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Retention of perceptual generalization of fear extinction

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ABSTRACT

Fear reduction obtained during a fear extinction procedure can generalize from the extinction stimulus to other perceptually similar stimuli. Perceptual generalization of fear extinction typically follows a perceptual gradient, with increasing levels of fear reduction the more a stimulus resembles the extinction stimulus. The current study aimed to investigate whether perceptual generalization of fear extinction can be observed also after a retention interval of 24 h. Fear was acquired to three geometrical figures of different sizes (CS^+, $CS1^+$ and $CS2^+$) by consistently pairing them with a short-lasting suffocation experience (US). Three other geometrical figures that were never followed by the US served as control stimuli (CS^-, $CS1^-$, $CS2^-$). Next, only the CS^+ was extinguished by presenting it in the absence of the US. One day later, fear responses to all stimuli were assessed without any US-presentation. Outcome measures included startle blink EMG, skin conductance, US expectancy, respiratory rate and tidal volume. On day 2 spontaneous recovery of fear was observed in US expectancy and tidal volume, but not in the other outcomes. Evidence for the retention of fear extinction generalization was present in US expectancy and skin conductance, but a perceptual gradient in the retention of generalized fear extinction could not be observed.

1. Introduction

Fear conditioning implies that an initially innocent stimulus becomes a predictor (conditioned stimulus — CS) for a biologically relevant aversive event (an unconditioned stimulus — US) because of an experienced contingency between both. As a result of this associative learning process not only the US evokes a fear response (UR — unconditioned response), but also the CS generates a preparatory, defensive response (conditioned response — CR, Domjan, 2005). Once a CR is established it can occur also to other stimuli that never have been paired directly with the US (generalized stimuli — GSs), because they share certain properties with the CS (e.g. Vervliet and Geens, 2014; Lissek et al., 2008; Dunsmoor et al., 2009). Experimental research has demonstrated that physical or conceptual resemblance of the GSs with the CS promotes fear generalization to the GSs (Hajcak et al., 2009; Vervoort et al., 2014). Perceptual generalization seems to vary along a continuum of perceptual similarity: the more a GS resembles a CS, the greater the CR (Lissek et al., 2008).

Fear learning and fear generalization can be very adaptive mechanisms (Dunsmoor et al., 2009) but the capacity to re-evaluate a stimulus as safe when it no longer predicts danger, is just as crucial (Lommen et al., 2013). When the CS is administered repeatedly without the US, the CS–US contingency decreases and the CR gradually declines. It was first assumed that such extinction procedure generates a form of *un*-learning, i.e. the gradual weakening of the CS–US connection (Rescorla and Wagner, 1972; McConnell and Miller, 2014). However, several return-of-fear phenomena have demonstrated that the original CS–US fear association is not erased following an extinction procedure (Myers and Davis, 2007). Laboratory studies and clinical practice have systematically documented return of fear and relapse phenomena, respectively (Vervliet et al., 2013). For example, the mere passage of time can partly reinstall the CR to a previously extinguished CS ('spontaneous recovery'). Also the phenomenon of 'renewal' demonstrates the context dependency of extinction learning (Vervliet et al., 2013).

It is now widely accepted that extinction is not a mere *un*-learning of the excitatory CS–US association, but encompasses a form of new learning (Bouton, 2002; Myers et al., 2006) through which a CS acquires an inhibitory CS–noUS connotation next to the already existing excitatory CS–US association. The efficacy of exposure therapy should thus be evaluated in the light of its ability to create strong and easily retrievable inhibitory CS–noUS memory traces that can outweigh the excitatory fear connection (Raio et al., 2014). Thus, what is learned during exposure therapy is ideally transferrable to contexts other than the therapeutical setting, to stimuli beyond those used in exposure therapy, and over time. However, whereas acquired fear is prone to generalize over contexts, stimuli and time (Vervliet et al., 2013), generalization of fear extinction seems more difficult to establish. With regard to the generalization of fear extinction over different stimuli, early studies of Pavlov indicated that CSs of different sensory modalities that were trained with the same US all evoked less fear after only one of them had been extinguished (Myers and Davis, 2007). This result was however not

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replicated in an animal study (Kasprow et al., 1984) that failed to show extinction to a stimulus that had been paired with the same US as an extinction stimulus. More recent experiments suggest that extinction effects are rather 'extinction cue' — specific (Vervliet et al., 2004, 2005; Vervoort et al., 2014). For example, in a series of experiments Vervliet et al. (2004, 2005) demonstrated that only extinction with the original CS, but not with a GS, promotes generalization of fear extinction over stimulus dimensions. Vervoort et al. (2014) replicated these findings but with conceptual instead of perceptual stimulus categories. Interestingly, several studies (Myers and Davis, 2007; Bass and Hull, 1934; Hovland, 1937) have documented generalization gradients of fear extinction, with the smallest CRs to the extinction cue and increasingly greater CRs to cues falling farther away along the similarity continuum.

A hiatus in extant human research is that perceptual generalization gradients of fear extinction have almost always been studied immediately after the extinction procedure, while especially their retention is of clinical relevance. To our knowledge, only one, old study (Hovland, 1937) aimed to investigate the retention of extinction gradients in humans. The results of this study are however flawed by a lack of a good control condition, problems with the basic design and poor statistical analysis.

The purpose of this experiment is therefore to study the perceptual gradient of fear extinction with a panic-relevant US after a retention interval of one day. To this end, we will first install fear to three similar geometrical figures of different sizes (CS^+, $CS1^+$, $CS2^+$) by reinforcing them 100% with a breathing occlusion (US — see Pappens et al., 2014). Control stimuli will consist of other geometrical figures of similar size (CS^-, $CS1^-$, $CS2^-$). We will subsequently extinguish only one of the three figures (CS^+) by administering unreinforced CS trials. One day later we will test fear responses to all stimuli.

After a successful acquisition and extinction phase, we expect the following effects to occur:

(1) Spontaneous recovery.

a. Early on in the test phase (test1), the extinguished differential effect ($CS^+ > CS^-$) will recover. That is, the differential effect will be higher during test (test1) compared to the end of extinction (ext2): $(CS^+_{ext2} - CS^-_{ext2}) < (CS^+_{test1} - CS^-_{test1})$

b. Spontaneous recovery will also be visible in a higher response to CS^+ than to CS^- early on in the test phase: $CS^+_{test1} > CS^-_{test1.}$

(2) Retention of generalization of fear extinction.

a. At the start of the test phase, the differential effects for the unextinguished CS1 and CS2 pairs will be reduced compared to the differential effect for the CSs at the start of the extinction phase: $[(CS1^+_{test1} - CS1^-_{test1})$ and $(CS2^+_{test1} - CS2^-_{test1})] < (CS^+_{ext1} - CS^-_{ext1})$.

b. We will also test whether the unextinguished CS^+s still evoke stronger fear responses than their control stimuli early on in the test phase: $(CS1^+_{test1}, CS2^+_{test1}) > (CS1^-_{test1}, CS2^-_{test1})$. The more retention of generalization of fear extinction, the less the difference should be between the reinforced and the unreinforced CS1 and CS2.

(3) Perceptual gradient of generalization of fear extinction. During the first block of the test phase (test1), differential responses will be smaller for the CS1 compared to the CS2 pair, because $CS1^+$ is perceptually closer to the extinguished CS^+ than $CS2^+$: $(CS1^+_{test1} - CS1^-_{test1}) < (CS2^+_{test1} - CS2^-_{test1})$.

2. Material and methods

2.1. Participants

Thirty-nine first year psychology students (9 men; 18–26 years; $M = 19{,}87$) participated in return for 15 euros/h of participation.

Exclusion criteria were: current or past history of cardiovascular disease, chronic or acute respiratory disease, pregnancy, current or past history of drug or alcohol abuse or dependence, psychotropic drug use and any current or past psychiatric disorder including panic and anxiety disorders. Participants were instructed to abstain from alcohol and caffeinated drinks 24 h before the study and from food and drinks 2 h before the study. The study protocol was approved by the Medical Ethical Committee in accordance with the Declaration of Helsinki; all subjects signed an informed consent form stating – among other information – that participation was voluntary and that they could withdraw from the study at any moment.

2.2. Stimuli and apparatus

2.2.1. Stimuli

2.2.1.1. Geometrical figures. Blue or yellow colored pictures of geometrical shapes (three triangles and three circles of different sizes) served as conditional stimuli (CSs). Circle 1 had a diameter of 5.25 cm; circle 2 of 10.5 cm and circle 3 of 21 cm. Triangle 1 consisted of a base of 3.6 cm and 4.2 cm height, the base of triangle 2 measured 7,2 cm with 8,4 cm height and the dimensions of triangle 3 were 14.4 cm base and 16.7 cm height.

2.2.1.2. Breathing occlusion. The unconditional stimulus (US) was a complete obstruction of the breathing circuitry, making it impossible for the participant to breathe for a period of time. The length of the breathing occlusion was individually tailored by taking 40% of the personal breath holding time (BHT) after expiration.

2.2.2. Breathing apparatus

A mouthpiece was mounted onto a bacterial filter that was fitted on a pneumotachograph (Fleisch No. 2, Epalinges, Switzerland). The pneumotachograph was attached to a non-rebreathing valve of which the inspiratory port was connected to a 3-way Y-valve (stopcock type) using a vinyl tube (inner diameter: 3.5 cm; length 100 cm). This set-up enabled easy switching between unrestricted breathing and the breathing occlusion. The signal from the pneumotachograph was amplified using a pressure transducer (Sine Wave Carrier Demodulator CD15, Validyne Engineering™) and was calibrated daily with a 1 liter syringe. Fractional end-tidal CO_2 ($FetCO_2$) was measured using an infrared capnograph (POET II, Criticare, USA) that sampled expired air from the breathing circuit close to the mouthpiece. The capnograph's output was calibrated daily using a calibration gas containing 7.5% CO_2. Airflow and CO_2 waveforms were digitized at 20 Hz.

2.2.3. Skin conductance

Electrodermal activity was recorded with Fukuda standard Ag/AgCl electrodes (1 cm diameter) filled with a Unibase electrolyte and attached to the hypothenar palm of the non-dominant hand, which was cleaned with tap water before the start of the procedure. The inter-electrode distance was 2.5 cm. A Coulbourn skin conductance coupler (LabLinc v71-23) provided a constant 0.5 V across electrodes. The signal was digitized at 10 Hz.

2.2.4. Eyeblink startle response

Orbicularis oculi electromyographic activity (EMG) was recorded as an index of the eyeblink component of the startle response with three Ag/AgCl SensorMedics electrodes (0.25 cm diameter) filled with electrolyte gel. After cleaning the skin to reduce inter-electrode resistance, electrodes were placed on the left side of the face (Blumenthal et al., 2005). The raw signal was amplified by a Coulbourn isolated bioamplifier with bandpass filter (LabLinc v75-04; 13 Hz–500 Hz). The signal was rectified online and smoothed by a Coulbourn multifunction integrator (LabLinc v76-23 A) with a time constant of 50 ms. The EMG signal was digitized and stored at 1000 Hz from 500 ms before the onset of the