International Journal of Psychophysiology 121 (2017) 63–71

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Registered Reports

Does fear extinction in the laboratory predict outcomes of exposure therapy? A treatment analog study

Eduard Forcadell[a,b], David Torrents-Rodas[a,c], Bram Vervliet[d,e,f], David Leiva[g], Miquel Tortella-Feliu[h,i], Miquel A. Fullana[a,j,k,*]

[a] Department of Psychiatry and Forensic Medicine, School of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Catalonia, Spain
[b] Mental Health Department, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain
[c] Specialized Department in Mental Health and Intellectual Disability, Institut Assistència Sanitària (IAS), Parc Hospitalari Martí i Julià, Salt, Catalonia, Spain
[d] Center for Excellence on Generalization in Health and Psychopathology, KU Leuven, Leuven, Belgium
[e] Department of Psychiatry, Harvard Medical School, Boston, USA
[f] Department of Psychiatry, Massachusetts General Hospital, Boston, USA
[g] Department of Social Psychology and Quantitative Psychology, School of Psychology, Universitat de Barcelona, Barcelona, Spain
[h] University Research Institute on Health Sciencies (IUNICS), Universitat de les Illes Balears, Mallorca, Spain
[i] PROMOSAM Red de Investigación en procesos, mecanismos y tratamientos psicológicos para la promoción de la salud mental, Spain
[j] Anxiety Unit, Institute of Neuropsychiatry and Addictions, Hospital del Mar, CIBERSAM, Barcelona, Spain
[k] IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

ARTICLE INFO

Keywords:
Fear learning
Fear conditioning
Extinction learning
Extinction recall
Exposure therapy
Anxiety disorders

ABSTRACT

Fear extinction models have a key role in our understanding of anxiety disorders and their treatment with exposure therapy. Here, we tested whether individual differences in fear extinction learning and fear extinction recall in the laboratory were associated with the outcomes of an exposure therapy analog (ETA). Fifty adults with fear of spiders participated in a two-day fear-learning paradigm assessing fear extinction learning and fear extinction recall, and then underwent a brief ETA. Correlational analyses indicated that enhanced extinction learning was associated with better ETA outcome. Our results partially support the idea that individual differences in fear extinction learning may be associated with exposure therapy outcome, but suggest that further research in this area is needed.

1. Introduction

Fear learning models are important for our understanding of anxiety disorders and their treatment (Graham and Milad, 2011; VanElzakker et al., 2014). In a typical fear learning experiment, an initially neutral stimulus (conditioned stimulus, CS) elicits a conditioned fear response (CR) and generates a fear memory (*conditioning*) after being repeatedly paired with an aversive unconditioned stimulus (US). In humans, most fear learning experiments use a differential conditioning paradigm, where one CS (CS+) is followed by the US and another is not (CS−).

After conditioning, if the CS is presented repeatedly without the US, the CR decays and a safety memory is formed (*extinction learning*). In experiments where conditioning and extinction learning occur in different contexts, if the CS is presented later in the context where extinction learning took place, this extinction memory is expressed again (*extinction recall*).

Abnormalities in some of these fear-learning processes could characterize anxious individuals in comparison to healthy controls and be a hallmark of anxiety disorders. For example, impaired extinction learning has been observed in individuals with panic disorder or generalized anxiety disorder (Michael et al., 2007; Otto et al., 2014; Pitman and Orr, 1986), while impaired extinction recall could characterize individuals with post-traumatic stress disorder (Milad et al., 2008). Several theories have been proposed to explain the association between fear learning and anxiety disorders, including failure to inhibit fear to safety cues (Davis et al., 2000), deficits in associative learning (Grillon, 2002), stimulus generalization (Mineka and Zinbarg, 1996), and enhanced conditionability (Orr et al., 2000) (reviewed by Lissek et al., 2005).

Apart from their possible role in the origin of anxiety disorders, fear-learning variables may have also an important role in the treatment of these disorders. In fact, there are many similarities between exposure therapy and fear extinction learning. Exposure therapy (one of the central components of cognitive-behavioral therapy - CBT - for anxiety-

* Corresponding author at: Department of Psychiatry and Forensic Medicine, School of Medicine, UAB Campus, 08193 Bellaterra, Cerdanyola del Vallès, Spain.
E-mail address: mafr@copc.cat (M.A. Fullana).

http://dx.doi.org/10.1016/j.ijpsycho.2017.09.001
Received 31 March 2017; Received in revised form 24 August 2017; Accepted 5 September 2017
Available online 08 September 2017

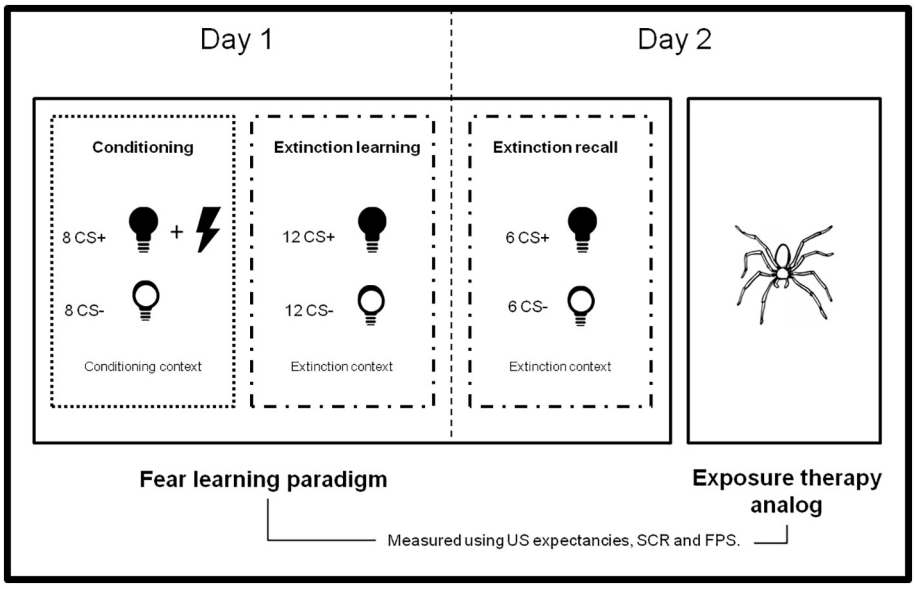

Fig. 1. Summary of experimental design.
US: unconditioned stimulus; SCR: Skin Conductance Response; FPS: Fear-Potentiated startle; CS +, conditioned stimulus associated with the unconditioned stimulus during the conditioning phase; CS −, conditioned stimulus never associated with the unconditioned stimulus.

related disorders) uses extinction learning principles by having the patient repeatedly confront a feared situation (CS) in the absence of danger (US) until fear diminishes (Myers and Davis, 2007). Moreover, extinction learning models may explain the mechanisms through which exposure therapy acts. For example, according to the inhibitory learning theory the original CS-US association learned during fear conditioning is not erased during fear extinction learning, but rather a new association (that the CS no longer predicts the US) is developed (Craske et al., 2008).

Research on fear extinction has gained momentum in recent years thanks to the exciting possibilities offered by translational research (Kindt, 2014; Milad and Quirk, 2012; Morrison and Ressler, 2014). Neuroimaging studies have shown that structural or functional variability in brain areas related to fear extinction is associated with the outcome of exposure therapy/CBT (Bryant et al., 2008; Fullana et al., 2014; Hoexter et al., 2013). Moreover, new pharmacological (Singewald et al., 2015) and behavioral (Schiller et al., 2010) approaches have been developed that focus on optimizing fear extinction abilities.

An important assumption from this research is that extinction learning in the laboratory is (almost) equivalent to exposure therapy (Berry et al., 2009; Hermans et al., 2006), and that the former should predict the latter (i.e. enhanced extinction learning would be associated with better outcomes from exposure therapy); however, this assumption has rarely been tested. One exception is a recent study by Waters and Pine (2016), who assessed fear conditioning and extinction learning in the laboratory using a differential conditioning paradigm and evaluative ratings (arousal and valence) and Skin Conductance Responses (SCR) as measures of fear in a group of clinically anxious children who then underwent CBT. The results showed that, during extinction learning, treatment non-responders did not show a significant decrease in fear (measured with the SCR) compared to responders and healthy controls. Waters and Pine (2016) assessed fear learning psychophysiologically using the SCR, and there is evidence that Fear-Potentiated startle (FPS) could be a more selective (i.e. less sensitive to declarative knowledge) measure of fear (Hamm and Weike, 2005; Sevenster et al., 2014; but see Luck and Lipp, 2015; Purkis and Lipp, 2001). Moreover, this study did not assess fear extinction recall, which may also be associated with exposure therapy outcomes (Milad and Quirk, 2012). Finally, it is not clear whether these findings can be replicated in adults, which is important because translational evidence suggests that extinction learning capacities may change over the life span (Baker et al., 2016; Pattwell et al., 2012).

Another recent study by Ball et al. (2016) explored the link between extinction learning and exposure therapy in a sample of 24 adults with public speaking anxiety. Brain activation and subjective ratings were assessed during extinction learning, and self-reported anxiety changes were collected during a massed exposure session, mimicking exposure therapy. Results showed that those with better extinction learning and changes in activation in brain regions associated with fear extinction (ventromedial prefrontal cortex, amygdala, insula, and periaqueductal gray) reported greater anxiety reduction during exposure therapy. This study focused only on extinction learning and did not assess extinction recall. Moreover, Ball et al. (2016) did not use psychophysiological measures of fear learning or anxiety reduction.

In the present study, we used a differential conditioning paradigm in adults with fear of spiders to test the hypothesis that individual differences in fear extinction in the laboratory would be associated with the outcome of an analog of exposure therapy (exposure therapy analog, ETA). Specifically, we expected that an enhanced fear extinction learning and fear extinction recall would be associated with a greater fear reduction from pre- to post-ETA. Following previous research (e.g. Pineles et al., 2016; Rabinak et al., 2013), we operationalized fear extinction as the difference between the CS + and CS − during extinction learning and extinction recall.

2. Materials and methods

See Fig. 1 for a summary of the experimental design.

2.1. Participants

We selected individuals with moderate to strong fear of spiders, as assessed by a dimensional instrument. Participants were recruited by advertisements to participate in a study on “physiological responses to anxiety”. Initially, 1504 individuals were screened with the validated Spanish version (Forcadell et al., 2014) of the *Fear of Spiders Questionnaire* (FSQ; Szymanski and O'Donohue, 1995) via a secure web system. Participants who scored in the top quartile of the study distribution (FSQ ≥ 33; n = 386) were invited to participate. Of those, 92 accepted to be interviewed by a doctoral-level clinical psychologist using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998).

Exclusion criteria were: (a) current or lifetime history of mental disorders other than specific phobia (animal type, spiders), as determined by the MINI, supplemented with the specific phobia section of