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Preexposure to (un)predictable shock modulates discriminative fear learning between cue and context: An investigation of the interaction between fear and anxiety

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ABSTRACT

It has been suggested that prior experiences with unpredictable/uncontrollable stressors facilitate subsequent fear learning and the development of anxiety disorders. However, animal research documents that preexposure to unpredictable stressors (USs) impede later fear conditioning with that US. These differential predictions were tested in a human experimental model of clinical anxiety. One (US-only) group was preexposed to unpredictable shocks, a second (Unpaired) group received explicitly unpaired presentations of a neutral shape and the shock, and a third (Paired) group received paired shape-shock presentations. Next, all groups received training with a novel shape, using the same shock (50% reinforcement). Fear responding was assessed through startle modulation and online shock-expectancy ratings. Results showed retarded fear learning in the unpredictable groups compared to the predictable group. We argue that prior experiences of unpredictability may still contribute to the development of clinical anxiety, by impeding adaptive fear learning and perpetuating the perception of unpredictability/uncontrollability.

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1. Introduction

The human fear conditioning paradigm has been used extensively as an experimental model to study and understand the etiology and maintenance of anxiety disorders (Craske et al., 2006). From a classical conditioning perspective, fear conditioning is an associative learning process that involves the pairing of a neutral stimulus (conditioned stimulus, CS) with an aversive (unconditioned) stimulus (US). After a few CS–US pairings, the CS becomes a signal for imminent threat and starts to elicit conditioned fear responding (CR) (e.g., Rescorla and Wagner, 1972). Intuitively, it seems reasonable that anxiety disorders would typically develop following a traumatic experience or during a period of increased stress to which many of us would respond anxiously. However, it is quite obvious that not everyone undergoing traumas or periods of excessive stress develops an anxiety disorder (for a review see Field, 2006). Although models of fear conditioning are useful to shed light on the acquisition of *adaptive* fear responses, they are not able to account for who does and who does not develop perpetuating *maladaptive* fear as is the case in anxiety disorders. In that respect, revealing the factors that *modulate* fear conditioning processes might contribute to our understanding of how and under which circumstances conditioning experiences might give rise to anxiety disorders.

Several etiological theories have advanced *(perceived) unpredictability* of stressful, traumatic or high impact life events as a key factor in the development of chronic anxiety (e.g., Barlow, 2000). For example, it has been argued that individuals with a history of unpredictability are more prone to develop anxiety disorders due to altered fear conditioning during later aversive encounters (e.g., stress-diathesis model; Mineka and Zinbarg, 2006). Nevertheless, little is known about the effects of prior experiences with unpredictable stressors relative to prior predictability of stressful experiences on subsequent fear conditioning in humans. From a clinical perspective, it might be interesting to pinpoint whether (un)predictable stressful experiences indeed affect later fear learning.

A large body of evidence from animal research demonstrates that US-only presentations can disrupt subsequent CS–US learning (US-preexposure effect; see Randich and Lolordo, 1979; Randich and Ross, 1985). These observations are consistent with the predictions derived from associative learning models (e.g., Rescorla and Wagner, 1972), that is, it is in essence the expression of the well-known blocking effect (Kamin, 1969). The basic blocking effect shows that conditioned responding to a stimulus (B) is blocked if the stimulus is reinforced in compound (AB+) with a previously reinforced stimulus (A+). The lack of conditioned responding to B is

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typically attributed to the fact that the US is fully predicted by A, as a result there is no incentive to learn the B–US association during the compound training. By analogy, in absence of discrete predictors (CSs) for the US, the context will gain associative strength producing conditioned responding to the context which subsequently blocks new (cued) fear conditioning (context blocking; Tomie, 1976). According to this *context blocking hypothesis*, processes of cue competition between the contextual cues and the new discrete CS result in reduced discriminative fear learning between cue and context when tested in the same context.

In the present study, we employed a human fear conditioning paradigm with a shock as US, geometrical shapes as CSs, and contexts were created by displaying a picture as a background on the computer screen (see procedure Fonteyne et al., 2009). Dependent variables were online shock-expectancy ratings and eyeblink startle modulation, the latter indexing *cued fear* when measured during the CS and indexing more *chronic anticipatory anxiety* when measured during the context alone (i.e., intertrial interval; ITI). The main question of interest of our study was whether prior (un)predictability experiences can modulate fear conditioning to a novel (CS) shape. An important strength of the present design is the fact that we used two unpredictable groups. In human conditioning research, unpredictable traumatic experiences are often modeled by delivering unsignaled shocks and CSs in an explicitly unpaired manner (Fonteyne et al., 2009; Grillon, 2002; Vansteenwegen et al., 2008). In animal research, however, US-only presentations are mostly used to produce US-unpredictability (Fanselow, 1980a, 1980b). Remarkably, possible divergent effects of these two US-unpredictability procedures have never been compared systematically in a human fear conditioning preparation. To monitor the effects of US-unpredictability more closely, two unpredictable groups were included, namely, the Unpaired group and the US-only group. During the *shock-preexposure* phase, both unpredictable groups repeatedly received unpredictable shocks: the Unpaired group received explicitly unpaired CS_1/US presentations, while the US-only group received temporally unpredictable USs in the absence of any discrete cues. In the predictable (Paired) group signaled shocks (immediately after CS_1 offset) were presented. ITI levels of both startle responses and online shock-expectancy ratings were expected to be elevated during the unpredictable shock-preexposure procedures (i.e., *contextual fear*) compared with the predictable shock-preexposure procedure. Following the safety signal hypothesis (Seligman and Binik, 1977), we also hypothesized that in the US-only group more fear would accrue to the context than in the Unpaired group (expressed in higher ITI responses), because in the former group safety signals (i.e. CS−) offering short periods of relief are absent. Next, all three groups received a *cued fear conditioning* procedure with a novel (50% reinforced) CS_2 in the same experimental context. We expected less discriminative CS/ITI learning in the unpredictable groups (at least in the beginning of the cued fear conditioning phase) due to remaining elevated ITI responses (i.e. contextual fear). In addition, we expected that more contextual fear would induce more contextual blocking and thus lead to worse discriminative CS/ITI learning in the US-only group than in the Unpaired group.

2. Method

2.1. Participants

A total of sixty-seven first-year healthy subjects including 35 economy students and 32 psychology students at the University of Leuven (27 males and 40 females) were invited to participate in the experiment in return for course credit. Their mean age was 18 years (ranging from 17 to 20). All participants gave written informed consent and were instructed that they were allowed to decline participation at any time during the experiment. The experimental protocol was approved by the Ethical Committee of the Department of Psychology.

2.2. Apparatus and experimental stimuli

2.2.1. Software

The entire experiment was run on a Windows XP computer with 256 Mb RAM and an AMD Athlon K7 processor (Pentium III class compatible) at 600 MHz and was programmed using Affect (version 4.0) developed by Hermans et al. (2005); see also Spruyt et al. (2010).

2.2.2. Shock-expectancy ratings

The expectancy of the shock-US was measured online using a custom built dial operated by the participants' right hand. Participants were instructed to indicate continuously throughout the experiment to what extent they expected the shock-US to occur. The pointer could be turned through 180° from 0 to 100, '*0*' indicating that the participant did not at all expect the shock to occur, and '*100*' indicating that the participant certainly expected the shock to occur. The custom-made expectancy dial generated an online analog signal that was digitized at 10 Hz by an A/D converter and saved on the computer.

2.2.3. Startle measurement

Orbicularis Oculi electromyographic activity (EMG) was recorded with three Ag/AgCl Sensormedics electrodes (0.25 cm diameter) filled with a TECA electrolyte. After cleaning the skin with a peeling cream to reduce inter-electrode resistance, electrodes were placed on the left side of the face according to the site specifications proposed by Fridlund and Cacioppo (1986). The raw signal was amplified by a Coulbourn isolated bioamplifier with bandpass filter (v75-04). The recording bandwidth of the EMG signal was between 10 Hz and 20 kHz (±3 dB). The signal was rectified online and smoothed by a Coulbourn multifunction integrator (v76-23A) with a time constant of 50 ms. In the startle probe presentations, signal measuring started 1 s before probe onset at 1000 Hz. From probe onset, the signal was digitized at 1000 Hz for 1000 ms. The startle probe was a 100 dBA burst of white noise with instantaneous rise time presented binaurally for 50 ms through headphones.

2.2.4. Stimulus material

In line with the procedure of Fonteyne et al. (2009), a picture of a room was continuously presented on the background of the computer screen to serve as the experimental context. Three geometrical shapes (black drawings of a circle, a triangle, and a star) were used as CSs and presented in the centre of the computer screen on top of the background picture. An electrocutaneous shock of 2 ms duration serving as the US was delivered by a commercial stimulator for percutaneous stimulation (DS7A, Digitimer, Welwyn Garden City, England) through surface Sensormedics electrodes (1 cm diameter) filled with K-Y gel that were attached to the left wrist. During the shock calibration procedure (mean shock intensity was 23.32 mA, $SD = 12.79$) the participants were asked to rate the shock-US on a scale ranging from 1 to 10 with the anchors '1', '2' and '10' respectively meaning "*You feel something but it is not painful, it is merely a sensation*", "*It starts to be painful but it is still a very small pain*", and "*This stimulation is the maximum tolerable pain for you in this experiment*". When reaching the highest individual level tolerated by the participant, the experimenter asked whether s/he thought s/he would be able to tolerate repeated shocks of this amplitude during the experiment. Notice that during this shock calibration procedure, participants were instructed to notify the experimenter when they did not want to proceed receiving the shock of higher intensity or if they wanted the amplitudes to be set back at a lower level.

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