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Secondary extinction reduces reinstatement of threat expectancy and conditioned skin conductance responses in human fear conditioning

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ABSTRACT

Background and objectives: Secondary extinction refers to the phenomenon that extinction of one conditioned stimulus (CS) results in the reduction of conditioned responses for other CSs conditioned with the same unconditioned stimulus (US). Previous research with rats has demonstrated that secondary extinction can interfere with the return of conditioned fear after a reinstatement manipulation. Here we investigated this phenomenon in two pre-registered studies in humans.

Method: In both experiments, distinct CSs were paired with an electrical stimulation. Next, conditioned reactions to both CSs were extinguished and thereafter reinstated through the administration of three unsignaled electrical stimulations. Crucially, before participants continued with the reinstatement test, half of the participants received secondary extinction trials whereas the other half did not receive these trials.

Results: Our results indicate that secondary extinction reduced reinstatement of threat expectancies and skin conductance responses, but the effect on skin conductance was only found in the second experiment.

Limitations: The studies were conducted in a laboratory setting with healthy students. Additional research will be required to determine the feasibility of applying secondary extinction in a (sub)clinical context.

Conclusions: To our knowledge, this is the first demonstration of secondary extinction and its effect on reinstatement of conditioned fear in humans. We relate our findings to the earlier research with rats and discuss their relevance for exposure therapy.

1. Introduction

Conditioning is a well-established procedure in which a conditioned stimulus (CS) is paired repeatedly with a biologically significant unconditioned stimulus (US). Due to these pairings, the CS comes to elicit conditioned responses (CRs). When the CS is repeatedly presented without the US, CRs typically reduce – which is referred to as extinction. These processes are ubiquitous behavioral phenomena that are found in nearly all animals. Studying these basic processes has contributed considerably to the understanding of (pathological) human and non-human behavior, such as preferences (De Houwer, Thomas, & Baeyens, 2001), fear (Rachman, 1991) and addictions (O'Brien, 1976).

A related process that has received relatively little empirical evaluation is secondary extinction. Secondary extinction refers to the situation in which two (or more) CSs are conditioned with one US, and extinction of one CS attenuates CRs to the other CS that has not undergone extinction (Vurbic & Bouton, 2011). Secondary extinction was previously observed by Pavlov and his associates in their experiments on appetitive conditioning with dogs (Pavlov, 1927). Pavlov conditioned dogs with three distinct CSs (a buzzer, a metronome pulse and a tactile stimulus) that were paired a US that elicited salivation. Following conditioning, CRs to the metronome were extinguished by presenting the metronome without the US. Interestingly, this also reduced CRs to the CSs that had not undergone extinction.[1] These early findings were confirmed in studies that investigated conditioned suppression with rats using fear conditioning (Vurbic & Bouton, 2011). In these studies, rats were conditioned with an auditory (a tone) and a visual (a flashing light) CS that were paired with a US (an electric foot shock). Through these conditioning trials, presentation of the CSs reduced the rats' instrumental behavior to obtain food pellets by pressing a lever (i.e., conditioned suppression), which is considered indicative of acquired fear. Importantly, and in line with Pavlov's earlier work, these studies demonstrated that extinction of fear with one of the CSs (partly) transferred to the unextinguished CS.

Another important finding relating to secondary extinction is that it can

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[1] The use of perceptually distinct CSs excludes an explanation in terms of simple perceptual generalization of extinction effects (Vervliet et al., 2005).

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interfere with reinstatement of conditioned fear (i.e., return of CRs after extinction through the unpaired presentation of the US). Specifically, Rescorla and Cunningham (1977; 1978) conditioned rats by pairing two distinct CSs (CS1: a flashing light, CS2: a 1800-Hz tone) with a footshock. Then, CRs to both CSs were extinguished, after which CRs were reinstated by the presentation of four unsignaled foot shocks. Crucially, following the unsignaled shocks, one group received two unreinforced CS1 presentations followed by two unreinforced CS2 presentations, while another group only received two unreinforced CS2 presentations (unreinforced CS1 presentations were replaced by a waiting period). Reinstatement of fear to the CS2 was attenuated in the group that was first exposed to CS1, suggesting that secondary (re-) extinction interfered with fear reinstatement to CS2.[2] Similar results were obtained by Vurbic and Bouton (2011) for renewal of conditioned fear (i.e., the return of CRs after extinction through a context change). These results are of particular interest from a behavioral therapeutic perspective because reinstatement and renewal are thought to be important underlying mechanisms for relapse after exposure therapy (Bouton, 2002). Hence, the finding that secondary extinction interferes with reinstatement and renewal of conditioned fear points to new potential behavioral interventions that may attenuate the return of fear (such as, for instance, brief occasional exposure sessions to reduce relapse after exposure therapy).

Despite these reports on secondary extinction and the potential theoretical and clinical relevance, only a few studies have investigated this phenomenon. To our knowledge, no studies have been conducted with humans as participants. Therefore, the aim of the current experiments was to replicate these secondary extinction effects in humans and, particularly, to investigate whether secondary extinction can reduce reinstatement of conditioned fear.

We also assessed the role of stimulus equivalence in our experiments. We define stimulus equivalence as interchangeability of two CSs as a predictor for the US (for a more technical and extensive definition of stimulus equivalence see Barnes-Holmes, Barnes-Holmes, Smeets, Cullinan, & Leader, 2004). Vurbic and Bouton (2011) demonstrated that different CSs should be presented in an intermixed fashion during conditioning to obtain the secondary extinction effect. They interpreted this finding as indicating that rats learned to associate the two CSs, which allowed for the generalization of extinction between the two CSs. Indeed, other studies have shown that trained stimulus equivalence can allow for the generalization of acquired fear and extinction between cues (e.g., Dougher, Augustson, Markham, Greenway, & Wulfert, 1994; Honey & Hall, 1989). However, mere intermixing of trials may not be sufficient to learn the equivalence between CSs. Indeed, even for humans, learning stimulus equivalence often requires extensive training (see Barnes-Holmes et al., 2004). Therefore, to measure perceived stimulus equivalence we explicitly asked participants at the end of our studies whether they thought that the non-reinforcement of one CS would indicate the non-reinforcement of the other CS. We expected that secondary extinction would be particularly pronounced for participants answered yes to this question.

2. Experiment 1

2.1. Pre-registration

The power calculation, sample size, design, procedure and data analyses steps were pre-registered on the Open Science Framework prior to data collection (https://osf.io/c3dtn/).

[2] In a strict sense, the procedure employed by Rescorla and Cunningham (1977) cannot be considered to be secondary extinction because both CSs have undergone extinction. In fact, Rescorla and Cunningham (1977) did not refer to the term secondary extinction in their paper, but argue that their findings indicate that the non-associative US representation is destructed through extinction. Their study was later referred to as an example of secondary extinction by Vurbic and Bouton (2011). Strictly speaking, the procedure of Rescorla and Cunningham (1977) could be referred to as secondary re-extinction.

2.2. Participants

Sixty students (43 women) from Utrecht University participated in exchange for €4 or course credit. Participants were recruited through flyers and posters on campus and were screened for self-reported physical and mental health. Trait anxiety level of the participants was determined with the Dutch translation of the State-Trait Anxiety Inventory – trait version (STAI-T, range: 20–80; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983; van der Ploeg, Defares, & Spielberger, 2000). All participants completed an informed consent form and were instructed that they could discontinue the experiment at any point without any negative consequences. The procedure of this study was approved by the ethics committee of the Faculty of Social and Behavioral Science at Utrecht University (FETC16-054). Detailed demographic information about the participants in each of the conditions of the experiment can be found in Table 1.

2.3. Material

2.3.1. Apparatus

The experiment was programmed in Inquisit and was run on a HP Z230 desktop computer running Windows 8.1 Pro. The electrical simulation was generated with a Coulbourn Transcutaneous Aversive Finger Stimulator. Skin conductance was measured using a Biosemi bioamplifier and two Biosemi GSR electrodes filled with Signa electrode gel. Skin conductance data were collected with Actiview and further analyzed with Brainvision Analyzer 2.0.

2.3.2. Stimuli

The unconditioned stimulus was a 1000-ms electrical stimulation administered through two electrodes attached to the index and middle finger of the right hand. The intensity of this stimulus could vary between 0.2 and 4 mA and was individually set for each participant with a work-up procedure (see the Procedure section). As in the experiments by Rescorla and Cunningham (1977; 1978) and Vurbic and Bouton (2011) we used a visual and an auditory CS. These were a blue square (300 by 300 pixels) presented on a 23-inch screen with a resolution of 1920 by 1080 pixels and a 500-Hz tone (65 dB) binaurally presented for 8 s through Sennheiser headphones.

2.4. Design

Using alternating allocation, participants were assigned to one of the two conditions. All participants went through the same procedure until the reinstatement manipulation. After this manipulation, participants in the control group were first subjected to a brief waiting period, after which they were exposed to four trials of the CS2 (counterbalanced over participants either the square or tone). Participants in the secondary extinction (SE) group were first presented with the CS1 in a secondary extinction trial (also counterbalanced as the square or tone, orthogonal to the counterbalancing of CS2), and were then exposed to four trials of the CS2. The number of trials in the different phases of our experiment correspond with the number of sessions in the acquisition, extinction and secondary extinction intervention phases of the first experiment of Rescorla and Cunningham (1977). See Table 2 for an overview of the design of the experiment.

2.5. Procedure

2.5.1. Startup and work-up procedure

Upon arrival in the lab, participants washed their hands and were then asked to read the information letter about the experiment, provide informed consent and complete the STAI-T. Next, skin conductance and shock electrodes were attached. Participants were then lead through a work-up procedure in which the US intensity was determined. They were asked to select an intensity level that they found unpleasant but tolerable. To operationalize the intensity, participants were asked to score the intensity of the US on a 0 to 10 scale (ranging from 0 = *no pain at all* to 10 = *maximum level*