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BRIEF COMMUNICATION

Dissociation of Neuronal, Electrodermal, and Evaluative Responses in Disgust Extinction

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Disgust extinction is an important mechanism relevant for the treatment of psychiatric disorders. However, only a few studies have investigated disgust extinction. Moreover, because disgust sensitivity (DS) is considered as a relevant factor for learning processes, this study also investigated the potential relationship between DS and disgust extinction learning. The aim of this study was to explore the neuronal correlates of disgust extinction, as well as changes in skin conductance responses (SCRs) and evaluative conditioning. Twenty subjects were exposed to a differential extinction paradigm, in which a previous conditioned, and now unreinforced, stimulus (conditioned stimulus, CS+) was compared to a second stimulus (CS−), which was previously not associated with the unconditioned stimulus (UCS). Extinction learning was measured on three different response levels (BOLD responses, SCRs, and evaluative conditioning). Regarding evaluative conditioning, the CS+ was rated as more unpleasant than the CS−. Interestingly, significantly increased amygdala responses and SCRs toward to the CS− were observed. Finally, a (negative) trend was found between DS scores and BOLD responses of the prefrontal cortex. The present findings showed a dissociation of different response levels. The increased CS− responses could be explained by the assumption that the increased amygdala activity may reflect a safety learning signal during the first extinction trials and the subjective focus may therefore shift from the CS+ to the CS−. The correlation finding supports previous studies postulating that DS hampers extinction processes. The present results point toward dissociations between the response levels in context of extinction processes.

Keywords: extinction, classical conditioning, disgust, amygdala, emotion regulation, fear

Anxiety disorders are the most common psychiatric disorders with a lifetime prevalence of about 30% (Shin & Liberzon, 2010). A growing number of studies have argued that disgust learning and disgust extinction processes are important mechanisms in the maintenance and treatment of psychiatric disorders; for example, obsessive-compulsive disorders (OCD), eating disorders, and phobias (Mason & Richardson, 2010; Rohrmann & Hopp, 2008; Rohrmann, Hopp, Schienle, & Hodapp, 2009; Schienle, Schäfer, Hermann, & Vaitl, 2009; Schienle, Stark, & Vaitl, 2001). Thus, the investigation of the underlying mechanisms of disgust extinction processes might contribute to a better understanding of these disorders.

In extinction learning, a previously conditioned stimulus (CS+) is no longer paired with the unconditioned stimulus (UCS), while another stimulus (CS−) was never paired with the UCS. Findings have repeatedly shown that this procedure results in the decrease and extinction of previous conditioned responses (CRs) and in the formation of an "extinction memory" (Kalisch et al., 2006; Lin, Wang, Tai, & Tsai, 2010; Milad et al., 2010; Milad, Wright et al., 2007; Milad & Quirk, 2002; for review see: Milad & Quirk, 2012; Myers & Davis, 2007; Quirk & Mueller, 2008). In the last decade, human extinction learning has gained increased attention. Typically, three response levels are investigated: skin conductance responses (SCRs), changes in preference ratings (evaluative conditioning), and hemodynamic responses. Interestingly, these three response systems show a dissociation with respect to the extinction of CRs: Regarding SCRs, no significant differences between CS+ and CS− were observed during extinction (Graham & Milad, 2011; Milad, Igoe, Lebron-Milad, & Novales, 2009; Milad, Wright et al., 2007; Milad & Quirk, 2002; Milad et al., 2010; Myers & Davis, 2007). In contrast, with respect to subjective ratings, previous studies have consistently observed significant differences between CS+ and CS− even after extinction learning (Blechert, Michael, Williams, Purkis, & Wilhelm, 2008; Dwyer, Jarratt, &

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Dick, 2007; Vansteenwegen, Francken, Vervliet, De Clercq, & Eelen, 2006). Regarding the neuronal correlates of extinction, previous studies have identified a neuronal circuit including the amygdala, the ventromedial prefrontal cortex (vmPFC), and the hippocampus (Milad & Quirk, 2012; Quirk & Mueller, 2008; Sotres-Bayon, Cain, & LeDoux, 2006).

Whereas considerable progress has been made in the understanding of the neuronal correlates of human fear extinction learning, to our best knowledge, disgust extinction has been almost neglected so far. Only few studies have investigated subjective ratings and peripheral-physiological responses during disgust extinction (Mason & Richardson, 2010; Olatunji, Forsyth, & Cherian, 2007). Notably, these studies showed important differences to fear extinction; implicating that disgust CRs (e.g., in SCRs) are resistant to extinction learning. For instance, Olatunji et al. (2007) found significant differences between CS+ and CS− in evaluative conditioning and SCRs during extinction learning. Mason and Richardson (2010) confirmed this resistance to extinction by showing CS+/CS− differences in evaluative conditioning and on the behavioral level (e.g., in a visual avoidance task). Importantly, the studies by Olatunji, Lohr, Smits, Sawchuk, and Patten (2009) and Mason and Richardson (2010) observed that disgust learning and extinction was altered by individual disgust sensitivity (DS). Consequently, the alteration of disgust learning and extinction through DS may provide an explanation for the robust observation that DS represents a vulnerability factor for certain psychiatric disorders (Aharoni & Hertz, 2012; Deacon & Olatunji, 2007; Engelhard, Olatunji, & de Jong, 2011; Moretz & McKay, 2008; Olatunji, Sawchuk, de Jong, & Lohr, 2006; Rohrmann et al., 2009; Schienle et al., 2003).

The aim of the present study was to explore hemodynamic responses, SCRs, and evaluative conditioning in disgust extinction. In addition, we also explored the potential influence of DS. On the neuronal level, we were especially interested in the amygdala, the hippocampus, and the vmPFC. Additionally, we investigated the insula due to its role in disgust conditioning and disgust processing (Calder et al., 2007; Klucken, Schweckendiek et al., 2012). Despite the fact that most studies found increased activity to the CS+, we also analyzed the contrast CS− > CS+ due to prior reports of increased activity to the CS− (for the different results see: Knight, Smith, Cheng, Stein, & Helmstetter, 2004; Milad, Wright et al., 2007; Milad & Quirk, 2012; Myers & Davis, 2007; Phelps, Delgado, Nearing, & LeDoux, 2004; Quirk & Mueller, 2008). Finally, we investigated the association between DS and disgust extinction.

This study—focusing on the extinction phase—is part of a larger project that investigated the role of disgust in associative learning. Data of the conditioning phase have already been presented in detail elsewhere and will be reported only briefly (Klucken, Schweckendiek et al., 2012).

Materials and Method

Participants and Sample Description

Twenty-two subjects participated in the study. The sample is identical to the sample in Klucken, Schweckendiek et al. (2012). Subjects were recruited from campus advertisements and received 8 Euro/h for participation. All subjects were right-handed and had normal or corrected-to-normal vision. None of them had a history of psychiatric or neurological disorders. Participants were informed about the procedure in general and gave written informed consent. All experimental procedures were in accordance to the Declaration of Helsinki. Due to technical problems and extensive head motion during scanning, two subjects were excluded from all analyses, leaving a total of 20 subjects in the analyses of the fMRI and the evaluative conditioning data (10 males: mean age: 23.4; *SD*: 2.1; 10 females: mean age: 23.2; *SD*: 3.6).

Stimuli

Two neutral visual stimuli (two squares, with either continuous or dotted borders) served as CS+ and CS− and were followed by one of the 21 UCS-pictures. The UCS consisted of 21 disgust-inducing pictures (e.g., poor hygiene, rotten food, etc.), which were taken from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2005) or were collected by the authors. These pictures have been used repeatedly in previous studies (Klucken, Kagerer et al., 2009; Klucken, Schweckendiek et al., 2012; Stark et al., 2007). The IAPS pictures were chosen based on a rating study by Libkuman and colleagues (Libkuman, Otani, Kern, Viger, & Novak, 2007) and were matched with respect to valence and arousal as far as possible. All stimuli had identical luminance and were presented in an 800 × 600 pixel resolution. The stimuli were projected onto a screen at the end of the scanner (visual field = 18°) using an LCD projector (EPSON EMP-7250, Seiko EPSON Corporation, Japan).

Extinction Procedure

The differential delay conditioning procedure contained an acquisition and an extinction learning phase. A detailed fMRI protocol and results from the acquisition phase can be found elsewhere (Klucken, Schweckendiek et al., 2012). Since contingency awareness may alter CRs (Hamm & Vaitl, 1996; Klucken, Kagerer et al., 2009; Klucken, Schweckendiek et al., 2009; Klucken, Tabbert et al., 2009; Tabbert et al., 2011; Weike, Schupp, & Hamm, 2007; for review see Lovibond & Shanks, 2002; Hamm & Weike, 2005), subjects were instructed to pay attention to all stimuli and to try to figure out possible connections between the CS and the UCS (e.g., Schiller et al., 2008). In the acquisition phase, 42 trials were presented (21 per CS; duration 8 seconds) with the CS+ being followed by one of the 21 disgust-related pictures in each trial (UCS) shown for 4s (100% reinforcement). Each UCS picture was shown only once. In the extinction learning phase, 22 trials were presented (11 per CS) with the same CS duration and without UCS reinforcement. The intertrial intervals (ITI) ranged from 12.5 s to 15 s. The first two trials (one CS+, one CS− trial) were excluded from the analyses because learning could not yet have occurred (Phelps et al., 2004). In an equally distributed interval of 1−2 s after UCS offset, participants had to react to a simple distractor task (duration 1 s) to enhance overall vigilance (Goldin, McRae, Ramel, & Gross, 2008; Schweckendiek et al., 2011). Finally, participants filled out the German version of the Questionnaire for the Assessment of Disgust Sensitivity (Schienle, Walter, Stark, & Vaitl, 2002).

Evaluative Conditioning

Participants rated valence and arousal of the CS+, the CS−, and the UCS on a 9-point Likert scale. The CS+ and the CS− were rated three times (for clarification, the word *block* will refer to the time point of measurement): (1) preacquisition, (2) postacquisition, and (3) postextinction. Statistical analyses were performed by analysis of variance (ANOVA) in a 2 (stimulus: CS+ vs. CS−) × 3 (block: preacquisition vs. postacquisition vs. postextinction) factorial design in the general linear model (Greenhouse-Geisser corrected) as implemented in SPSS Statistics 19 (IBM company, Armonk, NY). Appropriate post hoc *t* tests were conducted to further analyze significant effects. Finally, we correlated differential evaluative conditioning ratings with individual DS scores (corrected for multiple testing). Global UCS ratings were measured after the extinction procedure only and are presented elsewhere (Klucken, Schweckendiek et al., 2012).

Skin Conductance Responses

SCRs were sampled simultaneously with MR scans using Ag/AgCl electrodes filled with isotonic (0.05 M NaCl) electrolyte medium, placed hypothenar at the nondominant (left) hand. SCRs were defined in two analysis windows: the maximum response within the time window 1−5 s after each CS onset was counted as the first interval response (FIR), the time windows within 5−9 s as the second interval response (SIR). We investigated the first and the second interval response because both responses might be sensitive to reflect conditioned responses (e.g., Prokasy & Ebel, 1967; Knight, Waters, & Bandettini, 2009) and are associated with different functions (FIR to orienting reactions and SIR to anticipation; Knight et al., 2009; Tabber et al., 2011). A 100Hz low-pass filter was applied to the SCR data. The response amplitudes were computed as the differences between the starting point of a response and the local maximum (both defined by the points of inflection). A logarithmic transformation [ln(1 + SCR)] was conducted. Statistical analyses were performed via ANOVA in a 2 (stimulus: CS+ vs. CS−) × 5 (block: two trials in each block) design followed by post hoc tests in SPSS 19 (IBM company, Armonk, NY). Finally, DS scores were correlated with differential SCRs. Two subjects had to be excluded from SCR analyses because they did not show any SCRs (all responses < .05 μs), leaving 18 participants for the SCRs analysis. In addition, SCRs were correlated with individual DS scores (corrected for multiple testing).

MRI

Functional and anatomical images were acquired with a 1.5 Tesla whole-body tomograph (Siemens Symphony with a quantum gradient system) with a standard head coil. Structural image acquisition consisted of 160 T1-weighted sagittal images (MPRage, 1 mm slice thickness). For functional images, a total of 268 images were registered using a T2*-weighted gradient echo-planar imaging (EPI) sequence with 25 slices covering the whole brain (slice thickness = 5 mm; 1 mm gap; descending slice procedure; TR = 2.5 s; TE = 55 ms; flip angle = 90°; field of view 192 × 192 mm; matrix size = 64 × 64). Data were analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London UK) implemented in MATLAB 7.5 (Mathworks Inc., Sherbourn, MA). Standard preprocessing steps were used as described previously (Klucken, Schweckendiek et al., 2012; Klucken, Alexander et al, 2012).

The experimental conditions were CS+, CS−, UCS, non-UCS (defined as the time point after CS+/CS−), and the distractor task. Following a worthwhile reviewer's comment, the conditions were divided into two halves (early and late half, with the same number of trials). The six movement parameters of the rigid body transformation obtained by the realignment procedure were introduced as covariates in the model. Regressors were convolved with the canonical hemodynamic response function in the general linear model. The voxel-based time series was filtered with a high-pass filter (time constant = 128 s).

On the first level of analysis, the following contrasts were analyzed for each subject: CS+ > CS− and CS− > CS+, as well as early half versus late half. Scores of these contrasts were calculated for each subject and introduced as dependent variables in the group analyses. In the group analyses, one-sample *t* tests (e.g., CS+ > CS−; CS− > CS+) were conducted to test for significant differences. Further, regression analyses with individual DS scores were conducted. Whole-brain analyses were conducted using a family-wise-error (FWE) -corrected alpha level of $\alpha = .05$ with a minimum size of 5 voxels. Regions of interest (ROI) analyses were performed using the small volume correction in SPM8. For ROI effects, the significance level was set to a corrected alpha level of <.05 (FWE) with a minimum cluster size of $k = 5$ voxel. Insula, amygdala, hippocampus, and vmPFC were defined as ROI. All masks except the vmPFC mask were taken from the *Harvard-Oxford Cortical and Subcortical Structural Atlases* provided by the *Harvard Center for Morphometric Analysis* and from the Human Brain Project Repository database based on the BrainMap database (Fox & Lancaster, 1994; Nielsen & Hansen, 2002). Because no mask for the vmPFC exists in this atlas, an appropriate mask was designed using the software program MARINA (Walter et al., 2003). In addition, DS were correlated with the contrasts using multiple regression analysis in SPM8.

Results

Evaluative Conditioning

ANOVA revealed significant main effects of stimulus ($F_{(1,19)} = 5.15$; $p < .05$) and block ($F_{(2,18)} = 4.10$; $p < .05$) as well as a significant stimulus × block interaction effect ($F_{(2,18)} = 7.27$; $p < .01$) for valence ratings. Regarding the arousal ratings, a significant stimulus × block interaction effect ($F_{(2,18)} = 4.14$; $p < .05$) was observed. Follow-up *t* tests showed that the CS+ did not differ from the CS− prior to the experiment ($p > .29$) but was rated as significantly more aversive and more arousing after conditioning and also after the extinction block ($p < .05$; see Figure 1). No correlations with DS were found.

Skin Conductance Responses

During the conditioning phase, we found significantly enhanced conditioned responses to the CS+ as compared to the CS− (see Klucken, Schweckendiek et al., 2012). Regarding the extinction phase, no main effect of stimulus ($F_{(1,17)} = 1.04$; $p > .05$) or block

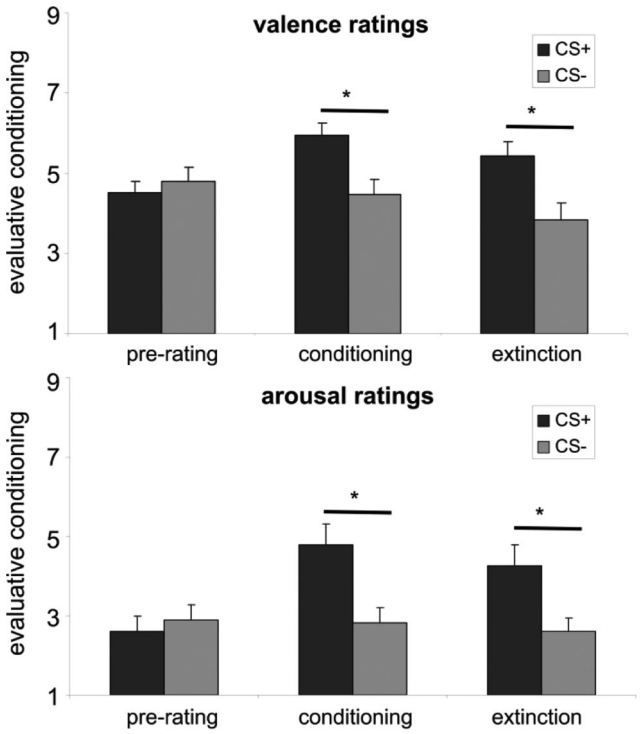

Figure 1. Stimulus × block interaction effect in evaluative conditioning. The CS+ significantly differs from the CS− after the conditioning and after the extinction, but not prior to the experiment. Error bars represent standard errors of the mean. * $p < .05$.

($F_{(4,13)} = 0.97$; $p > .05$) was found. We observed a stimulus × block interaction effect ($F_{(4,13)} = 3.43$; $p < .05$) in the FIR (see Figure 2). Contrary to the evaluative ratings, post hoc t tests showed significantly increased activation to the CS− as compared to the CS+ in the last block ($p = .013$), which is only a trend when correcting for multiple comparisons (but not in all preceding trials; all $p > .20$). Regarding the SIR, ANOVA did not show significant main effects of stimulus ($F_{(1,17)} = 3.48$; $p > .05$) or block ($F_{(4,13)} =$ 0.894; $p > .05$), nor a stimulus × block interaction effect ($F_{(4,14)} =$ 0.68; $p > .05$). No correlation of differential SCRs with DS was found.

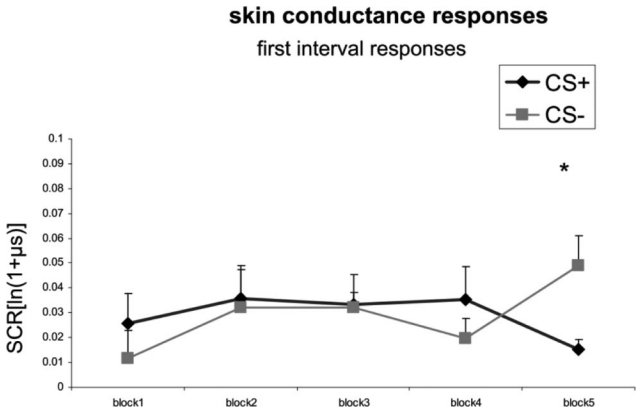

Figure 2. Skin conductance responses to the CS+ and to the CS− during the extinction process. Each block contains two trials. The CS− significantly differs from the CS+ in the last block. Error bars represent standard errors of the mean. * $p < .05$.

Neuronal Activation

Regarding the hemodynamic responses during the conditioning phase, strong CS+ > CS− differences were found in subcortical and cortical areas (e.g., insula, occipital cortex, see Klucken, Schweckendiek et al., 2012). In the extinction phase, whole-brain and ROI analyses revealed no significant differences in the contrast CS+ > CS−. Regarding the contrast CS− > CS+, we observed significant hemodynamic responses in the left amygdala (MNI-coordinates: $x = -15$; $y = -7$; $z = -14$; cluster size = 57 voxels; $Z_{max} = 3.05$; $p = .032$; FWE-corrected; see Figure 3). In addition, we found a marginally significant correlation between high DS scores and low hemodynamic responses in the left vmPFC in the contrast CS+ > CS− (MNI-coordinates: $x = -6$; $y = 38$; $z = -26$; cluster size = 165 voxels; $Z_{max} = 3.37$; $p = .059$; FWE-corrected). No correlation with SCRs was observed (FIR as well as SIR). In addition, we analyzed the early versus the late half of the extinction learning phase (early [CS+ vs. CS−]–late [CS+ vs. CS−] and vice versa) to gain further information about extinction learning and analyzed each half separately. It is interesting that we found the strongest amygdala activity in the first half of the experiment ($p = .024$). However, regarding the late phase, amygdala activation seemed slowly to shift to the CS+ over time, which was not significant as well as the comparison of both halves ($p = .17$).

Discussion

The aim of this study was to investigate different response systems in disgust extinction and the association of disgust extinction with disgust sensitivity. To our best knowledge, this is the first study exploring disgust extinction learning concurrently in three different response systems (SCRs, brain activity, and evaluative conditioning). As the main result, we found a dissociation of the different response systems during extinction learning: While the CS+ was rated as significantly more unpleasant than the CS−, SCRs and hemodynamic responses exhibited increased responses to the CS−. A trend was found between high DS scores and decreased hemodynamic responses in the contrast CS+ > CS− during extinction learning in the vmPFC.

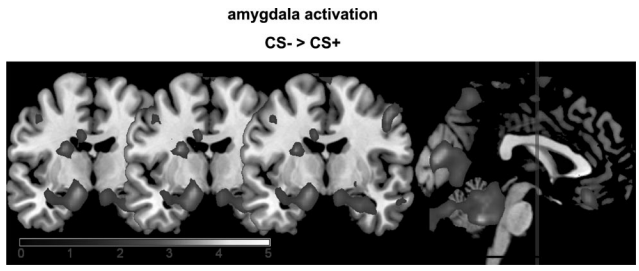

Figure 3. Neuronal activation in the left amygdala in the extinction phase for the contrast CS− > CS+. For illustration purposes, data are thresholded and masked with $t > 2.0$.

Regarding the dissociation between the different response systems, the present results are in line with recent fear extinction studies that report stable CS+/CS− differences in subjective ratings, while no CS+/CS− differences were found in other response systems during extinction (Blechert et al., 2008; Dwyer et al., 2007; Vansteenwegen et al., 2006). For instance, Blechert et al. (2008) observed no differences in SCRs, while CS+/CS− differences in evaluative conditioning remained stable even after extinction. These findings in evaluative conditioning have been observed across different emotions, healthy subjects, psychiatric patients, and even across different stimulus modalities as well as in different paradigms and methods (Hofmann, De Houwer, Perugini, Baeyens, & Crombez, 2010; Mason & Richardson, 2010; Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007; Olatunji, 2006; Olatunji et al., 2007, 2009; Stevenson, Boakes, & Wilson, 2000).

It is interesting to note that we found slightly increased SCRs to the CS− compared to the CS+ in the last part of the experiment, while most studies did not find any differences between CS+ and CS− in SCRs (Milad et al., 2010; Milad, Wright et al., 2007; Tabbert et al., 2010). This finding is rather puzzling considering the findings in the study by Olatunji et al. (2007), who reported higher SCRs to the CS+ compared to the CS− at the end of disgust extinction. One possible explanation for these differences could be that Olatunji et al. (2007) used highly negative pictures (e.g., of mutilations), which may evoke more arousal and might possess higher negative valence than the pictures used in the present study (e.g., rotten food). Therefore, it is possible that the high levels of arousal in response to the UCS, as in the study by Olatunji et al. (2007), may have caused increased SCRs to the CS+ as compared to the CS− in extinction learning or could also reflect a recall of the conditioning memory. In addition, substantial differences in the choice of CS (e.g., using pictures as CS vs. using neutral words as CS) and differences in the experimental protocol (duration, conditioning, and extinction trials, etc.) could provide explanations for some of these contrary results. However, due to the fact that disgust extinction has been investigated only very rarely, further studies are needed to determine the course of SCRs in more detail.

Regarding BOLD responses, significant effects were observed in the left amygdala in the contrast CS− > CS+. However, although most studies found increased amygdala activation to the CS+ in extinction learning (for in-depth reviews see Quirk & Mueller, 2008; Milad & Quirk, 2012), no differences or even greater responses to the CS− as compared to the CS+ have also been found in some extinction studies (Phelps et al., 2004; Merz et al., 2012). For instance, Phelps and colleagues (2004) reported greater amygdala and vmPFC activation to the CS− as compared to the CS+ in extinction learning. Several studies showed that different parts of the amygdala are also associated with safety learning (Pollak et al., 2010; Rogan, Leon, Perez, & Kandel, 2005). Thus, the amygdala activation observed in the present study might therefore reflect safety learning. Another (post hoc) interpretation for the amygdala findings is the possibility that subjects may have expected the CS− to be the new "danger signal," that is, a reversal of contingencies (Schiller & Delgado, 2010; Schiller et al., 2008). Therefore, subjects may have been uncertain about the new contingencies, which could have provoked the amygdala activity (Schiller et al., 2008; Whalen, 2007). Because additional data is needed to support either one of the different hypotheses, it is not clear whether the present finding reflects uncertainty or extinction learning. However, it should be noted, that such short extinction phase may also reflect a potential recall of CRs. Thus, these interpretations remain speculative and should be treated with caution.

The negative correlation of DS with activation within the vmPFC extends the understanding of DS. Since vmPFC activity is regarded as a correlate of emotion regulation and extinction (Delgado, Nearing, LeDoux, & Phelps, 2008; Goldin et al., 2008; Hermann et al., 2007, 2009), our correlational finding nicely fits to the assumption that high disgust-prone subjects have more difficulties in coping with disgust-related processes. The altered vmPFC activation might reflect an increased effort to cope and regulate emotions. Nevertheless, this conclusion should be noted as preliminary because it was not the aim of the study to investigate emotion regulation.

Surprisingly, in contrast to studies investigating the neuronal correlates of disgust experiences and disgust learning (Calder et al., 2007; Klucken, Schweckendiek et al., 2012; Kim & Jung, 2006; Sehlmeyer et al., 2009), we did not find insula activation in the extinction phase. For instance, Kim & Jung (2006) assumed that the insula is especially involved in the storage of a probably long-term CS memory. Since we investigated extinction learning without any consolidation between the acquisition and the extinction phase, the storage process may not have been finished yet.

In sum, the present findings extend the view of disgust extinction learning: First, evaluative conditioning showed significant differences between CS+ and CS− even after extinction leaning (Mason & Richardson, 2010; Olatunji et al., 2007). Second, we found increased amygdala responses to the CS−, which could be interpreted as a safety learning signal. Finally, we found a marginally significant negative correlation between DS scores and vmPFC responses, which could be interpreted as a neuronal correlate for the proposed association of DS and dysfunctional emotion regulation.

References

Aharoni, R., & Hertz, M. M. (2012). Disgust sensitivity and anorexia nervosa. *European Eating Disorders Review, 20,* 106–110. doi:10.1002/erv.1124

Blechert, J., Michael, T., Williams, S. L., Purkis, H., & Wilhelm, F. H. (2008). When two paradigms meet: Does evaluative learning extinguish in differential fear conditioning? *Learning and Motivation, 39,* 58–70. doi:10.1016/j.lmot.2007.03.003

Calder, A. J., Beaver, J. D., Davis, M. H., van Ditzhuijzen, J., Keane, J., & Lawrence, A. D. (2007). Disgust sensitivity predicts the insula and pallidal response to pictures of disgusting foods. *The European Journal of Neuroscience, 25,* 3422–3428. doi:10.1111/j.1460-9568.2007.05604.x

Deacon, B., & Olatunji, B. O. (2007). Specificity of disgust sensitivity in the prediction of behavioral avoidance in contamination fear. *Behaviour Research and Therapy, 45,* 2110–2120. doi:10.1016/j.brat.2007.03.008

Delgado, M. R., Nearing, K. I., LeDoux, J. E., & Phelps, E. A. (2008). Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron, 59,* 829–838. doi:10.1016/j.neuron.2008.06.029

Dwyer, D. M., Jarratt, F., & Dick, K. (2007). Evaluative conditioning with foods as CSs and body shapes as USs: No evidence for sex differences, extinction, or overshadowing. *Cognition & Emotion, 21,* 281–299. doi:10.1080/02699930600551592

Engelhard, I. M., Olatunji, B. O., & de Jong, P. J. (2011). Disgust and the development of posttraumatic stress among soldiers deployed to Afghanistan. *Journal of Anxiety Disorders, 25,* 58–63. doi:10.1016/j.janxdis.2010.08.003

Fox, P. T., & Lancaster, J. L. (1994). Neuroscience on the net. *Science, 266*(5187), 994–996. doi:10.1126/science.7973682

Goldin, P. R., McRae, K., Ramel, W., & Gross, J. J. (2008). The neural bases of emotion regulation: Reappraisal and suppression of negative emotion. *Biological Psychiatry, 63,* 577–586. doi:10.1016/j.biopsych.2007.05.031

Graham, B. M., & Milad, M. R. (2011). The study of fear extinction: Implications for anxiety disorders. *The American Journal of Psychiatry, 168,* 1255–1265. doi:10.1176/appi.ajp.2011.11040557

Hamm, A. O., & Vaitl, D. (1996). Affective learning: Awareness and aversion. *Psychophysiology, 33,* 698–710. doi:10.1111/j.1469-8986.1996.tb02366.x

Hamm, A. O., & Weike, A. I. (2005). The neuropsychology of fear learning and fear regulation. *International Journal of Psychophysiology, 57,* 5–14. doi:10.1016/j.ijpsycho.2005.01.006

Hermann, A., Schäfer, A., Walter, B., Stark, R., Vaitl, D., & Schienle, A. (2007). Diminished medial prefrontal cortex activity in blood-injection-injury phobia. *Biological Psychology, 75,* 124–130. doi:10.1016/j.biopsycho.2007.01.002

Hermann, A., Schäfer, A., Walter, B., Stark, R., Vaitl, D., & Schienle, A. (2009). Emotion regulation in spider phobia: Role of the medial prefrontal cortex. *Social Cognitive and Affective Neuroscience, 4,* 257–267. doi:10.1093/scan/nsp013

Hofmann, W., De Houwer, J., Perugini, M., Baeyens, F., & Crombez, G. (2010). Evaluative conditioning in humans: A meta-analysis. *Psychological Bulletin, 136,* 390–421. doi:10.1037/a0018916

Kalisch, R., Korenfeld, E., Stephan, K. E., Weiskopf, N., Seymour, B., & Dolan, R. J. (2006). Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. *The Journal of Neuroscience, 26,* 9503–9511. doi:10.1523/JNEUROSCI.2021-06.2006

Kim, J. J., & Jung, M. W. (2006). Neural circuits and mechanisms involved in Pavlovian fear conditioning: A critical review. *Neuroscience and Biobehavioral Reviews, 30,* 188–202. doi:10.1016/j.neubiorev.2005.06.005

Klucken, T., Alexander, N., Schweckendiek, J., Merz, C. J., Kagerer, S., Osinsky, R., . . . Stark, R. (2012). Individual differences in neural correlates of fear conditioning as a function of 5-HTTLPR and stressful life events. *Social Cognitive and Affective Neuroscience*. Advance online publication. doi:10.1093/scan/nss005

Klucken, T., Kagerer, S., Schweckendiek, J., Tabbert, K., Vaitl, D., & Stark, R. (2009). Neural, electrodermal and behavioral response patterns in contingency aware and unaware subjects during a picture-picture conditioning paradigm. *Neuroscience, 158,* 721–731. doi:10.1016/j.neuroscience.2008.09.049

Klucken, T., Schweckendiek, J., Koppe, G., Merz, C. J., Kagerer, S., Walter, B., . . . Stark, R. (2012). Neural correlates of disgust- and fear-conditioned responses. *Neuroscience, 201,* 209–218. doi:10.1016/j.neuroscience.2011.11.007

Klucken, T., Schweckendiek, J., Merz, C. J., Tabbert, K., Walter, B., Kagerer, S., . . . Stark, R. (2009). Neural activations of the acquisition of conditioned sexual arousal: Effects of contingency awareness and sex. *The Journal of Sexual Medicine, 6,* 3071–3085. doi:10.1111/j.1743-6109.2009.01405.x

Klucken, T., Tabbert, K., Schweckendiek, J., Merz, C. J., Kagerer, S., Vaitl, D., & Stark, R. (2009). Contingency learning in human fear conditioning involves the ventral striatum. *Human Brain Mapping, 30,* 3636–3644. doi:10.1002/hbm.20791

Knight, D. C., Smith, C. N., Cheng, D. T., Stein, E. A., & Helmstetter, F. J. (2004). Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. *Cognitive, Affective & Behavioral Neuroscience, 4,* 317–325. doi:10.3758/CABN.4.3.317

Knight, D. C., Waters, N. S., & Bandettini, P. A. (2009). Neural substrates of explicit and implicit fear memory. *NeuroImage, 45,* 208–214. doi:10.1016/j.neuroimage.2008.11.015

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2005). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual*. Technical Report A-6. Gainesville, FL: University of Florida.

Libkuman, T. M., Otani, H., Kern, R., Viger, S. G., & Novak, N. (2007). Multidimensional normative ratings for the International Affective Picture System. *Behavior Research Methods, 39,* 326–334. doi:10.3758/BF03193164

Lin, P.-Y., Wang, S.-P., Tai, M.-Y., & Tsai, Y.-F. (2010). Differential involvement of medial prefrontal cortex and basolateral amygdala extracellular signal-regulated kinase in extinction of conditioned taste aversion is dependent on different intervals of extinction following conditioning. *Neuroscience, 171,* 125–133. doi:10.1016/j.neuroscience.2010.08.066

Lovibond, P. F., & Shanks, D. R. (2002). The role of awareness in Pavlovian conditioning: Empirical evidence and theoretical implications. *Journal of Experimental Psychology: Animal Behavior Processes, 28,* 3–26. doi:10.1037/0097-7403.28.1.3

Mason, E. C., & Richardson, R. (2010). Looking beyond fear: The extinction of other emotions implicated in anxiety disorders. *Journal of Anxiety Disorders, 24,* 63–70. doi:10.1016/j.janxdis.2009.08.007

Merz, C. J., Tabbert, K., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., & Wolf, O. T. (2012). Neuronal correlates of extinction learning are modulated by sex hormones. *Social Cognitive and Affective Neuroscience, 7,* 819–830. doi:10.1093/scan/nsr063

Michael, T., Blechert, J., Vriends, N., Margraf, J., & Wilhelm, F. H. (2007). Fear conditioning in panic disorder: Enhanced resistance to extinction. *Journal of Abnormal Psychology, 116,* 612–617. doi:10.1037/0021-843X.116.3.612

Milad, M. R., Igoe, S. A., Lebron-Milad, K., & Novales, J. E. (2009). Estrous cycle phase and gonadal hormones influence conditioned fear extinction. *Neuroscience, 164,* 887–895. doi:10.1016/j.neuroscience.2009.09.011

Milad, M. R., & Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature, 420*(6911), 70–74. doi:10.1038/nature01138

Milad, M. R., & Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. *Annual Review of Psychology, 63,* 129–151. doi:10.1146/annurev.psych.121208.131631

Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert: Neurocircuitry and neuroplasticity abnormalities in mood and anxiety disorders. *Biological Psychiatry, 62,* 446–454. doi:10.1016/j.biopsych.2006.10.011

Milad, M. R., Zeidan, M. A., Contero, A., Pitman, R. K., Klibanski, A., Rauch, S. L., & Goldstein, J. M. (2010). The influence of gonadal hormones on conditioned fear extinction in healthy humans. *Neuroscience, 168,* 652–658. doi:10.1016/j.neuroscience.2010.04.030

Moretz, M. W., & McKay, D. (2008). Disgust sensitivity as a predictor of obsessive-compulsive contamination symptoms and associated cognitions. *Journal of Anxiety Disorders, 22,* 707–715. doi:10.1016/j.janxdis.2007.07.004

Myers, K. M., & Davis, M. (2007). Mechanisms of fear extinction. *Molecular Psychiatry, 12,* 120–150. doi:10.1038/sj.mp.4001939

Nielsen, F., & Hansen, L. K. (2002, June). *Automatic anatomical labeling of Talairach coordinates and generation of volumes of interest via the BrainMap database*. Paper presented at the Eighth International Conference on Functional Mapping of the Human Brain, Sendai, Japan.

Retrieved from http://www2.imm.dtu.dk/pubdb/views/publication_details.php?id=195

Olatunji, B. O. (2006). Evaluative learning and emotional responding to fearful and disgusting stimuli in spider phobia. *Journal of Anxiety Disorders, 20,* 858–876. doi:10.1016/j.janxdis.2006.01.005

Olatunji, B. O., Forsyth, J. P., & Cherian, A. (2007). Evaluative differential conditioning of disgust: A sticky form of relational learning that is resistant to extinction. *Journal of Anxiety Disorders, 21,* 820–834. doi:10.1016/j.janxdis.2006.11.004

Olatunji, B. O., Lohr, J. M., Smits, J. A. J., Sawchuk, C. N., & Patten, K. (2009). Evaluative conditioning of fear and disgust in blood-injection-injury phobia: Specificity and impact of individual differences in disgust sensitivity. *Journal of Anxiety Disorders, 23,* 153–159. doi:10.1016/j.janxdis.2008.06.002

Olatunji, B. O., Sawchuk, C. N., de Jong, P. J., & Lohr, J. M. (2006). The structural relation between disgust sensitivity and blood-injection-injury fears: A cross-cultural comparison of US and Dutch data. *Journal of Behavior Therapy and Experimental Psychiatry, 37,* 16–29. doi:10.1016/j.jbtep.2005.09.002

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron, 43,* 897–905. doi:10.1016/j.neuron.2004.08.042

Pollak, D. D., Rogan, M. T., Egner, T., Perez, D. L., Yanagihara, T. K., & Hirsch, J. (2010). A translational bridge between mouse and human models of learned safety. *Annals of Medicine, 42,* 127–134. doi:10.3109/07853890903583666

Prokasy, W. F., & Ebel, H. C. (1967). Three components of the classically conditioned GSR in human subjects. *Journal of Experimental Psychology, 73,* 247–256.

Quirk, G. J., & Mueller, D. (2008). Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology, 33,* 56–72. doi:10.1038/sj.npp.1301555

Rogan, M. T., Leon, K. S., Perez, D. L., & Kandel, E. R. (2005). Distinct neural signatures for safety and danger in the amygdala and striatum of the mouse. *Neuron, 46,* 309–320. doi:10.1016/j.neuron.2005.02.017

Rohrmann, S., & Hopp, H. (2008). Cardiovascular indicators of disgust. *International Journal of Psychophysiology, 68,* 201–208. doi:10.1016/j.ijpsycho.2008.01.011

Rohrmann, S., Hopp, H., Schienle, A., & Hodapp, V. (2009). Emotion regulation, disgust sensitivity, and psychophysiological responses to a disgust-inducing film. *Anxiety, Stress & Coping, 22,* 215–236. doi:10.1080/10615800802016591

Schienle, A., Schäfer, A., Hermann, A., & Vaitl, D. (2009). Binge-eating disorder: Reward sensitivity and brain activation to images of food. *Biological Psychiatry, 65,* 654–661. doi:10.1016/j.biopsych.2008.09.028

Schienle, A., Schäfer, A., Stark, R., Walter, B., Franz, M., & Vaitl, D. (2003). Disgust sensitivity in psychiatric disorders: A questionnaire study. *The Journal of Nervous and Mental Disease, 191,* 831–834. doi:10.1097/01.nmd.0000100928.99910.2d

Schienle, A., Stark, R., & Vaitl, D. (2001). Evaluative conditioning: A possible explanation for the acquisition of disgust responses? *Learning and Motivation, 32,* 65–83. doi:10.1006/lmot.2000.1067

Schienle, A., Walter, B., Stark, R., & Vaitl, D. (2002). A questionnaire for the assessment of disgust sensitivity. *Zeitschrift für Klinische Psychologie und Psychotherapie, 31,* 110–120. doi:10.1026//1616-3443.31.2.110

Schiller, D., & Delgado, M. R. (2010). Overlapping neural systems mediating extinction, reversal and regulation of fear. *Trends in Cognitive Sciences, 14,* 268–276. doi:10.1016/j.tics.2010.04.002

Schiller, D., Levy, I., Niv, Y., LeDoux, J. E., & Phelps, E. A. (2008). From fear to safety and back: Reversal of fear in the human brain. *The Journal of Neuroscience, 28,* 11517–11525. doi:10.1523/JNEUROSCI.2265-08.2008

Schweckendiek, J., Klucken, T., Merz, C. J., Tabbert, K., Walter, B., Ambach, W., . . . Stark, R. (2011). Weaving the (neuronal) web: Fear learning in spider phobia. *NeuroImage, 54,* 681–688. doi:10.1016/j.neuroimage.2010.07.049

Sehlmeyer, C., Schöning, S., Zwitserlood, P., Pfleiderer, B., Kircher, T., Arolt, V., & Konrad, C. (2009). Human fear conditioning and extinction in neuroimaging: A systematic review. *PloS ONE, 4*(6), e5865. doi:10.1371/journal.pone.0005865

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology, 35,* 169–191. doi:10.1038/npp.2009.83

Sotres-Bayon, F., Cain, C. K., & LeDoux, J. E. (2006). Brain mechanisms of fear extinction: Historical perspectives on the contribution of prefrontal cortex. *Biological Psychiatry, 60,* 329–336. doi:10.1016/j.biopsych.2005.10.012

Stark, R., Zimmermann, M., Kagerer, S., Schienle, A., Walter, B., Weygandt, M., & Vaitl, D. (2007). Hemodynamic brain correlates of disgust and fear ratings. *NeuroImage, 37,* 663–673. doi:10.1016/j.neuroimage.2007.05.005

Stevenson, R. J., Boakes, R. A., & Wilson, J. P. (2000). Resistance to extinction of conditioned odor perceptions: Evaluative conditioning is not unique. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 26,* 423–440. doi:10.1037/0278-7393.26.2.423

Tabbert, K., Merz, C. J., Klucken, T., Schweckendiek, J., Vaitl, D., Wolf, O. T., & Stark, R. (2010). Cortisol enhances neural differentiation during fear acquisition and extinction in contingency aware young women. *Neurobiology of Learning and Memory, 94,* 392–401. doi:10.1016/j.nlm.2010.08.006

Tabbert, K., Merz, C. J., Klucken, T., Schweckendiek, J., Vaitl, D., Wolf, O. T., & Stark, R. (2011). Influence of contingency awareness on neural, electrodermal and evaluative responses during fear conditioning. *Social Cognitive and Affective Neuroscience, 6,* 495–506. doi:10.1093/scan/nsq070

Vansteenwegen, D., Francken, G., Vervliet, B., De Clercq, A., & Eelen, P. (2006). Resistance to extinction in evaluative conditioning. *Journal of Experimental Psychology: Animal Behavior Processes, 32,* 71–79. doi:10.1037/0097-7403.32.1.71

Walter, B., Blecker, C., Kirsch, P., Sammer, G., Schienle, A., Stark, R., & Vaitl, D. (2003, June). *MARINA: An easy to use tool for the creation of MAsks for Region of INterest Analyses*. Paper presented at the Ninth International Conference on Functional Mapping of the Human Brain, New York, NY.

Weike, A. I., Schupp, H. T., & Hamm, A. O. (2007). Fear acquisition requires awareness in trace but not delay conditioning. *Psychophysiology, 44,* 170–180. doi:10.1111/j.1469-8986.2006.00469.x

Whalen, P. J. (2007). The uncertainty of it all. *Trends in cognitive sciences, 11,* 499–500. doi:10.1016/j.tics.2007.08.016

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