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Individual differences in fear relapse

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ABSTRACT

Vulnerability to anxiety disorders might be due to enhanced acquisition of aversive associations, impaired inhibition of those associations (extinction), and/or vulnerability to the return of fear (relapse). Animal research investigating the processes underpinning fear learning, extinction, and relapse will be critical to further advancing our understanding of anxiety disorders and their treatment. Here we examined whether individual differences in the rate of extinction might be related to vulnerability to relapse. Relapse of fear was examined by testing animals for conditioned freezing using renewal, reinstatement, and spontaneous recovery procedures. Across all three experiments we found that when tested under "milder" relapse conditions (in a novel context, after a mild reinstatement procedure, or 8 days after extinction training) Slow Extinguishers exhibited relapse of fear whereas Fast Extinguishers did not. However, when tested under "stronger" relapse conditions (in the training context, after a strong reinstatement procedure, or 29 days after extinction training) both Fast and Slow Extinguishers exhibited comparable relapse of fear. These results show that Slow Extinguishers are more vulnerable to relapse than Fast Extinguishers. These findings have clinical implications for identifying those most at risk of relapse following treatment and highlight the importance of developing further strategies to reduce relapse.

Anxiety disorders are one of the most common mental illnesses, with a lifetime prevalence rate of approximately 30% (Kessler et al., 2005). The gold-standard treatment is exposure, which involves repeatedly exposing the client to the anxiety-provoking situation so they overcome their anxiety and/or distress. While psychological and pharmacological interventions for anxiety disorders are very successful they have a major weakness: the fear often returns, with approximately a third of patients relapsing after treatment (Yonkers, Bruce, Dyck, & Keller, 2003) an outcome clearly at odds with the aims of therapy. Thus the current challenge is not how to reduce fear, but how to reduce relapse.

Given exposure therapy is based on fear extinction, which relies on a similar neural circuitry across species (Delamater & Westbrook, 2014; Milad & Quirk, 2012; Milad, Rauch, Pitman, & Quirk, 2006), research with animal models can provide valuable insights into the mechanisms of extinction and relapse (Goode & Maren, 2014; McNally, 2007). In Pavlovian fear conditioning a neutral conditioned stimulus (CS; e.g., a white noise) is paired with an aversive unconditioned stimulus (US; e.g., a footshock). With repeated presentations the subject learns the association between the CS and US such that subsequent presentations of the CS alone elicit a fear response (e.g., freezing in rats, increased skin conductance in humans). In contrast, extinction involves the repeated presentation of the CS without the US, leading to the formation of a new inhibitory CS-noUS association, which reduces the CS-elicited fear response. Relapse can then be modelled by the return of fear that occurs following the passing of time (spontaneous recovery), presentation of an aversive stimulus (reinstatement), or testing in a different context to that in which extinction occurred (renewal).

Preclinical research has provided many insights into how, through pharmacological or behavioral interventions, exposure therapy might be improved (for review see Fitzgerald, Seemann, & Maren, 2014; Graham, Langton, & Richardson, 2011; Milad & Quirk, 2012; Milad et al., 2006). However, despite the general acceptance that there are individual differences in vulnerability to mental disorders and treatment responsiveness in humans, until recently animal research has emphasized the "average" organism. There is now a growing interest in understanding individual differences, which might provide key insights into mental disorders and their treatment (Holmes & Singewald, 2013; Niermann, Figner, & Roelofs, 2017). For instance, Bush, Sotres-Bayon, and LeDoux (2007) reported that individual differences in rate of within-session extinction affected CS-elicited freezing the following day (i.e., extinction retention), such that rats that had a fast rate of extinction showed better extinction retention (i.e., less CS-elicited freezing at test the following day) than rats that had a slower rate of extinction (also see King, Scott, Graham, & Richardson, 2017; Reznikov, Diwan, Nobrega, & Hamani, 2015). However, the relationship between

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rate of extinction and vulnerability to relapse is unknown. Here, we examined whether individual differences in extinction rate predict the magnitude of renewal, reinstatement, and spontaneous recovery. For each relapse effect we looked at a "mild" relapse condition (i.e., ABC renewal, 1 reinstating US, or 8 days after extinction training) versus a "strong" relapse condition (i.e., ABA renewal, 2 reinstating USs, or 29 days after extinction training).

1. Experiment 1: renewal

To examine whether individual differences in the rate of extinction are related to vulnerability to relapse we first looked at renewal, the return of a previously extinguished response following a change in context (Bouton, 2002). In this experiment the mild relapse condition involved testing animals in a novel context (Context C), the strong relapse condition involved testing animals in the conditioning context (Context A), and the control condition was testing animals in the extinction context (Context B).

1.1. Methods

1.1.1. Subjects

Seventy-three experimentally-naïve adult male Sprague-Dawley rats bred at the School of Psychology at The University of New South Wales (UNSW) were used in this experiment (for number of rats per group see Table S1 in the Supplementary Material). Rats were housed in groups of 8 in plastic boxes (63 cm long x 42 cm wide x 22 cm high) with a wire lid. Animals were maintained on a 12-h light dark cycle (lights on a 0700 h), and food and water was available *ad libitum*. Animals were treated in accordance with *The Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (8th Edition, 2013) and all procedures were approved by the Animal Care and Ethics Committee at UNSW.

1.1.2. Apparatus

Conditioning, extinction, and test sessions were conducted in experimental chambers located within separate wood cabinets in order to minimize external noise and visual stimulation. Each chamber was fitted with a ventilation fan that produced a low, constant background noise (50 dB, measured by a digital sound level meter, Tenma model #72–942) and a wall-mounted infrared camera that was used to record the animal's behavior during the experiments. Chambers were cleaned with tap water between each session.

Context A consisted of a set of two identical rectangular chambers (13.5 cm long x 9 cm wide x 9 cm high). The front wall, rear wall, and ceiling consisted of clear Plexiglas. The floor and side walls consisted of 3 mm stainless steel rods set 1 cm apart. A custom-built, constant-current shock generator could deliver shock through the chamber floor. Two high-frequency speakers were mounted on either side of the chamber. These chambers had no source of illumination other than infrared LEDs.

Context B consisted of a set of two identical rectangular chambers (30 cm long x 30 cm wide x 23 cm high), with two opposing side walls consisting of 2 cm wide vertical black and white stripes. The other two walls and ceiling consisted of clear Plexiglas. The floor consisted of 3 mm stainless steel rods set 1 cm apart. A custom-built, constant-current shock generator could deliver shock through the chamber floor. Two high-frequency speakers were mounted in the ceiling of the chamber. A white LED light provided illumination in these chambers (approx. 12 lux; as measured by Digitech light meter QM1587).

Context C was identical to Context B except there was no source of illumination, other than infrared lighting, and the floor was clear Plexiglas.

1.1.3. Procedures

Conditioning, Extinction Training, and Test procedures occurred on consecutive days (see Fig. 1a), as detailed below. Freezing, a species-specific fear response defined as the absence of any movement except breathing (Fanselow, 1980), was measured in all experiments (for Data Analysis and Baseline Freezing scores in all three experiments see Supplementary Material).

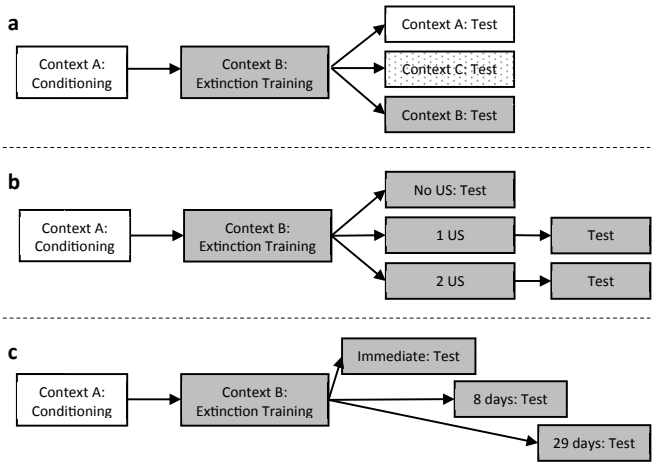

Fig. 1. Schematic for (a) Renewal procedure, (b) Reinstatement procedure, and (c) Spontaneous Recovery procedure. Context A is indicated by a white background, Context B by a grey background, and Context C by a stippled background.

1.1.3.1. Conditioning. Following a 2 min baseline period, the CS (white noise, 8 dB above background) was presented for 10 s and co-terminated with the footshock US (0.4 mA, 1 s). Animals received five CS-US pairings with an inter-trial interval that ranged from 85 s to 135 s, with a mean of 110 s. Animals were returned to their home cage approximately 20 s after the final CS-US pairing. Conditioning occurred in Context A.

1.1.3.2. Extinction training. One day after conditioning, animals underwent extinction training in Context B. Following a 2 min baseline period, the CS was repeatedly presented (10 s duration) with a 10 s inter-trial interval (ITI). Extinction training terminated once an animal reached a criterion of less than 35% freezing for 8 out of 10 consecutive blocks of CS presentations, where one block was three CS presentations. Based on pilot studies, animals extinguished to this criterion were expected to exhibit good extinction retention (i.e., low levels of freezing at test). Animals were returned to their home cage approximately 20 s after the final CS presentation.

The number of CS blocks required to reach extinction criterion was used to classify animals as having either a *Fast* or *Slow* rate of extinction (see Fig. 2a–c). Rather than using a median-split procedure to categorize animals as Fast or Slow Extinguishers, rats that reached criterion on $\leq$ 13 CS blocks were classified as the Fast fear extinction phenotype and those that reached criterion on $\geq$ 16 CS Blocks were classified as the Slow fear extinction phenotype, in all three experiments. Rats that reached extinction criterion on 14 or 15 CS Blocks were excluded from subsequent analyses. This procedure was followed to maximally differentiate the two phenotypes and to also avoid the situation where, depending on what the median value was in any given experiment, an intermediate number of trials to reach criterion could be categorized as being Fast in one experiment but Slow in another. In order to ensure that robust learning had occurred across all groups only rats that had greater than 50% CS-elicited freezing during either of the first two blocks of extinction were included for subsequent testing (for further details about exclusions see Supplementary Material).

1.1.3.3. Test. Test consisted of a 1 min baseline period followed by a 2 min presentation of the CS in Context A (i.e., ABA renewal), Context C (i.e., ABC renewal), or Context B (i.e., control ABB condition).

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