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Learning to fear obstructed breathing: Comparing interoceptive and exteroceptive cues

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ABSTRACT

The present study investigated interoceptive fear conditioning (IFC) to an interoceptive and exteroceptive conditional stimulus (CS) with a severe respiratory load applied for 30 s as the unconditional stimulus (US). CSs were another, weak respiratory load in the intero-IFC study ($N = 74$), and a neutral picture in the extero-IFC study ($N = 42$). CSs preceded the US in the paired groups, whereas the unpaired groups received the same number of unpaired CSs and USs. We measured startle blink EMG, self-reported fear and respiration. In the intero-IFC study, the CS-load was associated with larger startle blinks and a smaller decrease in respiratory rate and tidal volume in the paired compared to the unpaired group. In the extero-IFC study, the CS-picture evoked an increase in tidal volume and self-reported fear only in the paired group. In addition, startle potentiation during the CS-picture was greater for the paired than for the unpaired group.

1. Introduction

Influential theories (e.g., Bouton et al., 2001; Goldstein and Chambless, 1978; Mineka and Zinbarg, 2006) on panic disorder assume that occasional experiences of panic attacks can cause interoceptive conditioning of fear. For example, early signs of heart racing or breathing distress may become conditioned stimuli for a panic attack, thereby causing fear-related physiological arousal that spirals down in a full-blown panic attack. The concept of interoceptive conditioning was first introduced to the Western world by Razran (1961) who defined it as classical conditioning in which either the conditioned stimulus [CS], the unconditioned stimulus [US], or both are interoceptive. Accordingly, three different types of interoceptive conditioning can emerge: extero-interoceptive conditioning (exteroceptive CS, interoceptive US), intero-exteroceptive conditioning (interoceptive CS, exteroceptive US), and intero-interoceptive conditioning (interoceptive CS and US). Particularly extero-interoceptive fear conditioning (extero-IFC) and intero-interoceptive fear conditioning (intero-IFC) have been hypothesized to play a role in panic disorder. Whereas extero-IFC would underlie situational panic attacks as encountered in PD with comorbid agoraphobia, intero-IFC would instigate panic attacks without obvious external trigger (Bouton et al., 2001). In the latter type, panic attacks apparently come 'out of the blue', possibly because the sensations (CSs) are very close in time to and resemble those during the full-blown attack.

A few studies have documented extero-IFC in the laboratory (e.g., Fannes et al., 2008; Forsyth and Eifert, 1998), but we know of only one study that has attempted to experimentally demonstrate intero-IFC (Acheson et al., 2007). The latter study used a 5 s inhalation of 20% CO_2-enriched air as a CS for a more intense, unconditionally aversive stimulus (US, a 20 s 20% CO_2-inhalation). Paradoxically, participants who received the CS and the US in an unpaired fashion reported equal levels of fear and showed greater electrodermal responses to the CS than those who had received the CS and US in a paired fashion during the acquisition phase. The former group had also a slower extinction than the latter. Acheson et al. (2007) argue that the fear responding and retarded extinction in the unpaired group is due to the fact that the CS was perceptually identical to the first 5 s of the US, resulting in a partial reinforcement scheme and concomitant impaired extinction in the unpaired group. Although partial reinforcement of interoceptive CSs, unpredictability of the US, and CS–US resemblance are both clinically and theoretically relevant and ecologically valid themes in the context of panic disorder, it remains ambiguous whether the findings of Acheson et al. (2007) reflect intero-IFC. A difficulty with CO_2-inhalation may be that its interoceptive effects (increases in ventilation and general arousal) appear only gradually and need a relatively longer time than exteroceptive features of CO_2-inhalation (taste, smell) (Fannes et al., 2008; Pappens et al., 2010; Wise et al., 2004). During a 5 s inhalation of CO_2, it is very likely that the exteroceptive features of CO_2-inhalation dominate

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the interoceptive ones. In other words, the results reported by Acheson et al. (2007) may reflect extero-IFC rather than intero-IFC.

An alternative type of panic-relevant, respiratory stimulation that may have clearer interoceptive qualities right from the onset is loaded breathing. By adding a resistive load to the breathing circuit, an increased effort of the respiratory musculature is required to maintain ventilation (Kifle et al., 1997). Magnitude estimation studies show that the perception of an added load is rapid and produces a series of respiratory-related evoked potentials (RREP) with both short (P1) and late (P3) components that vary as a function of load magnitude (Webster and Colrain, 2000). Because the detection of resistive loads largely depends on mechanoreceptors, resistive loading has important interoceptive qualities following the most common conceptions on 'interoception' (e.g., Cameron, 2001; Dworkin, 2000; Craig, 2002).

In order to explore intero-IFC and extero-IFC with a new type of panic relevant, respiratory stimulation (resistive loading) two studies were run, one in which the US was preceded by another resistive load of low intensity (intero-IFC, study 1), and one in which it was preceded by a neutral picture (extero-IFC, study 2). Experimental groups received paired presentations of CS and US, control groups received these stimuli in an explicitly unpaired fashion. Self-reported fear, startle blink EMG and respiration were measured. For both studies, we expected that (1) only the paired group would report an increase in subjective fear in response to the CS, (2) startle would be more potentiated in the presence relative to the absence of the CS in the paired compared to the unpaired group. In line with earlier findings on fear conditioned changes in respiration (Van Diest et al., 2009), we expected also (3) that the paired group would breathe more during the CS than the unpaired group. We expected that these group differences would be absent during a pre-exposure trial, would emerge during acquisition, and would decrease again during extinction.

2. Methods

2.1. Participants

Healthy, non-smoking students participated in return for course credit or 8 Euros. In the intero-IFC study, N was 74 (58 women, M = 20.3 yrs, range 18–27 yrs), but the online fear rating was obtained from only 54 participants[1]. In the extero-IFC study, N was 42 (34 women, M = 19.7 yrs, range 18–24 yrs).

Participants who failed to show a blink to more than 30% of the probes (non-responders) were excluded for subsequent EMG analysis (Blumenthal et al., 2005), resulting in a data set of N = 65 (45 women) for the startle data of the intero-IFC and N = 40 (34 women) for the extero-IFC.

All participants provided informed consent. The experiment was approved by the Ethics Committees of the Department of Psychology and of the Faculty of Medical Sciences.

2.2. Materials and measures

Participants breathed through a mouthpiece and wore a nose-clip. The mouthpiece was connected to a microbial filter (MicroGard, VIASYS) mounted on a heated pneumotachograph (Fleisch n°2, Switzerland). The latter was connected to a non-rebreathing valve, ensuring the separation of inspiratory and expiratory air. Two vinyl tubes (3.5 × 100 cm) connected the inspiratory and expiratory side of the non-rebreathing valve with 3-way stopcock valves enabling easy switching between the CS load, US load and unloaded breathing. The signal from the pressure transducer (Sine Wave Carrier Demodulator CD15, Validyne EngineeringRM) was sampled at 50 Hz.

A non-aversive resistive load of 0.98 kPa × s/l (Pappens et al., 2010) and a neutral picture (#7006) of the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999), served as CSs in the IFC and EFC study, respectively. Both were applied for 8 s. An aversive RL of 3.91 kPa × s/l, applied for 30 s at the inspiratory and expiratory branch of the system, was the US.

The eyeblink startle response was measured by recording surface EMG activity over the m. orbicularis oculi just beneath the left eye, using Ag/AgCl Sensormedics electrodes (0.25 cm diameter). The raw signal was amplified by a Coulbourn isolated bioamplifier with bandpass filter (v75-04; 13 Hz–10 kHz) and routed to a Coulbourn contour-following integrator (S76-01) which rectified and smoothed the signal (time constant = 50 ms). The EMG signal was transmitted through a labmaster card (12 AD convertor) to a personal computer. During the 500 ms before the onset of white noise until 1000 ms after onset of white noise, the EMG signal was sampled and stored at 1000 Hz using Affect 4.0 software (Spruyt et al., 2010). Acoustic startle probes (95 dB white noise, 50 ms duration) were administered binaurally.

Participants continuously rated their fear level with a custom built dial (Vansteenwegen et al., 2008) on a scale ranging from 0 (no fear) to 100 (most extreme fear). The generated analogue signal was digitized and stored at 10 Hz.

2.3. Procedure

The experimenter told the participants that responses to different respiratory and/or picture stimuli would be measured. Then, she attached the EMG electrodes and told that brief bursts of noise would occur that should be ignored. Participants were instructed to continuously rate their level of fear during the entire experiment. Following this, participants took in the mouthpiece, put on the nose-clip and received 10 startle probes (30 s in between probes). After this habituation phase, participants went through the three experimental phases: pre-exposure (2 trials), acquisition (6 trials) and extinction (6 trials). There was one pre-exposure trial to the CS and one to the US; their order was counterbalanced across participants. A pre-exposure trial consisted of 20 s baseline, CS (8 s) or US (30 s) presentation and an intertrial interval (ITI) of 30 s without stimulus. For the paired groups, acquisition trials consisted of baseline (20 s), CS (8 s), US (variable between 25 and 35 s) and ITI (variable between 25 and 35 s). The unpaired groups received the following sequence during acquisition trials: baseline (20 s), CS (8 s), ITI (25–35 s) and US (25–35 s). Extinction trials consisted of baseline (20 s), CS (8 s) and ITI (55–65 s) for both groups. Startle probes were administered in each trial at random times between 6.5 and 7.5 s after CS onset, 21–23 s after US onset, and 21–23 s following the start of the ITI.

2.4. Data reduction and analyses

EMG and respiratory signals were treated off-line with PSychoPHysiological Analysis (PSPHA) (De Clerck et al., 2006).

Respiratory rate (RR, in cycles per minute, cpm) and tidal volume (V_T, in ml) were extracted on a breath-by-breath basis and then averaged across the CS episode, and across the 20 s baseline episode preceding the CS.

For startle EMG, PSPHA calculated a baseline for each 0–20 ms window following probe onset and subtracted this from the peak value detected in the subsequent 21–175 ms window.

Data of each person were averaged across each subsequent pair of trials during acquisition and extinction, leading to 3 acquisition and 3 extinction blocks. Prior to statistical analyses, startle data were standardized and T-transformed within persons.

To investigate eventual group differences prior to the conditioning procedure, a first set of analyses tested group differences in responding to the CS during the pre-exposure trial. For startle EMG, this was performed in a group (paired/unpaired) × probe (CS/ITI) design. Respiratory parameters during pre-exposure were tested in a repeated measures ANOVA with stimulus (baseline/CS) as within subject variable, and group (paired/unpaired) as a between subject variable. Self-reported fear during the CS pre-exposure trial was analyzed in a group (paired/unpaired) × time (first/last second) design.

Data from the experimental blocks (3 acquisition and 3 extinction blocks) were tested in repeated measurement ANOVA designs. Each analysis included a group (paired/unpaired), a phase (acquisition/extinction) and a block (1–3) variable. Additional factors in the design were probe (CS/ITI) for startle EMG, stimulus (baseline/CS) for respiratory rate and tidal volume, and time (first/last second of CS presentation) for self-reported fear. Only group was a between subject variable. Bonferonni corrections for multiple comparisons were applied to follow-up comparisons of significant interactions.

Alpha was set at .05. Greenhouse-Geisser corrections were applied where appropriate. Uncorrected degrees of freedom and corrected p's will be reported together with η^2_p. Statistical analyses were accomplished with Statistica 8.

3. Results intero-IFC study

3.1. Self-reported fear

Pre-exposure. Self-reported fear increased during presentation of the CS-load in the pre-exposure trial (main effect of time $F(1, 52) = 21.31$, $p < .01$, $\eta_p{}^2 = .29$, see upper panel of Fig. 1). As expected,

[1] An additional aim of the intero-IFC study was to investigate whether the application of an online fear rating influenced fear learning. Results (not reported here) indicated no differences in startle blink EMG between participants who performed the fear rating and those who did not. Therefore, EMG data from both groups (with/without online fear rating) were collapsed. Supported by research grants G054309 (FWO, Vlaanderen) and OT/06/22 (K.U.Leuven).