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Cold pressor test improves fear extinction in healthy men

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Summary Fear extinction is an important paradigm to study the neural basis of anxiety and trauma- and stressor-related disorders and for modeling features of extinction learning and exposure-based psychotherapy. To date the effects of acute stress on extinction learning in humans are not well understood. Models of stress effects on emotional memory suggest that learning during the so-called first wave of the stress response will be enhanced. The first wave includes (among others) increases of noradrenaline in the brain and increased sympathetic tone, adrenaline and noradrenaline in the periphery while the second wave includes genomic glucocorticoid-actions. The cold pressor test (CPT) is a valid way to induce the first wave of the stress response. We thus hypothesized that the CPT will facilitate extinction. In a 2-day fear-conditioning procedure with 40 healthy men, using differential skin conductance responses as a measure of conditioned fear, we placed the CPT versus a control procedure prior to extinction training on Day 1. We tested for extinction learning on Day 1 and extinction retrieval on Day 2. During extinction training (Day 1) only the CPT-group showed a significant reduction in differential responding. This was still evident on Day 2, where the CPT group had less differential responding during early trials (retrieval) and a higher extinction retention index. This is the first human study to show that a simple procedure, triggering the first-wave stress response — the CPT — can effectively enhance fear extinction in humans.

1. Introduction

Pavlovian fear extinction is a model for exposure therapy—an effective treatment for anxiety, trauma- and stressor-related disorders (Norton and Price, 2007). In fear extinction, a conditioned stimulus (CS) previously paired with an aversive outcome (unconditioned stimulus, US) is repeatedly presented without the US and fear responses decline. Rather than erasing the fear memory, extinction leads to the formation of a new inhibitory CS-noUS association, vulnerable to the return-of-fear phenomena such as contextual renewal and spontaneous recovery (Bouton, 2004). Moreover, extinction learning

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and retrieval are impaired in anxiety and stress disorders (Michael et al., 2007; Milad et al., 2009). Although exposure to fearful stimuli is inherently aversive, the stress response mediators noradrenaline (NA) (Mueller and Cahill, 2010) and cortisol (De Quervain et al., 2011) were both proposed to improve fear extinction and exposure therapy in humans. However, the effects of stress on extinction learning in humans are not so well understood.

The stress response involves multiple neuroendocrine changes over time: The first wave includes fast noradrenaline (NA), corticotropin releasing hormone (CRH), and non-genomic glucocorticoid (GC) effects in the brain, and increased sympathetic tone, adrenaline and noradrenaline (NA) release in the periphery. The second wave includes slower genomic GC-actions (Joëls and Baram, 2009). Models of stress effects on emotional learning and memory (e.g., Schwabe et al., 2012) predict that learning during the first wave should be enhanced, but learning during the second wave should be impaired.

We have recently shown that inducing the first-wave stress response (without GC-increases), by using the cold pressor test (CPT) *prior to fear acquisition*, renders fear memory more resistant to immediate extinction in humans (Antov et al., 2013). This raised the question if the CPT had enhanced fear learning manifesting in elevated extinction resistance — in accordance with the model (Schwabe et al., 2012) — or if the CPT impaired extinction learning. To assess the effect of a CPT-induced first-wave stress response on extinction, we conducted the present study, where the CPT (vs. control) was positioned prior to extinction training in a 2-day human fear conditioning paradigm. According to Schwabe et al. (2012), we hypothesized that the CPT will enhance extinction learning and extinction retrieval in healthy men.

2. Methods

2.1. Participants

40 healthy male university students aged 18—30 years ($M = 22.2$, $SEM = 0.41$) were tested. We applied inclusion and exclusion criteria as described previously (Antov et al., 2013). Assignment to the CPT or control group was random with the restriction that groups were matched on age and body mass index as close as possible. The study was approved by the ethics committee of the University of Osnabrück and carried out with the adequate understanding and written informed consent of the participants.

2.2. Cold pressor test and control

Participants were instructed to immerse their dominant hand up to the wrist in cold water (CPT, $M = 3.0$, $SEM = 0.11\,^{\circ}C$) or in warm water (control, $M = 36.9$, $SEM = 0.26\,^{\circ}C$) for a maximum of 3 min. During hand immersion participants gave 3 pain ratings on a scale from 0 (*no pain*) to 100 (*most severe pain imaginable*). Blood pressure was measured 100 s after hand immersion.

2.3. Fear acquisition and extinction

Conditioning included habituation, acquisition, and extinction training on Day 1, and extinction retrieval test on Day 2 (Fig. 2A). The US was a 2-s section of a ''car-wreck'' sound, as previously described (Antov et al., 2013), presented binaurally at 95 dB(A). A triangle and a pentagon were counterbalanced to serve as the CS+ (associated with the US) and the CS− (not followed by US). Each was presented for 5 s on a 22″-screen (visual angle 8.7°). On Day 1, each CS was presented once for habituation. For acquisition, 12 CS+ and 12 CS− were presented. Using 75% reinforcement, the offset of 9 CS+ was immediately followed by the US (Fig. 2A). During extinction training (Day 1) and for extinction retrieval (Day 2), 12 CS+ and 12 CS− were presented without US. Trial order was pseudorandom, with the restriction of no more than 2 consecutive CS+ or CS− trials. Intertrial intervals ranged from 12 to 26 s ($M = 21$ s), closely related to our previous study (Antov et al., 2013).

2.4. Dependent measures and procedure

2.4.1. Treatment validation measures

Systolic (sysBP) and diastolic blood pressure (diaBP), heart rate (HR), the number of nonspecific skin conductance responses (nsSCR), subjective mood, and salivary cortisol (CORT) were repeatedly measured for treatment validation. BP was recorded by a sphygmomanometer with the sensor over the left brachial artery at heart level. HR was computed as the mean (bpm) over a 256-s interval per measurement period and during hand immersion derived from electrocardiogram sampled at 1000 Hz. Skin conductance was recorded with a constant voltage coupler (BrainProducts, Germany), sampled at 1000 Hz. Two Ag/AgCl electrodes, filled with 0.05 M NaCl paste were fixed on the thenar and hypothenar of the non-dominant hand. nsSCR was scored by counting the number of responses >0.02 μS over a 2-min window. Cortisol level was measured with an ELISA kit (IBL, Hamburg, RE52611). Saliva samples were kept at −20° C until analysis. Assay sensitivity was 0.138 nmol/L, intra- and inter-assay coefficients of variation were 3.1—7.3%, and 6.4—9.3%, respectively. Cortisol values were log-transformed for statistical analysis. Subjective mood was assessed using a multidimensional German mood rating scale (BSKE) derived from the ''Eigenschaftswörterliste'' (EWL, Janke and Debus, 1978): Items consist of one noun, entitling a feeling (e.g., anxiety), and two adjectives (e.g., anxious, afraid). The intensity is rated on a 7-point scale, ranging from 0 (not at all) to 6 (very strong). Here, we report anxiety and arousal.

2.4.2. Conditioning measures

Skin conductance responses (SCRs) to the conditioning stimuli were scored and range-corrected as described previously (Antov et al., 2013), and square root transformed. Differential SCR (diffSCR) was computed by subtracting each CS− from the corresponding CS+ response. For acquisition, we compared diffSCR during habituation, early acquisition (mean of trials 1—4), and late acquisition (mean of trials 9—12). We compared early (mean of trials 1—4) vs. late (mean of trials 9—12) extinction on Day 1 and extinction retrieval on Day 2. To assess extinction memory expression