NeuroImage 133 (2016) 233–243

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Cortisol disrupts the neural correlates of extinction recall

Valerie L. Kinner [a], Christian J. Merz [a], Silke Lissek [b], Oliver T. Wolf [a,*]

[a] Department of Cognitive Psychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum, Universitätsstraße 150, 44780 Bochum, Germany
[b] BG University Hospital Bergmannsheil, Department of Neurology, Ruhr-University Bochum, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany

ARTICLE INFO

Article history:
Received 1 December 2015
Accepted 3 March 2016
Available online 10 March 2016

Keywords:
Extinction recall
Functional magnetic resonance imaging
Functional connectivity
Renewal effect
Sex differences
Stress hormones

ABSTRACT

The renewal effect describes the recovery of extinguished responses that may occur after a change in context and indicates that extinction memory retrieval is sometimes prone to failure. Stress hormones have been implicated to modulate extinction processes, with mostly impairing effects on extinction retrieval. However, the neurobiological mechanisms mediating stress effects on extinction memory remain elusive. In this functional magnetic resonance imaging study, we investigated the effects of cortisol administration on the neural correlates of extinction memory retrieval in a predictive learning task. In this task, participants were required to predict whether certain food stimuli were associated with stomach trouble when presented in two different contexts. A two-day renewal paradigm was applied in which an association was acquired in context A and subsequently extinguished in context B. On the following day, participants received either cortisol or placebo 40 min before extinction memory retrieval was tested in both contexts. Behaviorally, cortisol impaired the retrieval of extinguished associations when presented in the extinction context. On the neural level, this effect was characterized by a reduced context differentiation for the extinguished stimulus in the ventromedial prefrontal cortex, but only in men. In the placebo group, ventromedial prefrontal cortex was functionally connected to the left cerebellum, the anterior cingulate and the right anterior parahippocampal gyrus to express extinction memory. This functional crosstalk was reduced under cortisol. These findings illustrate that the stress hormone cortisol disrupts ventromedial prefrontal cortex functioning and its communication with other brain regions implicated in extinction memory.

Introduction

Extinction is defined as a process during which an organism learns that once acquired information is no longer valid and in consequence ceases to respond to it (Myers and Davis, 2007; Vervliet et al., 2013). However, the retrieval of extinction memory is sometimes prone to failure (Bouton, 2002). Extinguished responses do not disappear but may return for example after a change in context (Bouton and Bolles, 1979; Milad et al., 2005), a phenomenon known as the renewal effect. This recovery of once acquired responses indicates that extinction does not lead to forgetting or an erasure of the initial memory trace. It rather constitutes a new learning process in which a second, inhibitory association between a stimulus and another outcome is acquired (Bouton, 1993; Delamater, 2004; Myers and Davis, 2002). Which of the two now competing associations will be retrieved at a later point in time depends critically on the context (Bouton, 2002), which can either be identical to the one shown during acquisition (AAA or ABA), during extinction (ABB) or a novel one (ABC or AAB; see Rescorla, 2008).

Among these variants, the ABA renewal has been demonstrated in numerous different paradigms, such as appetitive conditioning (Bouton and Peck, 1989) and taste aversion learning (Rosas and Bouton, 1997) in rats, as well as in human fear conditioning (Alvarez et al., 2007; Effting and Kindt, 2007; Milad et al., 2005; Vansteenwegen et al., 2005) and predictive learning (Üngör and Lachnit, 2006, 2008). In particular, the predictive learning task provides a more systematic exploration of the basic mechanisms underlying associative learning and extinction processes using contextually gated changes in stimulus–outcome relations without an emotional component. The enhanced context sensitivity often observed after extinction is assumed to be caused by the unexpected change in stimulus–outcome relations occurring during this second learning phase (Rosas and Callejas-Aguilera, 2006, 2007), which in turn might draw attention to external stimuli that have been concurrently presented, such as the context (Bouton, 2002; Lucke et al., 2013; Nelson et al., 2013; Vervliet et al., 2013). In accordance, it has been proposed that contextual cues might serve to regulate the retrieval of ambiguous memories related to the same stimulus (Bouton, 1993).

Abbreviations: vmPFC, Ventromedial prefrontal cortex; GC, Glucocorticoid; PHG, Parahippocampal gyrus; ACC, Anterior cingulate cortex; OC, Oral contraceptives.

* Corresponding author.
E-mail addresses: valerie.kinner@rub.de (V.L. Kinner), christian.j.merz@rub.de (C.J. Merz), silke.lissek@bergmannsheil.de (S. Lissek), oliver.t.wolf@rub.de (O.T. Wolf).

http://dx.doi.org/10.1016/j.neuroimage.2016.03.005
1053-8119/

With regard to the underlying brain structures, the hippocampal formation is known to be crucially relevant for contextual processing (Smith and Mizumori, 2006) and memory (Hirsh, 1974; Kennedy and Shapiro, 2004) and thus suggested to play a prominent role for extinction learning and the renewal effect alike (Kalisch et al., 2006; Milad et al., 2007). For instance, pharmacological inactivation of the hippocampus (Corcoran and Maren, 2001) and the ventromedial prefrontal cortex (vmPFC; Sierra-Mercado et al., 2006) disrupts the context-specific expression of extinction. Correspondingly, a recent study by Lissek et al. (2013) found increased hippocampal activity during extinction learning, whereas vmPFC was recruited during extinction recall in the predictive learning task.

Importantly, these brain structures are known to be specifically susceptible to the effects of stress hormones (Arnsten, 2009; Herry et al., 2010; Kim et al., 2006). Under stress, the consecutive activation of the sympathetic nervous system and the hypothalamus–pituitary–adrenocortical axis leads to the release of (nor)adrenaline and glucocorticoids (GCs; Joels and Baram, 2009). GCs bind to mineralocorticoid and glucocorticoid receptors (de Kloet et al., 2005) which are predominantly located in the PFC, hippocampus and amygdala (de Kloet, 2004) and activated by acute stress or cortisol administration alike. In particular, the main human GC cortisol has been shown to be a potent modulator of learning and memory (Joels et al., 2006; Schwabe et al., 2010; Wolf, 2009), with mostly impairing effects on memory retrieval (Roozendaal and McGaugh, 2011; Wolf, 2009).

First evidence from animal and human data indicates that acute stress also impairs the recall of extinction memory in fear conditioning (Deschaux et al., 2013; Raio et al., 2014) and in the non-aversive predictive learning task (Hamacher-Dang et al., 2013b). However, neuroimaging studies exploring the neural mechanisms underlying the impact of cortisol on extinction recall are lacking so far.

In the present study, we therefore aimed to investigate the potential modulatory role of cortisol on the neural correlates of extinction memory retrieval within an ABA renewal paradigm, applied in the predictive learning task (Hamacher-Dang et al., 2013a, 2013b; Üngör and Lachnit, 2006). On two consecutive days, the participants underwent acquisition and extinction in different contexts (context-dependent learning) and a renewal test (context-dependent recall of associations) prior to which participants either received an oral dose of cortisol or a placebo. In line with previous laboratory studies (Deschaux et al., 2013; Hamacher-Dang et al., 2013b; Raio et al., 2014), we expected cortisol to impair the retrieval of extinction memory. Similar to the well documented GC-induced reductions in hippocampal and prefrontal activation associated with impaired declarative memory retrieval (de Quervain et al., 2003; Oei et al., 2007; Weerda et al., 2010), this effect should be reflected in decreased activation of the hippocampus and the vmPFC during extinction recall as well.

Although there is a large body of neuroimaging literature concerning the regions involved in extinction processes, there are only few studies yet examining how these brain regions flexibly interact to express extinction (Milad et al., 2007; Schiller et al., 2013). Given the crucial role of vmPFC for extinction recall, aberrant functioning of this region or alterations in its connectivity to other structures of the extinction circuit might reflect the extinction retrieval deficits which have been observed after stress exposure. Consistent with this hypothesis, a recent study using resting-state functional connectivity analyses demonstrated a stress-induced disruption of interregional coupling between the vmPFC and the amygdala (Clewett et al., 2013). In order to enhance our understanding of the mechanisms mediating the expression of extinction and to further elucidate how they might be modulated by stress hormones, we investigated the functional connectivity of the emerging brain structures relevant for extinction recall. Since sex-dependent cortisol effects on brain activation in associative learning and extinction processes have been reported previously (for example Merz et al., 2010, 2012a) we additionally aimed to explore the potential interaction of sex and cortisol in the current study.

Materials and methods

Participants and general procedure

In total, 60 healthy, right-handed male and female students were recruited for participation in this study. Exclusion criteria were checked beforehand in a telephone interview and comprised chronic or acute illnesses, history of psychiatric or neurological treatment, a body mass index (BMI) outside the range of 18–27 kg/m^2, age outside the range of 18–40 years, drug use, smoking or regular intake of medicine, and standard fMRI exclusion criteria. All participants had normal or corrected-to-normal vision. Women were required to have been taking oral contraceptives (only monophasic preparations with an ethinylestradiol and a gestagenic component) for at least 3 months and were tested during pill intake to reduce potential influences of circulating sex hormones across the normal menstrual cycle (Merz et al., 2012b). In addition, the participants were instructed to refrain from physical exercise and consumption of food and drinks except water 2 hours prior to testing.

Individual sessions were conducted in the afternoons of two consecutive days (between 1 and 6 pm) to guarantee relatively low and stable endogenous cortisol concentrations. After arrival on day 1, the participants received an explanation of the procedure, the pharmacological agents and the fMRI protocol. After signing the informed consent form they filled out questionnaires regarding their demographic data and were prepared for scanning. In a first fMRI session, the participants underwent acquisition and extinction in a computer-based predictive learning task. On the following day, the participants were tested for renewal 40 min after receiving either cortisol or placebo (described in detail below). At the end of the second testing session, the participants were reimbursed with 40€ for their participation and received additional information regarding the aim of the study. All procedures conformed to the Declaration of Helsinki and were approved by the ethics committee of the Medical Faculty of the Ruhr-University Bochum.

Predictive learning task

A modified version of the predictive learning task (Hamacher-Dang et al., 2013a, 2013b) developed by Üngör and Lachnit (2006) was applied and adapted to the fMRI setting. In this task, the participants were asked to imagine being a doctor of a patient who sometimes suffers from stomach trouble after having meals in his two favorite restaurants. During scanning, the participants underwent three phases including acquisition and extinction on day 1 and a retrieval test on day 2.

In the acquisition phase, the participants learned to associate a food stimulus with a specific outcome. At the beginning of each trial, one of eight food stimuli (pictures of fruits and vegetables, for example strawberries or tomatoes) was presented for 3 s in one of the two contexts (indicated by a colored frame and the restaurant names “the bell” and “the dragon”). Afterwards, the participants had to predict whether the patient will experience stomach trouble or not after this meal (the question ‘Do you expect, that the patient will experience stomach trouble’ was superimposed, with the response options ‘Yes’ and ‘No’) by pressing the corresponding button on an fMRI-ready keyboard (Lumitouch, Photon Control Inc. Canada) within a response time window of 2.5 s. After expiration of the 2.5 s, feedback with the correct answer was presented for another 2.5 s. Feedback was displayed either in green color for correct predictions or in red color for wrong predictions and in case of a missing response. Inter-trial intervals depicting a white fixation cross on a black screen were randomly jittered between 5 and 7.5 s.

During extinction, two stimuli shown during acquisition were again presented but differed in regard to their context or changed both, its outcome and context (see Table 1). In particular, stimulus a+ had been associated with stomach trouble in context A during acquisition,