucleus of the amygdala. Elaborating on the role of the prefrontal cortex, Quirk et al (2006, in this issue) describe converging lines of evidence from their laboratories, suggesting that the infralimbic (IL) prefrontal cortex is necessary for proper recall of extinction in rodents: 1) extinction enhances IL neuronal activity; 2) extinction behavior is correlated with IL activity; and 3) augmenting IL activity with electrical or metabolic methods enhances extinction. Thus, enhancing the function of ventral prefrontal cortex area may be a goal of future therapies for anxiety disorders. An emerging model suggests that while extinction is learned within the basolateral amygdala, the expression of extinction at a later time (which depends on contextual and temporal factors) requires prefrontal and hippocampal inputs to the amygdala.

Translation to Humans

How well does extinction research in animals translate to humans? Hermans et al (2006, in this issue) show that the behavioral properties of extinction discovered in animals are also

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observed in people undergoing fear conditioning within the laboratory. These include stimulus specificity, renewal of fear after a context shift, reinstatement of fear by an aversive event, and protection from extinction by pharmacological and behavioral interventions that decrease fear expression. This suggests that methods used to facilitate extinction in rodents may also facilitate exposure therapy for individuals with anxiety disorders. For example, phobics show renewal of fear responses after exposure therapy, but this can be reduced by mentally rehearsing the context in which exposure was given.

A particular compelling example of translating rodent research to humans is provided by Davis et al (2006, in this issue). Reversing the logic that extinction is prevented by NMDA receptor antagonists, they show that extinction can be facilitated with a partial agonist of NMDA receptors, d-cycloserine (DCS), in rats. They go on to show that DCS improves the response of height phobics to exposure therapy in a virtual reality simulation of heights. Phobics receiving DCS in conjunction with exposure showed faster decreases in fear responses and exposed themselves to more real-life height situations months after treatment. The promise of this drug as an adjunct to exposure therapy is strengthened by new studies in rats showing that extinction learned with d-cycloserine generalizes to other conditioned stimuli and is not susceptible to shock-induced reinstatement of fear. The use of drugs implicated in animal studies of extinction as adjuncts to exposure therapy is likely to grow and may include monoaminergic or cannabinoidergic compounds.

A critical question for translational studies of extinction is how similar are extinction-related areas in the brains of rodents and humans? Rauch et al (2006, in this issue) address this question with human neuroimaging of normal subjects undergoing conditioning and extinction. Similar to rodents, extinction activates the ventral prefrontal cortex as well as the amygdala. Subjects' ability to recall extinction when retested 24 hours after training is correlated with the size and activity of vmPFC. This initial map of extinction circuitry overlaps with neuroimaging studies of posttraumatic stress disorder (PTSD), which implicate a triad of structures: amygdala, vmPFC, and hippocampus. The amygdala is generally overactive, while the vmPFC and hippocampus are underactive. Taken together, these findings suggest that extinction circuits are deficient in PTSD and raise the exciting possibility that imaging results may predict clinical response to cognitive-based therapies for PTSD.

While extinction is an old phenomenon, the neural mechanism of extinction is a new field that has already shown promise for improving the treatment of anxiety disorders (Hofmann et al 2006; Ressler et al 2004). Future research will distinguish the roles of the amygdala, hippocampus, and prefrontal cortex in extinction learning and retention. Clinical dividends of extinction research are likely to consist of: 1) new behavioral methods for optimizing exposure therapy; 2) pharmacological adjuncts for optimizing exposure therapy; 3) methods to partially erase fear memories; and 4) imaging-based diagnostic tools to predict clinical outcome and assess therapeutic progress. To achieve these goals, it will be important to maintain an active dialogue between basic and clinical researchers working on extinction and its applications.

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