Published in final edited form as:

Biol Psychiatry. 2006 August 15; 60(4): 319–321.

The Promise of Extinction Research for the Prevention and Treatment of Anxiety Disorders

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A conservative estimate indicates that almost 30% of the U.S. population will be afflicted with an anxiety disorder at some point in their lives, and preliminary data suggest that this risk is increasing (Kessler et al 2005a). A significant proportion of people diagnosed with an anxiety disorder will experience severe and chronic symptoms that can significantly interfere with the ability to carry out normal daily activities and increase the risk of suicide (Kessler et al 2005b). Specific phobias, social phobia, and post-traumatic stress disorder (PTSD) constitute the most prevalent anxiety disorders, and their incidence is likely to rise with increasing numbers of Iraq and Afghanistan war veterans and as the victims of Katrina and other disaster survivors continue to process and cope with their losses. Recent estimates indicate that at least 17% of Iraq veterans will develop PTSD, generalized anxiety disorder, or depression, twice as many as would be expected before deployment and four times that found in the general population (Hogue et al 2004). This figure does not include severely wounded or disabled veterans and thus likely underestimates what the actual rates will be. Exposure to combat, duration of deployment, and injury considerably increase the risk of developing mental health problems, particularly with regard to PTSD. Although soldiers returning from Iraq are significantly more likely to develop mental health problems, the majority of those who are diagnosed with a psychiatric disorder and/or acknowledge that they have a problem will not seek treatment for fear of being stigmatized (Hogue et al 2004). These findings emphasize the importance and urgency of not only finding effective treatments for PTSD and other anxiety disorders but also for discovering ways to prevent their onset. The development of new approaches to anxiety disorders that are based on the basic neurobiology of extinction represents perhaps the best current opportunity for translating neuroscience discoveries into clinical applications for the prediction, pre-emption, and personalized treatment of a mental disorder.

The inability to extinguish or inhibit maladaptive fear responses is a hallmark of most anxiety disorders and PTSD in particular. Current treatments for anxiety disorders involve the use of medications and/or behavioral therapy. The major class of drugs that is currently used to treat anxiety disorders, the selective serotonin reuptake inhibitors or SSRIs, can be effective at reducing the symptoms of some anxiety disorders but are not cures. Cognitive and behavioral therapies use exposure techniques that require patients to confront the fear-inducing situation in a safe environment. The aim of these treatments is to teach the patient that the fearful stimulus no longer predicts harmful consequences. One of the ways the National Institute of Mental Health (NIMH) seeks to enhance the effectiveness of pharmacological and behavioral therapies for anxiety disorders is through basic research on extinction learning and its consolidation into long-term memory. Like exposure therapy, extinction learning occurs after repeated exposure to a previously fearful event that is no longer associated with an aversive outcome. Animal models of extinction learning are particularly powerful for investigating the behavioral and neural mechanisms underlying this form of learning and how it can be enhanced and strengthened. Fortunately, there has been an enormous increase in interest in understanding the neurobiology of extinction learning, perhaps best illustrated by the more than three-fold increase in the number of basic research papers published per year on extinction learning within the past 6 years.

To assess how basic research on extinction learning could accelerate the development of improved treatments for anxiety disorders, NIMH convened a workshop in 2003 that brought together basic and clinical researchers investigating extinction learning in animals and anxiety disorders in humans. One of the key conclusions of this meeting was that research at the behavioral, systems, cellular, and molecular levels is needed to understand the mechanisms underlying extinction learning and that each of these approaches will yield important insights that will facilitate the development of better therapies for anxiety disorders. Similarly, clinical studies of patients suffering from fear and anxiety disorders can inform the development of animal models that more closely parallel the behavioral and psychological deficits associated with these disorders.

Research at the behavioral level has shown that most (although not all) forms of extinction learning do not involve the reversal or forgetting of learned fear associations but rather represent new learning that inhibits the original fear association (Bouton 2004 and Rescorla and Heth 1975). This finding has significant implications for when and where to target treatments that enhance extinction learning after development of a fear association versus those that might prevent the initial development of the fear association. Additional research on the effects of timing and intensity of exposure to a nonreinforced fear stimulus would provide insights that would have clinical utility. Behavioral research has also effectively demonstrated the effects of the context in which extinction learning takes place on subsequent long-term retention of extinction learning. This is a significant clinical issue, because most treatments are context-specific and do not generalize to the real world once the patient is outside the therapist's environment. Work in both animals and humans is critical for determining how contextual cues can be used to strengthen extinction learning and for preventing relapse in novel environments.

At the systems level, physiological and lesion studies in animals and imaging studies in humans have begun to elucidate the circuitry that supports extinction learning. It is now well accepted that this circuitry includes the amygdala, prefrontal cortex, and hippocampus, and recent studies have implicated the medial prefrontal cortex as a potential site for the consolidation and expression of extinction learning (Milad and Quirk 2002). Functional and structural imaging studies in humans are demonstrating differences in prefrontal and amygdala volumes and activation patterns that might differentiate people with PTSD (Shin et al 2001) and might predict vulnerability to develop anxiety disorders (Milad et al 2005). Other studies are focusing on the role of the hippocampus in encoding the context of extinction learning and the factors that affect generalization to novel contexts (Corcoran et al 2005). The existence of multiple sites of plasticity for extinction processes has significant implications for translational research and treatment development.

Research at the cellular and molecular level is leading to the identification of molecular and genetic factors that might contribute to the inability to extinguish fearful memories. Research in genetically altered mice implicates the gastrin-releasing peptide receptor gene (GRPR) in fear memories and suggests that stimulation of the GRPR system might reduce anxiety (Shumyatsky et al 2002). Genetic differences in the expression of GRPR might also provide a biomarker for vulnerability to anxiety. The use of simple model organisms including snails, *Drosophila*, and *C. elegans* could be particularly powerful for understanding the molecular and genetic factors that contribute to extinction learning. Research on these species indicates that they can undergo sophisticated forms of associative learning, including aversive learning and contextual conditioning, and might also show extinction (e.g., Rankin 2000, Sangha et al 2003, Schwaerzel et al 2002 and Zhang et al 2005). These organisms are particularly well suited for exploring the genes that control learning and how these genes modulate protein expression in the circuitry critical for extinction learning and consolidation.

Several lines of basic and clinical research have begun to identify promising new pharmacological targets for treating anxiety disorders on the basis of findings implicating alterations in glutamate and γ -aminobutyric acid (GABA)ergic transmission after fear conditioning and extinction. A seminal finding from Michael Davis's group showed that D-cycloserine (DCS), a partial N-methyl-D-aspartate (NMDA) glutamate agonist, can facilitate the extinction of fear conditioning in rats (Walker et al 2002). This finding has led to several clinical studies that tested whether DCS can facilitate recovery from specific anxiety disorders when used in combination with exposure therapy and is an outstanding example of how research on the basic mechanisms of extinction learning in animals is being successfully translated into novel treatments for human fear disorders. One study by Dr. Davis's group that is discussed in this issue shows that the use of DCS can facilitate recovery from specific phobias in humans and might prevent relapse in novel contexts (see also Ressler et al 2004). A preliminary report also indicates that DCS, in combination with exposure therapy, is effective for treating social anxiety disorder (Hofmann et al 2006). There has also been an increased focus on the regulation of GABAergic inhibitory interneurons within the amygdala because they regulate the output of the amygdala to downstream structures that in turn regulate the expression of fear. Findings that activation of CB1 cannabinoid receptors facilitates extinction through inhibitory effects on GABAergic neurons in the amygdala of rats and mice suggest that the use of CB1 agonists could potentially enhance extinction learning in humans (Chhatwal et al 2005 and Marsicano et al 2002). These findings and others highlight the importance of glutamate and GABA transmission in extinction and the need to understand the balance between the excitatory and inhibitory influences that control amygdala output. As we understand these various influences on extinction learning in humans, we hope to realize the ultimate goal of personalized therapy: identifying individual patterns of pathophysiology that indicate which pharmacological or behavioral treatment will be most useful for any individual patient.

The NIMH priorities of prediction and pre-emption will require the discovery of biomarkers (behavioral, physiological, genetic, etc.) that indicate whether an individual will develop a mental disorder. Some interesting work is underway to determine whether gene expression patterns can differentiate individuals at risk for the development of anxiety disorders after a traumatic event. Research from Ariel Shalev and his colleagues illustrates the promise of this approach (Segman et al 2005). They examined gene expression profiles of peripheral blood cells collected from trauma survivors and were able to identify a pattern of gene expression that successfully predicted which of the survivors would develop PTSD and the severity of the disorder. It will be interesting to see if this or similar genetic signatures correlate with the extinction of fear. Similarly, attempts to link variations in genetic polymorphisms to brain function and behavior are yielding important insights into the factors that might bias vulnerability to psychiatric disorders. For example, relatively common variations in the gene coding for the human serotonin transporter (5-HTTLPR) have been linked with alterations in amygdala activity, changes in the amygdala-prefrontal circuit that is thought to support emotional regulation, and variations in experimental measures of anxiety (see Hariri et al 2006 and Pezawas et al 2005). Efforts to combine molecular "fingerprinting" and variations in single nucleotide polymorphisms represent exciting diagnostic approaches that could be used to develop predictive and pre-emptive strategies for PTSD and other anxiety disorders.

From the NIMH perspective, the strides made in understanding both the behavioral and biological mechanisms that give rise to extinction learning are exceptionally promising and present new opportunities for understanding how deficits in extinction learning are related to psychiatric disorders characterized by maladaptive fear responses. The field is now poised to take advantage of basic research findings to make significant advances in the treatment and prevention of these disorders. This includes not only new drug development but also the identification of biomarkers that can predict vulnerability to these disorders.

To encourage these efforts, the NIMH was very excited to have the opportunity to support the conference “Extinction: The Neural Mechanisms of Behavior Change” held at the Ponce School of Medicine in February 2005, the proceedings of which make up this special issue. This conference brought together the largest group of basic and clinical researchers studying extinction and anxiety disorders and underscored the importance of doing research at multiple levels (molecular, cellular, systems, behavioral, and clinical) to understand the mechanisms that prevent the development of fear disorders and facilitate extinction learning. The presentations at this conference and the papers in this journal issue provide outstanding examples of recent findings from each of these domains and highlight the many opportunities for basic research on extinction to be translated into clinical treatments for anxiety disorders. The NIMH encourages innovative basic research at multiple levels to understand the mechanisms driving extinction as well as clinical research that translates basic findings on extinction mechanisms into more effective treatments for anxiety disorders.

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