Fear Conditioning in Panic Disorder: Enhanced Resistance to Extinction

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Enhanced conditionability has been proposed as a crucial factor in the etiology and maintenance of panic disorder (PD). To test this assumption, the authors of the current study examined the acquisition and extinction of conditioned responses to aversive stimuli in PD. Thirty-nine PD patients and 33 healthy control participants took part in a differential aversive conditioning experiment. A highly annoying but not painful electrical stimulus served as the unconditioned stimulus (US), and two neutral pictures were used as either the paired conditioned stimulus (CS+) or the unpaired conditioned stimulus (CS−). Results indicate that PD patients do not show larger conditioned responses during acquisition than control participants. However, in contrast to control participants, PD patients exhibited larger skin conductance responses to CS+ stimuli during extinction and maintained a more negative evaluation of them, as indicated by valence ratings obtained several times throughout the experiment. This suggests that PD patients show enhanced conditionability with respect to extinction.

Keywords: anxiety disorders, panic attacks, classical conditioning, electrodermal activity, emotion

Fear learning is considered to be a highly adaptive response to aversive events that ensures survival in changing and novel environments (LeDoux, 1995). One form of fear learning is fear conditioning (FC), which involves the pairing of a neutral (conditioned) stimulus (CS) with an aversive (unconditioned) stimulus (US). The CS becomes a signal for imminent US onset and thus provokes a conditioned response (CR). This serves to prepare the organism for the US and the associated unconditioned response (UR). Extinction refers to the decrement in response to subsequent CS-alone trials, which is now recognized as additional learning (that the CS has a different meaning) rather than erasure of the original CS–US association (Bouton, 2002).

Although FC is generally an adaptive process, it may turn into clinically relevant fear when reactivity to the CS persists in the absence of a CS–US contingency. While FC accounts of anxiety disorders (ADs) have been widely criticized since the 1970s (Rachman, 1990), more recently a resurgence of interest has occurred. FC is an integral part of modern learning accounts of ADs that incorporate some complexities of contemporary learning theory and provide a compelling explanation for the development and persistence of ADs (e.g., Mineka & Zinbarg, 1996, 2006). Lissek et al. (2005) recently conducted a meta-analysis of FC studies of ADs that shows a modest elevation in both acquisition of fear and conditioned responding during extinction among anxiety patients. Thus, it has been proposed that AD patients are characterized by enhanced conditionability and that this is one of the reasons why, upon exposure to fearsome incidents, only some individuals develop pathological fears, whereas others show an adaptive fear response (Orr et al., 2000).

It has further been suggested that ADs are associated with elevated stimulus generalization (Mineka & Zinbarg, 1996) or insufficient inhibition of the fear response in the presence of safety signals (Davis, Foa, & Grewitz, 2000). These proposals cannot be tested within the simple FC procedures that have been employed in most studies (a single CS is paired with a US) but require a differential FC procedure whereby one stimulus (the CS+) is paired with the US, and another stimulus (the CS−) is not. Recent studies in posttraumatic stress disorder (PTSD) found enhanced responding to the CS− (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Grillon & Morgan, 1999; Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 2000) and thus provide preliminary evidence for these proposals, at least with respect to PTSD.

Both traditional (Goldstein & Chambless, 1978) and contemporary (Bouton, Mineka, & Barlow, 2001) models of panic disorder (PD) assign a prominent role to conditioning mechanisms. In short, Bouton et al. (2001) have argued that panic attacks are strong conditioning episodes during which feelings of anxiety and panic become associated with exteroceptive (e.g., escalators) and interoceptive (e.g., dizziness) cues present during the attacks. Subsequent encountering of these cues can thus trigger feelings of anticipatory anxiety, which may serve to exacerbate or potentiate the next panic attack, or panic itself. If people have certain genetic, temperamental, or experiential vulnerabilities, they will show stronger conditioning during the initial and subsequent attacks, thereby explaining why only some people who experience panic attacks develop PD.

In accordance with these theoretical considerations, a number of laboratory analogue studies in healthy populations (Forsyth & Eifert, 1998; Godemann et al., 2001) have confirmed that condi-
tioning experiences may serve as a “minimodel” for PD (Marks & Tobena, 1990). Despite this interest in conditioning in PD and a considerable number of FC studies in other ADs, so far only one previous study has assessed whether PD patients differ from healthy controls in their CRs (Grillon, Ameli, Goddard, Woods, & Davis, 1994). No group differences were found during acquisition, and extinction learning was not assessed. Therefore, we conducted a differential FC study with PD patients and healthy controls to test the assumption that PD is characterized by abnormal FC during acquisition or extinction. Most important, we examined the hypothesis of enhanced conditionability, since this assumption can be directly derived from the conditioning model of PD. Additionally, we explored whether PD patients show larger CRs to the CS—

The main dependent variable was skin conductance response (SCR), since this is the most established outcome measure in human FC studies. We further assessed the subjective valence of the CSs, as it has recently been suggested that this is an important dimension in human FC (Hermans, Vansteeneuwegen, Crombez, Baeyens, & Eelen, 2002). CSs were two neutral inkblot pictures with which the participants had no prior experience, because we wished to study conditioning for de novo stimuli. An electrical aversive stimulus served as US.

### Method

**Participants**

Participants were referred by mental health institutions or answered advertisements in the local press. Exclusion criteria were as follows: age below 18 or above 65 years; medical history of conditions affecting the physiological systems under examination (e.g., myocardial infarction) or regular use of medications with strong autonomic side effects (e.g., sympathomimetic drugs); fulfillment of diagnostic criteria for schizophrenia, bipolar disorder, any other psychotic disorder, or alcohol or other substance abuse in the past year; current use of recreational drugs; and consumption of more than 20 units of alcohol per week. In addition, to be included in the analyses we required that participants had been aware of the contingency between CS and US in the conditioning task (e.g., Lovibond & Shanks, 2002).

We assessed diagnostic status using the Diagnostic Interview for Mental Disorders—Research Revision (Margraf, Schneider, Soe-

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>PD</th>
<th>Control</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, %</td>
<td>71.8</td>
<td>69.7</td>
<td>$\chi^2(1, N = 72) = 0.38, p = .84$</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>28.2</td>
<td>30.3</td>
<td></td>
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<tr>
<td>Education, low/middle/high, %</td>
<td>46.2/28.2/25.6</td>
<td>21.2/30.3/48.5</td>
<td>$\chi^2(2, N = 72) = 5.8, p = .06$</td>
</tr>
<tr>
<td>Age (years), M (SD)</td>
<td>40.3 (10.6)</td>
<td>42.6 (8.96)</td>
<td>$t(70) = 0.98, p = .33$</td>
</tr>
<tr>
<td>MI, M (SD)</td>
<td>2.37 (0.93)</td>
<td>1.24 (0.44)</td>
<td>$t(70) = 6.35, p &lt; .001$</td>
</tr>
<tr>
<td>ASI, M (SD)</td>
<td>32.6 (12.3)</td>
<td>7.12 (4.50)</td>
<td>$t(70) = 11.27, p &lt; .001$</td>
</tr>
<tr>
<td>STAI–Trait, M (SD)</td>
<td>48.9 (12.1)</td>
<td>36.1 (8.30)</td>
<td>$t(70) = 5.12, p &lt; .001$</td>
</tr>
<tr>
<td>BDI, M (SD)</td>
<td>51.0 (11.0)</td>
<td>33.2 (8.92)</td>
<td>$t(70) = 7.45, p &lt; .001$</td>
</tr>
<tr>
<td></td>
<td>14.7 (10.1)</td>
<td>4.58 (4.59)</td>
<td>$t(70) = 5.26, p &lt; .001$</td>
</tr>
</tbody>
</table>

Note. PD = panic disorder; MI = Mobility Inventory; ASI = Anxiety Sensitivity Index; STAI–State/Trait = Spielberger State–Trait Anxiety Inventory; BDI = Beck Depression Inventory.

1 Psychoactive drugs like benzodiazepines or antidepressants were allowed, but inclusion required that participants had been on a constant regimen for at least 2 weeks before testing to avoid possible side effects or withdrawal symptoms due to dose alternations.

2 Four participants with PD and 3 controls were excluded for this reason. An analysis including these participants showed the same pattern of results.

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rating dial was introduced. The rating dial was a linear slider on which a visual analog scale was affixed; the lower anchor label was −100 and the upper label was +100. Participants then gave a retrospective rating of US aversiveness (anchor labels: −100 = very slightly unpleasant to +100 = extremely unpleasant/painful; no anchor for 0).

The conditioning task commenced with the instructions that two pictures would be presented repeatedly, and one of them would occasionally be accompanied by the electric stimulus. Two colored Rorschach inkblot pictures (12 in. [30.48 cm] × 12 in. [30.48 cm]) were presented on a 19-in. (48.26-cm) monitor and served as CS+ and CS− (counterbalanced across participants). The conditioning task consisted of a habituation, an acquisition, and an extinction phase. In each phase, both the CS+ and CS− were presented six times. CS duration was 8 s, and the intertrial interval was 18 ± 2 s (determined at random). During acquisition, each CS+ was immediately followed at stimulus offset by a 500-ms US. Otherwise, all stimuli were presented alone.

During the conditioning procedure several online ratings of stimulus valence (−100 = pleasant to 100 = unpleasant) were collected. A previous study established that these ratings do not influence the SCR measurement (Bleichert, Michael, Williams, Purkis, & Wilhelm, in press). Participants rated stimulus valence in the middle and at the end of each conditioning phase. Following extinction, contingency awareness was assessed by presenting the CS+ and the CS− along with a control stimulus and asking which of the three pictures was paired with the US. Finally, all participants were orally debriefed, and the PD patients were given information about PD and treatment options.

Apparatus and Physiological Recordings

The experiment took place in a temperature-controlled, fully lit, sound-attenuated room electrically connected to an adjacent control room in which the experimental apparatus was located. An electrical stimulator (constant current unit, Biopac Systems, Inc., Goleta, CA) was used to deliver the US via Ag/AgCl electrodes at the right lower arm. Stimulus delivery and physiological data acquisition were controlled by two computers that used E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA) and AcqKnowledge software (Biopac Systems, Inc., Goleta, CA).

We recorded physiological channels and rating dial information using the Biopac MP150 system at a sample rate of 1000 Hz. We obtained skin conductance (SC) using 11-mm inner diameter Ag/AgCl electrodes filled with isotonic electrode paste. Electrodes were placed on the middle phalanx of the index and middle fingers of the left hand. Respiration and movement were measured to enable detection and exclusion of spurious SCRs.

Data Reduction and Statistical Analysis

**SCR.** An SCR was calculated by subtracting the average SC level (SCL) for the 2 s immediately before CS onset from the maximum SCL recorded between 4 s after CS onset and CS offset (4 s duration, second interval response). Conditioning effects were based on the second interval response, as it is relatively unaffected by nonassociative processes like dishabituation of the orienting response and is considered to represent the signal value of the CS (Lovibond, 1992). The UR was computed by subtracting the average SCL within 2 s preceding the US from the maximum increase in SCL during the 7.5 s following the US. SCRs below 0.025 μS were scored as zero. We normalized SCR data using the natural logarithm of 1 + SCR.

**Statistical analyses.** Separate analyses were conducted for each outcome measure and each conditioning phase. Responses to each stimulus type (CS+, CS−) were averaged for each experimental phase (6 SCRs, 2 ratings). For habituation, we tested differences in responses using analysis of variance with stimulus Type (CS+, CS−) as within-subjects factors and diagnostic Group (PD, control) as between-subjects factors. Since acquisition and extinction effects depend on the response level of the respective previous phase, the analyses of these phases contained an additional within-subjects factor, Time (Time 1, Time 2). Analyses of variance were followed by analyses of interaction contrasts between diagnostic Group and Time within each stimulus type. F values derived from contrasts were based on the full model error term (pooled over both stimulus types) to preserve adequate power. Effect sizes (ηp², in percentages) were calculated. If the sphericity assumption was not met, a Greenhouse–Geisser correction was computed, with nominal degree of freedom values being reported. An alpha level of .05 determined statistical significance.

**Results**

**Control Variables**

Groups did not differ on important control variables, such as SCL baseline, US current level, perceived aversiveness of US, strength of UR, sigh count, and skin temperature, ps > .42.4

**SCR**

Means for each experimental phase are presented in Figure 1. The statistical analysis for habituation found no main effects for the factors Type and Group or their interaction, thus demonstrating that there was no difference in responding to the CS+ and the CS− when the stimuli were presented alone, and no difference between the diagnostic groups. Regarding acquisition, a significant interaction between the factors Time and Type, F(1, 70) = 30.11, p < .01, ηp² = 30.1%, revealed that the acquisition phase yielded successful conditioning with participants differentiating between CS+ and CS− during acquisition but not during habituation. However, no main or interaction effects emerged that involved diagnostic group. With respect to the extinction phase, a significant interaction between Time and Type, F(1, 70) = 20.22, p < .01, ηp² = 22.4%, revealed a general extinction effect. In line with the assumption, this effect was modulated by diagnostic group. A close to significant interaction, F(1, 70) = 3.95, p = .051, ηp² = 5.3%, between Type, Time, and Group indicated that PD patients exhibited a reduced extinction response to the CS+ trials. Planned interaction contrasts between the groups for each stimulus type showed that the PD group had less reduction in its response to the CS+ than the control group, F(1, 140) = 4.98, p = .027, ηp² =

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3 The pattern of results was, however, the same when the first interval response or the maximum response during CS presentation was analyzed.  
4 Details available on request.
7.1%, whereas the groups did not differ regarding the CS−, $F(1, 140) = 0.05, p = .823, \eta^2_p = 0.1%$.

**Negative Valence Rating**

For habituation none of the main effects or the interaction effect was statistically significant. A significant interaction between Type and Time, $F(1, 70) = 53.89, p < .01, \eta^2_p = 43.5%$, showed that the acquisition phase resulted in successful conditioning, but acquisition was not influenced by diagnostic Group. There was a general extinction effect, as indicated by a significant interaction between Time and Type, $F(1, 70) = 10.22, p < .01, \eta^2_p = 12.7%$. A significant interaction, $F(1, 70) = 4.28, p = .042, \eta^2_p = 5.8%$, between Time, Type, and Group revealed that PD patients exhibited a reduced extinction response to the CS+ trials. Interaction contrasts between groups for each stimulus type showed that the PD group reduced its negative evaluation of the CS+ less strongly than the control group, $F(1, 140) = 5.5, p = .020, \eta^2_p = 7.9%$, but that the groups did not differ with respect to the CS−, $F(1, 140) = 0.28, p = .598, \eta^2_p = 0.4%$ (see Figure 1).

**Discussion**

In this study, we investigated whether PD patients differ from healthy control participants in their CRs to both paired and unpaired stimuli during an FC procedure. We examined several variables that might bias conditioning results but found no group difference on any of these control variables, so results can be interpreted straightforwardly. With respect to the reinforced stimulus (CS+), we found no difference between the groups at acquisition. However, the PD patients showed a reduced extinction response, which was evidenced both by the primary conditioning outcome measure SCR and by the negative valence ratings. Thus, the CS+ was a stronger danger signal and continued to be appraised more negatively in the PD group than in the control group. Groups did not differ regarding their CRs to the CS−.

The current finding of reduced extinction in a differential FC paradigm is in line with previous research that employed similar procedures in other ADs and mainly found group differences with respect to extinction (Hermann, Ziegler, Birbaumer, & Flor, 2002; Orr et al., 2000; Peri et al., 2000; Pitman & Orr, 1986). In contrast to a recent meta-analysis (Lissek et al., 2005), we found no differences during acquisition. However, most of the studies included in the meta-analysis used a single CS design that cannot control for nonassociative processes like sensitization. Sensitization, an increase of responding due to the introduction of the US, is confounded with conditioning effects in single CS designs during the acquisition phase. Moreover, given that fear acquisition is an important survival mechanism, whereas fear extinction is a flexible response to a changing environment, it is unsurprising that pathological fear seems to be more strongly characterized by deficits in extinction. Extinction is a fragile learning process that can be attenuated by the passage of time or shift of context (e.g., Bouton, 2002). Extinction learning is characterized by ambiguity, induced by the rivalry of the acquisition and the extinction contingency. Interestingly, research in cognitive biases has repeatedly shown that patient–control differences are most frequently observed under conditions of conflict or ambiguity (e.g., Michael, Ehlers, & Halligan, 2005).

The reduced-extinction result also agrees with the general assumption of the conditioning model of PD (Bouton et al., 2001), which asserts that conditioned anxiety partly explains why only a subgroup of people who have panic attacks develops persistent PD.

![Figure 1. Means and standard errors of skin conductance responses (SCRs, left panel) and negative valence ratings (right panel) in response to the paired conditioned stimulus (CS plus) and the unpaired conditioned stimulus (CS minus) across the habituation (Hab), acquisition (Acq), and extinction (Ext) phases for the panic disorder (PD) and control groups.](image-url)
The model of Bouton et al. (2001) is based on a complex interplay of different conditioning processes and cannot, for reasons of brevity, be discussed in detail. To give one example, Bouton et al. stated that several CSs (e.g., change in respiration, being alone in a closed space) need to be present before a CR (panic attack) is triggered. Assuming that PD patients show reduced extinction to all or most CSs, they would reach the critical summation value for experiencing a panic attack more easily, with each attack reinforcing the CS/US association, thereby enhancing the likelihood of further attacks.

Most formal classical conditioning models (e.g., Rescorla & Wagner, 1972) assume that inhibitory conditioning, which is based on a negative CS/US association, is responsible for the extinction response and for low responding to a CS. As we found no group differences regarding responses to the CS, one can assume that PD patients may not have a deficit in general inhibitory conditioning—or, expressed slightly differently, a deficit in learning safety cues (Davis et al., 2000). Elevated responding to the CS has repeatedly been found in PTSD (Blechert, Michael, Friends, & Wilhelm, in press; Grillon & Morgan, 1999; Peri et al., 2000). This interesting difference in conditioning findings between PD and PTSD may indicate that some learning processes are disorder specific and may reflect the clinical features of these disorders. While PTSD patients experience a global sense of threat (Ehlers & Clark, 2000) and an easy triggering of anxiety by cues that bear only a vague perceptual similarity to those that occurred during the trauma (Michael et al., 2005), PD patients typically fear only stimuli that are directly linked with episodes of panic and easily feel safe in the presence of safety signals.

Though this study may be regarded as initial evidence for the reduced extinction hypothesis in PD, the observed effect sizes were small (which is in line with findings of FC studies in other ADs). Besides the high variability in our measures, the relatively mild nature of the US and the nonspecificity of both the CS and the US for PD could be responsible for this. The use of disorder nonspecific stimuli allowed us to use de novo stimuli as CSs and a US that was comparable for both groups. A PD-specific US like CO₂-enriched air (e.g., Forsyth & EIFERT, 1998) would have been likely to produce stronger URs or CRs in the PD patients, but would have entailed the risk of provoking panic attacks. Further, the stimuli used in the current study are similar to those employed in other FC studies and thus allow a comparison between the CRs of patients with PD and patients with another AD (although testing different patient groups with exactly the same paradigm would provide the best basis for this). Yet, a conditioning procedure with disorder-specific stimuli would probably result in stronger group differences and would allow testing more specific hypotheses like abnormal interoceptive conditioning in PD (Bouton et al., 2001).

A limitation of the present study is its cross-sectional design, which can only provide circumstantial evidence within an etiological model. The conditioning model of PD (and other ADs) assumes that enhanced conditionability is a trait-like predisposition (i.e., the current differences between the groups should reflect a vulnerability factor for PD). Support for this assumption comes from studies showing that conditionability demonstrates considerable heritability (HETTMAA, ANNAS, NEALE, KENDLER, & Fredrikson, 2003) and that children qualifying for an AD diagnosis already show retarded FC extinction (LIBERMAN, LIPP, SPENCE, & MARCH, 2005). First evidence from longitudinal research supports the idea of FC as a vulnerability factor (Guthrie & BRYANT, 2006), and genetic association studies are starting to explore its genetic basis (Garpenstrand, Annas, Ekbom, Oreland, & Fredrikson, 2001). Clearly, research has to surpass the stage of cross-sectional designs in patient populations and move on to prospective designs, possibly in high-risk populations. On a more general note, given that ADs in general, and not only PD specifically, are characterized by reduced extinction, it might be best considered as a nonspecific biological marker for PD that has to interact with more specific biological processes (e.g., to easily experience symptoms of panic) to result in PD (Barlow, 2002).

Inhibitory conditioning is formally assessed in designs that use compound CS (e.g., Chan & Lovibond, 1996). Thus, responding to the CS in differential FC designs can only provide indirect evidence for inhibitory conditioning.

References