REVIEW ARTICLE

Translating findings from basic fear research to clinical psychiatry in Puerto Rico

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Recent advances in the neuroscience of classical fear conditioning from both rodent and human studies are beginning to be translated to the psychiatry clinic. In particular, our understanding of fear extinction as a form of "safety learning" holds promise for the treatment of anxiety disorders in which extinction learning is thought to be compromised. The Department of Psychiatry at the UPR, School of Medicine promotes the development of innovative strategies for treating mental health problems. Given the burden resulting from anxiety disorders in Puerto Rico, and the lack of evidence-based treatment practices, there is a pressing need for a future center specializing in the treatment of anxiety related disorders. This center would also serve research and training functions, with the ultimate goal of translating extinction research into clinical practice. This review presents the current developments in extinction research and its relationship to anxiety disorders and treatment. We also analyze the available literature on the epidemiology of anxiety disorders and the existing evidence-based treatments for these conditions.

Key words: Anxiety disorders, Extinction, Prefrontal cortex, Amygdala.

Why research in fear learning?

While some of our fears may be innate (such as fear of heights or loud noises), the majority of our fears are learned through experience. Fear learning is highly conserved evolutionarily, and is thought to help organisms detect and avoid danger (1-4). In fact, the neural mechanisms of fear learning are remarkably similar across vertebrates. Basic fear memories are formed and stored in the amygdala (5). Expression of fear memories is regulated by the hippocampus and other cortical areas based on contextual or other parameters. Deficits in regulation of fear expression are thought to underlie anxiety disorders such as post-traumatic stress (PTSD) and phobias (6). A convenient model for understanding fear learning is classical fear conditioning in which a sensory stimulus such as a tone is paired with an electric shock. Both humans and rodents rapidly learn that the tone predicts the shock and show conditioned fear responses to the tone. In rodents, this takes the form of freezing, whereas in humans, there is a mild sweating response (skin conductance response, SCR). These learned fear responses can then be correlated with neural activity and pharmacological manipulations. Classical fear conditioning models the "automatic" fear learning that occurs when a person undergoes an aversive or life-threatening event.

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Overcoming fear through extinction learning

The main objective of fear research is to reduce pathological forms of fear and anxiety. An important experimental model of fear inhibition is extinction of conditioned fear, in which the conditioned tone is presented repeatedly without the shock. Under these circumstances, the subject learns that the tone no longer predicts the shock, and fear responses diminish. Indeed, following extinction, the subject responds to the tone as if conditioning never took place. However, it has been known since Pavlov's classic studies with dogs that extinction training does not erase the original fear learning, but is a form of learned inhibition (7). Simple behavioral experiments show that extinguished fear responses can return following the passage of time, or change of context. Thus, extinction training generates a new memory of safety that co-exists with fear memory (Figure 1). Healthy emotional regulation depends on which of these opposing memories is selected for expression at any given time. For this reason, there is considerable recent interest in

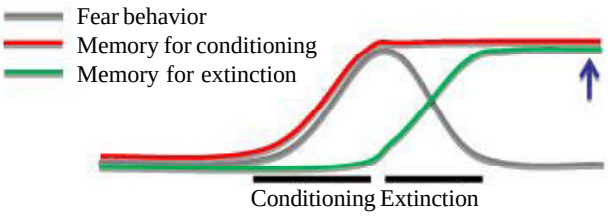

Figure 1. Schematic relating conditioned behavior to memory for conditioning and extinction. As first suggested by Pavlov, extinction training does not eliminate memory for conditioning, but generates a new memory that competes with conditioning for control of behavior. Following extinction, there exists two opposing memories (arrow), whose expression depends on contextual and temporal factors (11).

understanding how the hippocampus and prefrontal cortex interact with each other and the amygdala to regulate fear expression. From a clinical perspective, a fuller understanding of extinction mechanisms could lead to new ways to facilitate exposure-based therapies, which use extinction to desensitize patients to the stimuli that trigger fear responses (see below).

Neuroanatomy of extinction in rodents and humans

Much has been learned within the past 10 years about the neuroanatomy of extinction, building on the extensive literature on fear conditioning (8-10). In addition to its central role in learning fear associations, the amygdala also contains inhibitory circuits capable of learning extinction. The expression of fear memories after extinction, however, is regulated by contextual and temporal factors via projections to the amygdala by the hippocampus and prefrontal cortex. In rodents, interrupting medial prefrontal (mPFC) function with lesions or pharmacological manipulations does not prevent extinction learning, but impairs later retrieval of extinction, causing abnormally high levels of fear (11). Similarly, interrupting the hippocampus does not prevent extinction, but removes the contextual modulation of extinction retrieval (12). Thus the mPFC, hippocampus, and amygdala work together in the healthy brain to learn both fear and extinction, and to regulate accordingly the expression of fear (Figure 2).

In healthy humans, learned fear can be studied by administering auditory or visual stimuli paired with mild electric shocks, while measuring the skin conductance response (SCR) from the palm of the hand. Combining SCR measurements with functional magnetic resonance imaging (fMRI) of the brain indicates that the neuroanatomy of fear extinction in rodents is highly conserved in humans. While the amygdala is activated by fear conditioning, the ventral mPFC is activated by extinction (13-15). Importantly, the vmPFC is activated when subjects are recalling extinction learned the previous day, similar to rodent studies. The hippocampus is also activated, suggesting that these structures work together to inhibit amygdala-dependent fear responses.

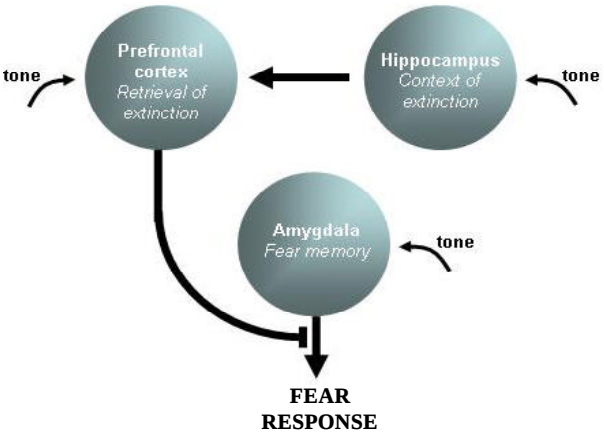

Figure 2. Extinction learning and expression relies on a network of three structures. The amygdala stores both conditioning and extinction memories. Tone information enters the amygdala, hippocampus, and prefrontal cortex. The prefrontal cortex integrates tone information with contextual information from the hippocampus in order to gate extinction retrieval. Inside the extinction context, the prefrontal cortex inhibits amygdala output, to reduce the expression of fear. Outside the extinction context, amygdala output is uninhibited, and fear is expressed (9).

Neuroanatomy of anxiety disorders: overlap with extinction

The neuroanatomy and neurophysiology of anxiety disorders overlaps to a large degree with that of extinction. People with post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and phobias show increased activity in the amygdala coupled with decreased activity in the vmPFC (16-18), consistent with a failure of "top down" control of fear responses. In further support of this, the volume tissue in the ventral mPFC and the hippocampus is reduced in individuals with PTSD (19-20), consistent with decreased function of regulatory systems. This suggests that there is a failure of extinction processes in anxiety disorders, an idea which has received direct experimental support in patients with PTSD (21-22). A failure of extinction in anxiety disorders has two important implications: 1) it could contribute to the etiology or maintenance of the disease, as patients are unable to control anxiety responses, and 2) it could impair treatments that rely on extinction, such as exposure therapy and other forms of cognitive behavioral therapy (CBT). Indeed, it has been hypothesized that failure to extinguish fear could explain why a minority of trauma victims are vulnerable to

developing PTSD (6).

Facilitating extinction learning

Can extinction be facilitated via pharmacological or other means? This is the key question for translating extinction research to the clinic. Preclinical rodent studies in the last few years have demonstrated facilitation of extinction by various compounds, administered systemically to rats during extinction training. Table 1 lists these compounds, which include agonists of receptor systems implicated in extinction learning. The most promising of these has been d-cycloserine (DCS), a partial agonist of the n-methyl-d-aspartate (NMDA) receptor. In pilot data, DCS has been shown to strengthen extinction memory in subjects undergoing exposure therapy for fear of heights as well as social phobia (23-24). This suggests that DCS or other drugs can be used as adjuncts to therapy to increase the effectiveness and/or shorten the duration of the therapy. Clinical trials of DCS by NIH are underway. Extinction learning can also enhanced by electrical stimulation of the prefrontal cortex or its inputs in rodents (25-26). Paralleling this, deep brain stimulation of prefrontal sites in humans is now being tested for treatment for refractory OCD (27) and depression (28). Extinction learning varies with menstrual cycles in rodents and humans (29-30), suggesting that extinction-based therapies in women may need to be properly timed for maximal effectiveness. Thus, research on extinction has great potential to be translated to the psychiatric clinic for treatment of anxiety and other disorders (31).

Table 1. Pharmacological enhancers of extinction (systemic)

	Drug	Action	Reference
Preclinical			
	d-cycloserine	partial NMDAr agonist	Walker et al., 2002 (63)
	methylene blue	metabolic enhancer	Gonzalez-Lima and Bruchey, 2004 (64)
	yohimbine	noradrenergic a2r antagonist	Cain et al., 2004 (65)
	sulpiride	dopamine D2r antagonist	Ponnusamy et al., 2005 (66)
	AM-404	cannabinoid reuptake inhibitor	Chhatwal et al., 2005 (67)
	WIN 55,212-2	cannabinoid receptor agonist	Pamplona et al., 2006 (68)
	dexamethasone	glucocorticoid receptor agonist	Yang et al., 2006 (69)
	PEPA	AMPA receptor potentiator	Zushida et al., 2007 (70)
Clinical			
	d-cycloserine	partial NMDAr agonist	Ressler et al., 2004 (71)
	cortisol	endogenous glucocorticoid	Soravia et al., 2006 (72)

General concepts of anxiety

Anxiety is a normal and transitory feeling experienced by most people in response to a threat. When this feeling of anxiety becomes extreme and impairs function, it is considered pathological (32). Iosifescu and Pollack describe three criteria to identify pathological vs. normal anxiety: pathological anxiety often has no environmental trigger (autonomy); symptoms persist for long periods of time, and the individual resorts to maladaptive strategies such as avoidance or withdrawal (33). The presence of pathological anxiety usually indicates an anxiety disorder.

Epidemiology of anxiety disorders in the US

Evidence suggests that anxiety disorders are the most common psychiatric disorder in the U.S. In the NIMH Epidemiologic Catchment Area (ECA) study, an estimated 6-month prevalence rate of 8.9% and a lifetime prevalence rate of 14.6% were reported for the general population of the US, affecting 26.9 million individuals in the United States (34). Costs associated with anxiety disorders amounted to $46.6 billion in 1990, accounting for 31.5% of total expenditures in that year for mental health (35-36). Individuals with anxiety disorders show higher than normal rates of impairment in work and relationships, and even subthreshold forms of the disorders are associated with impairments (37).

Epidemiology of anxiety disorders in Puerto Rico

Anxiety disorders are a worldwide phenomenon and cut across cultural boundaries. Data from epidemiological studies carried out in Puerto Rico with 1.8 million subjects as presented by Canino et al, suggest a similar prevalence compared with the US data (Canino et al., 1987). In Puerto Rico, the 6-month prevalence rate of anxiety disorders was estimated to be 7.5% and lifetime prevalence was 13.6%. In other words, more than 500,000 people in Puerto Rico will be affected by an anxiety disorder in their lifetime. Women are twice as likely as men to present with an anxiety disorder (9.9% vs. 4,7% in a 6 month period), and the incidence of anxiety disorders will increase 5% over the

next six years (39). Thus, there is a pressing need to treat anxiety disorders in Puerto Rico.

Spectrum of Disorders and Comorbidities

Among the anxiety spectrum disorders, the most common diagnoses include Generalized Anxiety Disorder, Panic Disorder, Posttraumatic Stress Disorder (PTSD), Social Anxiety Disorder, and Obsessive Compulsive Disorder. These represent a heterogeneous group of disorders featuring anxiety as a core symptom. Anxiety disorders often show comorbidities with other physical or psychiatric illnesses. The most common comorbidities include depression, substance abuse, eating disorders, other anxiety disorders, and illnesses, such as cancer, cardiac conditions, hypertension, irritable bowel syndrome, thyroid conditions and migraine headaches (40-41). In the Puerto Rican population, several studies have reported physical complaints associated with anxiety disorders, usually described as somatization (42-43). In particular, the term "*ataques de nervios*" has been used to describe a culture-bound syndrome involving somatization and anxiety symptoms (42). Complaints of "ataques de nervios" have not been related to increased psychopathology, but it must be recognized as an important cultural aspect related to anxiety disorders in Puerto Rico (44-47).

Anxiety in the Primary Care Setting

Since most patients with anxiety disorders first experience general somatic symptoms, they initially present to their primary care physician. At this level of care, most of these symptoms are unrecognized or misdiagnosed and therefore not treated. In a study that included 965 patients from family practices and internal medicine clinics in 12 states, nearly 20% of these patients had at least one anxiety disorder and many had more than one (48). Of the 20% showing one disorder, 41% reported not receiving any kind of treatment (medications, counseling or psychotherapy). In a study of anxiety disorders among Puerto Rican primary care patients, similar results were reported (49), suggesting that anxiety disorders are both underdiagnosed and undertreated in Puerto Rico.

Treatment of anxiety disorders

The fact that disabling conditions such as anxiety disorders are often under recognized and under treated is even more worrisome since there are several evidence based treatments available for these conditions (50-51). Anxiety disorders have been found to be associated with anatomical, physiological, and biochemical changes in the brain that have led to the use of psychopharmacological interventions. One of the most commonly used medications for the treatment of anxiety disorders is the selective serotonin reuptake inhibitors (SSRIs), sertraline or paroxetine, which increase serotonin levels within the synapse. Long-term exposure to SSRI's induces changes in second messenger systems that lead to modifications in the individual's response to anxiety provoking stimuli (52). Another important neurotransmitter etiologically related to anxiety is norepinephrine, which has been consistently associated with the physiological manifestations of anxiety (53). Medications that increase norepinephrine at the synaptic level, such as venlafaxine, have shown great efficacy in the treatment of anxiety disorders. Although most patients improve with adequate treatment, most cases do not achieve full or sustained remission (54).

Non-pharmacological treatments for anxiety disorders

More recently, psychological modalities based on neuroscience principles have been developed for treatment of anxiety disorders. The two main modalities are exposure therapy and cognitive-behavioral therapy (CBT) (55). Exposure therapy involves repeatedly exposing the patient to stimuli that trigger anxiety, under safe circumstances, so that fear responses extinguish. It is thought that repeated exposure reduces activity in limbic structures that mediate fear, thereby teaching the brain to interpret these stimuli as non-threatening (4). Exposure therapy is based on a growing literature detailing the neural mechanisms of extinction of fear (56-58). This type of treatment has been effectively used in specific phobia, social phobia, obsessive-compulsive disorder and post-traumatic stress disorder (55).

In contrast to exposure therapy, CBT strengthens the patient's cognitive ability to reduce anxiety responses, by fortifying the cortical processes (especially the prefrontal cortex) that help suppress the subcortical expressions of anxiety. Both exposure therapy and CBT involve cortical inhibitory processes which could potentially be strengthened by agents that facilitate extinction (e.g. Table 1). Comparisons of the effectiveness of pharmacotherapy vs. psychotherapy suggest that both are effective, and combined therapy is even more so (59-62). While symptoms can be reduced, no treatment yet exists that cues anxiety disorders.

Table 2. Anxiety disorders in P.R. and U.S.

Prevalence anxiety disorders	United States	Puerto Rico
6-month prevalence	8.90%	7.50%
Lifetime prevalence	14.60%	13.60%

Sample treatment vignette for anxiety disorder

This is the case of a 28 years old female patient with a specific phobia to heights. The patient has presented the symptoms of phobia since she was a child and has had great dysfunction due to her symptoms, including not being able to keep a job due to her inability to use elevators and never leaving the Island due to her fear of flying. The patient finally decided to seek treatment after being unable to take her child to the playground due to fear of slides.

Pharmacological treatments

Since the symptoms of this patient affect everyday activity, it would be useful to use a medication that can help change the response to anxiogenic stimuli, which can include an SSRI such as sertraline or venlafaxine. In addition, a benzodiazepine can be used to treat episodes of breakthrough anxiety.

Psychological treatments

The patient can be treated with both exposure therapy and cognitive therapy. In exposure therapy, a list of anxiety provoking stimuli will be made and the patient will give them an anxiety index (for example, in a scale from 1-100). The therapy would start with exposing the patient to the stimuli that have the lowest anxiety indexes. For example, seeing a photo of a person on top the Empire State Building. The person will be exposed to this stimulus until she states that she no longer feels anxious when seeing the photo and when no physiological anxiety responses are seen. The exposures will continue, using stimuli with higher anxiety levels, until the patient states that she does not feel anxious to any of the stimuli. This could take the form of literally exposing the patient to heights. In cognitive therapy, the patient will be asked to identify her thoughts related to increased height and these thoughts would be challenged. For example, the patient might say that she does not go up more than three flights of stairs since she might fall and die. The therapy would consist of examining the probability of falling down a flight of stairs and looking for options to decrease this probability until a point in which it is tolerable to the patient.

Combination treatment

The patient can be started on medication and psychotherapy at the same time, since much of the evidence on anxiety disorders presents a synergistic effect of both treatments. In addition, both exposure and cognitive techniques can be combined to increase the effect of the psychological interventions.

What is needed to reduce the burden of anxiety disorders in Puerto Rico?

The mission of the Department of Psychiatry at the UPR, School of Medicine is to develop and promote innovative strategies for treating mental health problems that will best serve the needs of our community. Taking into consideration the burden that anxiety generates in our society, and the deficiencies in available treatment and response, our aim is to develop a center specialized in anxiety related disorders that would fill this gap (Figure 3). Such a Center would have three main functions:

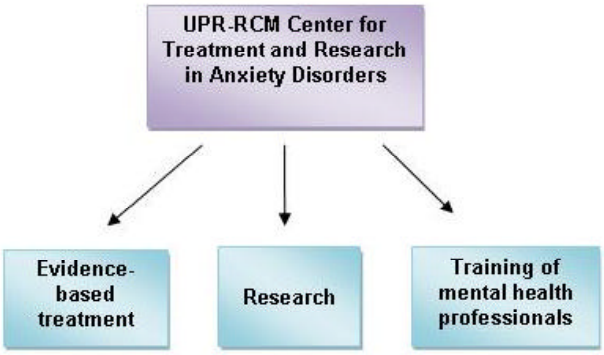

Figure 3. Proposed Center for Treatment of Anxiety Disorders, at the University of Puerto Rico School of Medicine.

1) **Service** (to make available to the Puerto Rico population the latest proven treatments for anxiety disorders),
2) **Research** (to translate animal research findings to humans with the goal of developing novel treatment strategies),
3) **Training** (to disseminate treatment strategies to the community of mental health professionals in Puerto Rico and Latin America). This center will be modeled after existing state-of-the-art centers for anxiety, such as the Center for the Treatment and Study of Anxiety, at the University of Pennsylvania, and the Massachusetts General Hospital Center for Anxiety and Traumatic Stress Disorders.

A specialized academic center with an interdisciplinary approach provides multiple benefits to the community. The first advantage is increased access to integrated care involving psychopharmacology and cognitive behavioral therapies. All members of the team will work together in preparing a treatment plan based on the individual needs of the patient. In addition, the academic atmosphere provides a fertile ground for conducting research aimed at

developing new treatment alternatives for our most challenging and refractory patients. Our team is now establishing human fear conditioning at UPR, with the initial objective of correlating physiological indices of extinction learning with performance on psychological tests of behavioral inhibition. A successful outcome could lead to the use of simple psychological tests to predict susceptibility to anxiety disorders, or to determine which anxiety patients are likely to benefit from extinction-based therapies. Finally, the ultimate goal is to transmit the knowledge and experienced acquired to our students, residents, and other mental health professionals, so that treatment advances can be disseminated to other communities in Puerto Rico, including rural areas. In this way, neuroscience and clinical practice can be integrated to reduce the impact of anxiety disorders throughout Puerto Rico.

Resumen

Los más recientes descubrimientos acerca de la neurociencia del condicionamiento clásico del miedo, tanto en estudios con humanos como con ratas, han comenzado a ser traducidos a la práctica clínica psiquiátrica. En especifico, nuestro conocimiento acerca de la extinción del miedo como una manera de "aprendizaje de seguridad" puede ayudar efectivamente en el desarrollo de tratamientos más específicos para los trastornos de ansiedad ya que se entiende que en estas condiciones puede haber un defecto en el aprendizaje de extinción. El Departamento de Psiquiatría de la Escuela de Medicina de la UPR promueve el desarrollo de estrategias innovadoras para tratar los problemas de salud mental. Dado el impacto en la salud pública de los trastornos de ansiedad en Puerto Rico y dado a la falta de practicas basadas en la evidencia, hay una necesidad urgente de un centro que se especialice en el tratamiento de trastornos de ansiedad. Este centro también podría ser un taller de entrenamiento e investigación con la meta final de traducir la investigación en extinción a la clínica practica. En este artículo presentamos un repaso de la literatura con los últimos hallazgos en la investigación de extinción y su relación a los trastornos de ansiedad y su tratamiento. También analizamos la literatura existente acerca de la epidemiología de los trastornos de ansiedad y los tratamientos basados en la evidencia que existen en este momento.

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