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Influence of stress on fear memory processes in an aversive differential conditioning paradigm in humans

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Summary It is widely assumed that learning and memory processes play an important role in the pathogenesis, expression, maintenance and therapy of anxiety disorders, such as phobias or post-traumatic stress disorder (PTSD). Memory retrieval is involved in symptom expression and maintenance of these disorders, while memory extinction is believed to be the underlying mechanism of behavioral exposure therapy of anxiety disorders. There is abundant evidence that stress and stress hormones can reduce memory retrieval of emotional information, whereas they enhance memory consolidation of extinction training. In this study we aimed at investigating if stress affects these memory processes in a fear conditioning paradigm in healthy human subjects. On day 1, fear memory was acquired through a standard differential fear conditioning procedure. On day 2 (24 h after fear acquisition), participants either underwent a stressful cold pressor test (CPT) or a control condition, 20 min before memory retrieval testing and extinction training. Possible prolonged effects of the stress manipulation were investigated on day 3 (48 h after fear acquisition), when memory retrieval and extinction were tested again. On day 2, men in the stress group showed a robust cortisol response to stress and showed lower unconditioned stimulus (US) expectancy ratings than men in the control group. This reduction in fear memory retrieval was maintained on day 3. In women, who showed a significantly smaller cortisol response to stress than men, no stress effects on fear memory retrieval were observed. No group differences were observed with respect to extinction. In conclusion, the present study provides evidence that stress can reduce memory retrieval of conditioned fear in men. Our findings may contribute to the understanding of the effects of stress and glucocorticoids on fear symptoms in anxiety disorders and suggest that such effects may be sex-specific.

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1. Introduction

Classical fear conditioning is a well-established paradigm to investigate emotional learning and memory processes thought to be involved in the pathogenesis and symptomatology of anxiety disorders (LaBar and Cabeza, 2006). Within the conditioning framework, anxiety disorders like panic disorder, phobias or post-traumatic stress disorder (PTSD) are considered as manifestations of conditioned fears (Bouton et al., 2001; Mineka and Oehlberg, 2008; Mahan and Ressler, 2012). Fear conditioning refers to an association of an originally neutral stimulus (conditioned stimulus, CS) with an aversive or traumatic experience (unconditioned stimulus, US). After fear acquisition, a later encounter with the CS leads to retrieval of the associated fear memory and to subsequent fear response (conditioned reaction, CR) and to further stabilization of the fear memory trace (Myers and Davis, 2002; Phelps and LeDoux, 2005; Bentz et al., 2010). Fear conditioning is usually sensitive to extinction, a form of learning characterized by a decrease in the amplitude and frequency of the CR when the CS is repeatedly presented without the US (Myers and Davis, 2002; Hermans et al., 2006). The inability to extinguish or inhibit maladaptive fear responses is a characteristic for most anxiety disorders (Hermans et al., 2006; Bentz et al., 2010). Experimental studies indicate that patients with anxiety disorders have deficits in extinction learning compared to healthy controls (Blechert et al., 2007; Michael et al., 2007).

Most fear conditioning studies in healthy humans and patients with anxiety disorders typically measure skin conductance responses (SCR) or fear potentiated startle to indicate fear learning and extinction. Both measures quantify implicit (non-conscious, unintentional) aspects of fear memory rather than explicit (conscious, intentional) memory processes that also operate in fear learning and expression (LaBar and Cabeza, 2006). During fear acquisition participants continuously develop expectancies about stimulus associations (Lovibond, 2006). Moreover as a result of repeated US—CS pairings, an affective valence is transferred from the US to the CS (evaluative conditioning) (de Houwer et al., 2001). Expectancy and evaluative learning have emotional components, but are also associated with explicit memory processes and can be verbalized and measured online in humans throughout conditioning paradigms (Carter et al., 2006). Neuropsychological findings from human lesion- and imaging studies indicate that explicit and implicit memory processes involved in fear conditioning are neurally dissociable and can be assigned to different brain regions, the hippocampus and the amygdala, respectively (Bechara et al., 1995; Knight et al., 2004). Further, there is evidence that patients with anxiety disorders have deficits in fear extinction of conditioned responses indicated by measures associated with both hippocampal and amygdaloidal memory processes (Blechert et al., 2007; Michael et al., 2007).

Evidence from animal and human studies indicates that stress and stress hormones influence learning and memory processes. The effect of glucocorticoids (GCs) on memory processes depends on several factors, such as the stage of memory process (acquisition, consolidation, or retrieval), emotional characteristics of the material and sex (de Quervain et al., 2009). There is abundant evidence that acute administration of GCs enhances memory consolidation (Roozendaal, 2000; Buchanan and Lovallo, 2001). Additionally to the enhancing effects of GCs on memory consolidation, GCs impair long-term memory retrieval processes (de Quervain et al., 1998, 2000; Roozendaal et al., 2004; Het et al., 2005; Kuhlmann et al., 2005a,b; Kuhlmann and Wolf, 2005; Buchanan et al., 2006). Especially emotionally arousing memory contents seem to be sensitive to the retrieval-impairing effects of GCs (Kuhlmann et al., 2005a,b; de Quervain et al., 2007). Therefore GCs might enhance extinction learning by inhibiting fear retrieval processes and promoting consolidation of extinction learning. There is preliminary evidence from studies with patients with different anxiety disorders (social phobia, specific phobia, PTSD) for the extinction enhancing effect of GCs. These studies found, besides lower stimulus-associated fear under GC treatment, prolonged effects outlasting the treatment period that may indicate enhanced extinction of fear (Aerni et al., 2004; Soravia et al., 2006; de Quervain et al., 2011). This is in line with animal studies that showed that GCs facilitate the consolidation of extinction memory, whereas suppression of GCs impairs extinction processes (Cai et al., 2006; Yang et al., 2006; Blundell et al., 2011). So far only a few studies investigated the effect of GCs or stress on fear and extinction learning in healthy humans (Zorawski et al., 2005; Grillon et al., 2006; Jackson et al., 2006; Stark et al., 2006; Zorawski et al., 2006; Nees et al., 2008; Luethi et al., 2009; Wolf et al., 2009; Kuehl et al., 2010; Merz et al., 2010, 2012a,b, 2013; Tabbert et al., 2010). Most studies used exclusively implicit measurements such as SCR (Zorawski et al., 2005; Jackson et al., 2006; Stark et al., 2006; Merz et al., 2010, 2012a,b, 2013; Tabbert et al., 2010), fear potentiated startle (Grillon et al., 2006; Nees et al., 2008; Wolf et al., 2009; Kuehl et al., 2010) and BOLD (blood oxygenation level dependent)-contrasts (Stark et al., 2006; Merz et al., 2010, 2012a,b, 2013; Tabbert et al., 2010) to identify fear acquisition and extinction. These studies indicate that stress-induced elevations of cortisol levels affect fear conditioning processes with different effects in men and women (interaction between stress and sex). Some studies utilizing SCR as indicator for fear acquisition show that high endogenous (Zorawski et al., 2005) and stress-induced cortisol levels (Jackson et al., 2006) seem to be associated with enhanced fear acquisition in men, but not women. fMRI studies that measured the influence of exogenously administered cortisol on neural correlates of fear acquisition show the opposite pattern with enhanced fear acquisition in women and impaired fear acquisition in men (Stark et al., 2006; Merz et al., 2010). However, there is no study so far that investigated the specific effects of stress on memory retrieval and extinction processes of conditioned fear (i.e. without affecting initial memory acquisition or consolidation processes).

In the present study we aimed at investigating the effects of stress on memory retrieval and extinction processes in a fear conditioning paradigm in healthy male and female participants. After fear memory has been acquired in a differential conditioning paradigm on day 1, cold pressor test (CPT) was used to induce stress before retrieval (as measured with the first extinction trial on day 2) and extinction training on day 2 (24 h after fear acquisition). Possible prolonged effects of the stress manipulation were investigated on day 3 (48 h after fear acquisition). CPT consisted of