



Conditioned Fear Acquisition and Generalization in Generalized Anxiety Disorder

Daniella Tinoco-González

Universitat Autònoma de Barcelona, Bellaterra

Miquel Angel Fullana

Universitat Autònoma de Barcelona, Bellaterra

Institute of Neuropsychiatry and Addictions, Hospital del Mar, Parc de Salut MAR, Barcelona

David Torrents-Rodas

Albert Bonillo

Universitat Autònoma de Barcelona, Bellaterra

Bram Vervliet

Leuven University

María Jesús Blasco

Institute of Neuropsychiatry and Addictions, Hospital del Mar, Parc de Salut MAR, Barcelona

Magí Farré

Human Pharmacology and Clinical Neurosciences Research Group, Neuroscience Research Program, Hospital del Mar Research Institute (IMIM), Parc de Salut MAR, Universitat Autònoma de Barcelona

Rafael Torrubia

Universitat Autònoma de Barcelona, Bellaterra

Abnormal fear conditioning processes (including fear acquisition and conditioned fear-generalization) have been implicated in the pathogenesis of anxiety disorders. Previous

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Address correspondence to Miquel A. Fullana, Ph.D., Institute of Neuropsychiatry & Addictions (INAD), Hospital del Mar, Passeig Marítim, 25/29. 08003 Barcelona, Spain; e-mail: miguelangelfullana@gmail.com.

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research has shown that individuals with panic disorder present enhanced conditioned fear-generalization in comparison to healthy controls. Enhanced conditioned fear-generalization could also characterize generalized anxiety disorder (GAD), but research so far is inconclusive. An important confounding factor in previous research is comorbidity. The present study examined conditioned fear-acquisition and fear-generalization in 28 patients with GAD and 30 healthy controls using a recently developed fear acquisition and generalization paradigm assessing fear-potentiated startle and online expectancies of the unconditioned stimulus. Analyses focused on GAD patients without comorbidity but included also patients with comorbid anxiety disorders. Patients and controls did not differ as regards fear acquisition. However, contrary to our

hypothesis, both groups did not differ either in most indexes of conditioned fear-generalization. Moreover, dimensional measures of GAD symptoms were not correlated with conditioned fear-generalization indexes. Comorbidity did not have a significant impact on the results. Our data suggest that conditioned fear-generalization is not enhanced in GAD. Results are discussed with special attention to the possible effects of comorbidity on fear learning abnormalities.

Keywords: fear conditioning; fear generalization; generalized anxiety disorder

FEAR CONDITIONING IS A FORM OF ASSOCIATIVE LEARNING by which a neutral stimulus is repeatedly paired with an aversive unconditioned stimulus (US), becoming a conditioned stimulus (CS), which is capable of eliciting a conditioned fear response (CR). Although fear conditioning is an adaptive form of learning, it may become a source of pathology when anxious reactivity to a CS persists in the absence of a CS/US association.

Several fear conditioning processes have been implicated in the pathogenesis of anxiety disorders (Lissek et al., 2005; Mineka & Zinbarg, 2006). These processes include acquisition, within-session extinction, extinction recall, conditioned inhibition, and conditioned fear-generalization. For example, an enhanced fear acquisition may be characteristic of social phobia (Lissek et al., 2008a), generalized anxiety disorder (GAD; Thayer, Friedman, Borkovec, Johnsen, & Molina, 2000), or posttraumatic stress disorder (PTSD; Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 2000). Impaired within-session fear extinction has been shown for individuals with panic disorder (PD; Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007; Otto et al., 2014) or GAD (Pitman & Orr, 1986), whereas impaired extinction recall could be present in PTSD (Milad et al., 2008) or obsessive-compulsive disorder (OCD; Milad et al., 2013). Moreover, conditioned inhibition deficits may characterize PTSD (Jovanovic et al., 2009, 2010). However, these results have not been always replicated. For example, “normal” (i.e., not enhanced) fear acquisition has been reported in PD (Michael et al., 2007), social phobia (Hermann, Ziegler, Birbaumer, & Flor, 2002; Tinoco-González et al., 2014), or GAD (Pitman & Orr, 1986).

Conditioned fear-generalization occurs when fear CRs extend to a range of novel stimuli (generalization stimuli) that resemble the original CS. It can become maladaptive (i.e., excessive) when some of these stimuli are perceived as harmful

given the similarity and (non) discriminability to previously learned stimuli (Dunsmoor, Mitroff, & LaBar, 2009).

The possible role of conditioned fear-generalization in pathological anxiety has gained increased research recognition during the last decade (Hajcak et al., 2009; Lissek et al., 2008b, 2010, 2013; Vervliet, Vansteenwegen, Baeyens, Hermans, & Eelen, 2005; Vervliet, Vansteenwegen, & Eelen, 2004). Indeed, recent etiological accounts of anxiety disorders suggest that conditioned fear-generalization could be a central pathogenic marker of some anxiety disorders (Lissek, 2012), although prospective studies supporting this assumption are lacking. In several case-control studies, individuals with specific anxiety disorders have shown abnormal (i.e., enhanced) conditioned fear-generalization in comparison to healthy controls. This has been the case for PD (Lissek et al., 2010), PTSD (cited in Lissek et al., 2008b), and recently, GAD (Lissek et al., 2013). In GAD, generalization may contribute to an increase in the number of events triggering worry, the hallmark of the disorder (Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013). It may also contribute to worry about topics that only have a moderate relatedness with the original triggers (Lissek et al., 2013).

In the aforementioned study, Lissek et al. (2013) compared fear acquisition and conditioned fear-generalization using a validated experimental paradigm (Lissek et al., 2008b) among 22 patients with GAD and 26 healthy controls. GAD patients showed abnormally broad conditioned fear-generalization gradients, compared to controls, as measured by the fear-potentiated startle, despite showing similar fear acquisition. However, in a recent study no evidence for enhanced conditioned fear-generalization in subjective (risk ratings) or autonomic (pupillary response) measures was found in women with GAD in comparison to healthy controls (Greenberg et al., 2013). A limitation of these two studies on conditioned fear-generalization in GAD is that almost 50% of patients had a comorbid anxiety (Lissek et al., 2013) or depressive (Greenberg et al., 2013) disorder. This casts doubts about the specificity of conditioned fear-generalization impairments in GAD. Additionally, studies on the role of certain individual differences variables that are closely related to GAD (e.g., trait-anxiety or trait-worry) in nonclinical or subclinical individuals using fear conditioning paradigms have also provided inconsistent results. For example, high-trait anxiety has been associated with enhanced fear acquisition in some studies (Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011), but not in others (Torrents-Rodas et al., 2013). The same is true for trait-worry

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