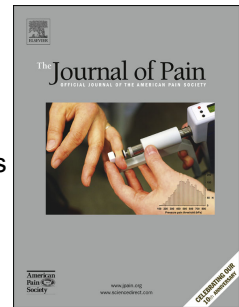


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# **Altered pain perception and fear-learning deficits in subjects with posttraumatic stress disorder**

Running head: Pain perception and fear learning deficits in PTSD

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**Abstract**

There is growing evidence that fear-learning abnormalities are involved in the development of posttraumatic stress disorder (PTSD) and chronic pain. More than 50% of PTSD patients suffer from chronic pain. This study aimed to examine the role of fear-learning deficits in the link between pain perception and PTSD. We included 19 subjects with PTSD and 21 age- and sex-matched healthy controls in a fear-conditioning experiment. The conditioned stimulus (CS) consisted of visual signs flashed upon a screen in front of each subject. The unconditioned stimulus was either a low or high temperature impulse delivered through a thermal contact thermode on the subjects hand. A designation of 'CS-' was assigned to CS always followed by non-painful low-temperature stimuli; a designation of 'CS+' was given to CS that were randomly followed by either a low or a more-painful high temperature. Skin conductance was used as a physiological marker of fear. In healthy controls, CS+ induced more fear than CS-, and a low-temperature stimulus induced less subjective pain after CS- than after CS+. PTSD subjects failed to demonstrate such adaptive conditioning. Fear ratings after CS presentation were significantly higher in the PTSD group than in controls. There were significant interaction effects between group and the type of CS on fear and pain ratings. Fear-learning deficits are a potentially-promising, specific psychopathological factor in altered pain perception associated with PTSD. Deficits in safety learning may increase fear and, consequently, pain sensations. These findings may contribute to elucidating the pathogenesis behind the highly-prevalent comorbidity that exists between PTSD and pain disorders, and to developing new treatments.

**Perspective**

This study provides new insights into the pathogenesis of chronic pain in patients with PTSD. The findings may help to develop new treatment strategies for this highly-prevalent comorbidity in PTSD.

**Key words**

Anxiety, fear, fear-learning, chronic pain, PTSD

## INTRODUCTION

Excessive fear and anxiety, hypervigilance and other symptoms of hyperarousal are among the core characteristics of posttraumatic stress disorder (PTSD). There is growing evidence that fear-learning abnormalities are involved in the development of these symptoms. In the fear - learning paradigm, a previously neutral stimulus (later the conditioned stimulus = CS+) is presented together with an aversive stimulus (unconditioned stimulus = US), while the other neutral stimulus (CS-) is never paired with the US. Hence, the CS+ acquired the same aversive qualities as the negative event, such that subjects learned to fear it. Initial findings of increased fear, excitation and hyper-conditionability in PTSD patients (29) have not yet been confirmed in subsequent studies. In contrast, meta-analyses and recent qualitative reviews suggest that deficits in fear learning — which result in associative learning deficits, sustained contextual anxiety, and fear over-generalization — contribute to PTSD (22-24). Such deficits lead to a person's impaired ability to differentiate between specific environmental cues that indicate danger from cues not associated with danger, and from non-specific contextual cues. This unawareness of predictive danger cues leads to a more general link between the aversive event and the environment in which the event is experienced, including whatever safety cues are present. We believe that this generalization of fear may play a key role in the strong association that exists between PTSD and chronic pain.

As many as 50-75% of PTSD patients suffer from chronic pain and up to 37% of pain patients have PTSD (33). Twin studies point to non-inheritable factors that contribute to this association (19). The mutual maintenance model postulates that chronic pain and PTSD are mutually-maintaining conditions (21, 35). Psychological mechanisms underlying this process include exacerbated pain perception due to elevated anxiety (9). For instance, the development of chronic pain in patients with PTSD after severe accidents has been associated more strongly with PTSD symptoms than other accident-related variables, like the type of accident, or like the Injury Severity Score or Glasgow Coma Scale score immediately post accident (14, 15). Others have proposed shared vulnerability underlying the comorbidity of PTSD and pain (3), like the abnormal processing of threat cues.

In a previous study, we examined associations between anxiety and pain in subjects with either fibromyalgia syndrome or rheumatoid arthritis, versus controls (13), using a fear-conditioning experiment that involved an alternatively painful or non-painful unconditioned stimulus, and visual conditioned stimuli flashed on a screen in front of the patient immediately prior to the unconditioned

stimulus. In our experiment, in both healthy controls and rheumatoid arthritis subjects, a visual stimulus sometimes followed by pain (CS+) induced more fear than one never followed by pain (CS-); in addition, pain ratings were higher following CS+ than after CS- , suggesting that fear itself increased pain perception. In addition, all of the healthy controls and 86% of the rheumatoid arthritis subjects were aware of the association between danger cues and both fear and increased pain. Subjects with fibromyalgia failed to exhibit such adaptive conditioning.

In the currently-presented study, we used the identical experiment in 19 patients with PTSD and 21 healthy controls to examine the influence of fear learning on the link between pain perception and PTSD. Prior work has shown that fear-conditioning experiments can be used to elicit hyperalgesia in healthy subjects, something related to the level of fear evoked by the experiment (1, 30). Based upon the learning model for PTSD (22), we hypothesized that PTSD would be associated with fear learning deficits in our “fear of pain” conditioning experiment. The inability to correctly learn predictive cues in the environment leaves someone in a state of chronic anxiety, because they are unable to identify periods of safety. From this perspective, contingency learning deficits might conceivably contribute to hyperalgesia and related chronic pain conditions in such individuals.

## MATERIALS AND METHODS

### Participants

The study sample consisted of 40 subjects, ranging in age from 18 to 65 years old, among whom there were 19 with PTSD and 21 age- and sex-matched healthy controls. The PTSD subjects were recruited through the outpatient clinical services within the Department of Psychiatry and Psychotherapy at Zurich University Hospital, while all of our healthy controls responded to advertisements in local newspapers. Exclusion criteria for both comparison groups included pregnancy, any major physical illness, psychosis, suicidal ideation or suicide attempts within the previous 8 weeks, substance abuse within the past year, and a lifetime history of substance dependence (to reduce potential confounding by learning and memory deficits caused by acute and chronic substance use). Table 1 summarizes the demographic and clinical characteristics in the two groups. In the PTSD group, 8 of the 19 patients were being treated with at least one psychotropic drug (mainly antidepressants, see Table 1). Subjects provided written informed consent after receiving a full explanation of the study purpose, procedures, and risks. The study was approved by the local ethics committee of the Canton of Zurich.

### Diagnostic and psychometric assessments

Psychiatric diagnoses were established using the Mini International Neuropsychiatric Interview (MINI) (36), which is a short structured diagnostic interview for 17 Axis-I diagnoses, as defined in the Diagnostic and Statistical Manual of Mental Disorders, version IV, and the International Classification of Diseases -10<sup>th</sup> Revision. Additionally, for the diagnosis of PTSD and the assessment of PTSD symptoms, the Clinician-Administered PTSD Scale (CAPS, validated German version) was administered (5, 32). This instrument allows for quantification of the frequency and intensity of each of the 17 PTSD symptoms in the DSM-IV (2). Prior to the experiment, clinical characteristics were assessed with the State-Trait Anxiety Inventory (20) and the Beck Depression Inventory (4). The patients average level of ongoing chronic pain, which was defined as the average pain that subjects had suffered over the two weeks prior to the measurement, was assessed with a 100mm visual analog scale (VAS) that ranged from 0 (no pain) to 10 (worst possible pain).

### Pain stimuli

Thermal stimuli were applied to the thenar aspect of the nondominant hand with a 27-mm-diameter thermal contact thermode (CHEPS, Medoc Ltd., Ramat Yishai, Israel). The CHEPS thermode has a heating rate of 70°C/s and a cooling rate of 40°C/s. The same heating and cooling rate was applied throughout the experiment. Pain threshold estimates were based on five thermal stimuli that slowly increased in temperature (1°C/s) until either (1) research subjects stopped the heating process by pressing a button, or (2) a maximum-allowed temperature of 50°C was reached. As a second step, temperature that was rated as moderate pain (approximately 50 mm on the VAS) was assessed individually for each subject and used as that subject's low-temperature unconditioned stimulus ( $US_{low}$ ). The temperature that was established for  $US_{low}$  then was increased by 2.5°C to obtain that individual subjects high-temperature stimulus ( $US_{high}$ ). This increase in temperature has been found to clearly discriminate between  $US_{high}$  and all other painful stimulations (30).  $US_{high}$  was only presented during the experiment itself. There was a 30 minute interval between the pain threshold estimate and commencement of the conditioning experiment.

### Conditioning Experiment Protocol

For this study, the same protocol was used as in a prior study by our group that investigated

fear learning in patients with fibromyalgia or rheumatoid arthritis versus controls (13). Prior to the experiment, study participants were instructed that they would see shapes on a screen in front of them and feel heat bursts on their hand, but we did not provide any information about the relationship between these two stimuli. Thermal stimulation and the recording of physiological activity (skin conductance) were controlled using a BIOPAC MP150 System (Biopac Systems, Inc., Goleta, CA). Visual stimuli (simple black squares and triangles on a white background) were presented on a monitor located one meter in front of the subjects. Subjects were exposed to thermal stimuli of different temperatures for a duration of six seconds each. During the experiment, the perceived pain intensity, evoked by the thermal stimuli, and fear levels, evoked by the visual stimulus, were assessed with two linear VAS scales, both 100-mm in length. one ranging from 0 (no pain) to 100 (worst possible pain), and the other from 0 (no fear) to 100 (maximal fear) (34). Subjects were told that their pain ratings should relate explicitly to their perceived sensory intensity and not the unpleasantness of the pain. The scale was presented to them for a period of five seconds after the thermal stimulus was terminated.

The experimental paradigm (Figure 1) used delay-conditioning contingencies. The whole paradigm consisted of 20 trials, 10 for each of two conditions (CS-, CS+). One visual signal (CS-) was always followed by a low-temperature stimulus ( $US_{low}$ ). This signal ultimately evoked low-level fear about the impending thermal stimulus. The other visual signal ( $CS+_{low}$ ) was followed, in a pseudorandomized way, with  $US_{low}$  administered in half of the trials. In the other half of the trials, the same visual signal ( $CS+_{high}$ ) was followed by a higher-temperature, and therefore more painful stimulus ( $US_{high}$ ). This signal ( $CS+_{high}$ ) was used to elicit higher-level fear about impending pain. The delay between the visual signal and the onset of thermal stimulation was randomized to range from 8 to 15 seconds, so as to render the visual-thermal stimulus contingency learning more efficient. The interval between trials was 30 seconds.

### **Physiological assessment of fear**

Skin conductance, as a measure of the electrical conductance of the skin, is a sensitive psychophysiological index of changes in autonomic sympathetic arousal related to emotional and cognitive states. In this study, it was used as an indicator of fear conditioning and, in particular, contingency learning (7). Skin conductance data were recorded using a BIOPAC MP150 System (Biopac Systems, Inc., Goleta, CA). For this, electrodes were placed on the thenar and hypothenar

eminence of the left palmar surface using Ag/AgCl electrodes filled with isotonic electrolyte gel. Skin conductance was 0.05-10Hz band-pass filtered online and 1 Hz low-pass filtered offline.

The software program *Autonomic Nervous System Laboratory 2.5* (ANSLAB; Wilhelm, F. H. & Peyk, P., 2005; available at the SPR Software Repository: <http://www.sprweb.org>) was used to filter the raw data offline and to extract mean scores for event and baseline intervals for each subject. Raw data were visually inspected to identify artifacts which were then manually excluded. Skin conductance data were inspected for technical artifacts. Mean skin conductance values were extracted for the one-second interval prior to the onset of the anticipation cue (baseline) and for each one second interval within the 8-15 second anticipation period.

### Contingency learning

Contingency awareness was assessed immediately following postacquisition using a short-recognition interview, as suggested by both Dawson and Reardon, and Lovibond et al (8, 25). The first two questions asked each subject to identify (1) which of the two visual cues (CS+ or CS-) had previously been associated with the more painful/ fearful stimulation, and (2) their level of certainty about this (completely certain, fairly certain, don't know). The next two questions asked participants to rate how often the CS+ and CS- were followed by a high versus low-temperature thermal stimulus (never, most of the time, always). If the subjects reported that they were *completely* or *fairly certain* that the CS+ was *mostly* paired with the high-temperature stimulus, and that the CS- was *always* accompanied by the low-temperature stimulus, they were considered aware of the existing contingency.

### Data analysis

We used SPSS version 22.0 for Windows (IBM Corporation, Armonk, NY, USA) to analyze the self-reported experiences of pain intensity and fear, and the skin conductance data. Linear mixed model analyses were computed with diagnostic group differences for the pain and fear ratings, as well as the skin responses, tested with full factorial models, with group (healthy controls vs. PTSD) and signal (type of conditioned/visual stimulus) or group and temperature (intensity of thermal stimulus) as fixed factors. We used interaction effects to evaluate for inter-group differences. The model-predicted estimated marginal means of the measures in each group allowed us to compare the types of signal and temperature. Models were optimized by selecting a covariance structure for repeated measures that produced the lowest Akaike's Information Criterion. For fear and pain ratings, a first-order ante-dependence covariance structure was appropriate. For skin conductance, a first-order factor analytic



with heterogenous diagonal offsets covariance structure was appropriate. A restricted maximum likelihood model estimate was used. The threshold for statistical significance was set at  $p \leq 0.05$ . In linear mixed models,  $R^2$  as a measure of effect size can be calculated (28). For each linear mixed model analysis, we report  $R^2_{LMM(m)}$ , which indicates the variance explained by the fixed factors (short:  $R^2$ ) as measures of model fit.

To evaluate the effects of contingency learning (i.e., predictability of the impending stimulus) on pain perception, we included only CS- and CS+<sub>low</sub> trials (i.e., CS followed by a low-temperature stimulus). The reason for excluding CS+<sub>high</sub> trials was that pain and fear were assessed retrospectively; consequently, they could bias the comparison of CS- and CS+ ratings and thereby influence one of the main questions of this study, which was whether the same pain stimulus (US<sub>low</sub>) would be rated differently depending on the preceding conditioned stimulus (CS-, CS+). CS+<sub>high</sub> trials were included in all other mixed model analyses. This was because the effects of temperature on pain ratings and skin conduction responses could be tested only when the high-temperature stimuli were included; and because skin responses directly following the conditioned stimulus were presumed to be unbiased by the subsequently-applied heat impulses. To reduce possible habituation effects, we consistently excluded the first trial from data analysis.

## RESULTS

### Effects of the conditioned stimulus (CS) on fear and pain experience

Figure 2 and Table 2 display the ratings of subjective pain and fear perception as assessed on a 100mm VAS during the conditioning experiment (means and standard deviations of self-reported fear and pain after CS-/low-temperature stimulation, CS+/low-temperature stimulation, and CS+/high-temperature stimulation). Mixed model analyses were used to examine the effects of the group and the type of conditioned stimulus (CS- vs. CS+<sub>low</sub>) on fear and pain ratings. Fear ratings were significantly higher in the PTSD group (main effect of group,  $F=12.1$ ,  $df=1$ ,  $38.0$ ,  $p=0.001$ ), but pain ratings were not significantly different between the two subject groups ( $F=2.4$ ,  $df=1$ ,  $37.9$ ,  $p=0.132$ ). In general, fear ratings (main effect of type of CS,  $F=32.8$ ,  $df=1$ ,  $162.6$ ,  $p<0.001$ ) as well as pain ratings ( $F=27.9$ ,  $df=1$ ,  $166.3$ ,  $p<0.001$ ) were higher after CS+<sub>low</sub> than CS-. Most important and consistent with our *a priori* hypotheses were significant interaction effects between group and the type of CS on both ratings (fear:  $F=13.2$ ,  $df=1$ ,  $162.6$ ,  $p < 0.001$ ,  $R^2=22.3\%$ ; pain:  $F=5.4$ ,  $df=1$ ,  $166.3$ ,  $p=0.021$ ,  $R^2=6.3\%$ ), indicating that the two subject groups exhibited significantly different patterns of fear and pain

responses to conditioned stimulus presentation. Pairwise comparisons of the estimated marginal means revealed that fear and pain experiences differed significantly between CS- and CS<sub>low</sub> in controls (fear:  $F=46.1$ ,  $df=1$ ,  $162.6$ ,  $p<0.001$ ; pain:  $F=30.5$ ,  $df=1$ ,  $166.3$ ,  $p<0.001$ ). On the other hand, in the PTSD group, the difference between CS- and CS<sub>low</sub> was significant for pain ( $F=4.2$ ,  $df=1$ ,  $166.3$ ,  $p=0.043$ ), but not for fear ( $F=2.1$ ,  $df=1$ ,  $162.6$ ,  $p=0.148$ ). Thus, low-temperature stimulation was experienced as less painful when it was predicted by a safety cue (CS-), especially among healthy controls. PTSD subjects failed to correctly differentiate between the CS+ and CS-, in terms of fear. Directly comparing fear and pain ratings related to CS- and CS<sub>low</sub>, PTSD subjects reported significantly higher fear after CS- and CS<sub>low</sub> than healthy controls (CS-:  $F=16.3$ ,  $df=1$ ,  $38.2$ ,  $p<0.001$ ; CS<sub>low</sub>:  $F=8.0$ ,  $df=1$ ,  $41.5$ ,  $p=0.007$ ), but there was no significant difference in pain ratings.

In the PTSD group, eight of the 19 patients were being treated with psychotropic drugs (mainly antidepressants). However, there was no interaction between pain/fear responses and medication.

### Effects of the unconditioned stimulus (US) on the pain experience

The mean low temperature for the thermal stimulus was  $46.5^{\circ}\text{C}$  ( $SD=0.8$ ) in the PTSD group versus  $46.7^{\circ}\text{C}$  ( $SD=0.8$ ) in controls ( $t=-0.65$ ,  $df=38$ ,  $p=0.52$ ). There was a significant main effect of the type of thermal stimulus (low versus high temperature) on self-reported pain ( $F=492.4$ ,  $df=1$ ,  $167.1$ ,  $p<0.001$ ). There was also a significant interaction effect between subject group and the type of stimulus in this mixed model analysis ( $F=5.7$ ,  $df=1$ ,  $167.1$ ,  $p=0.018$ ,  $R^2=25.6\%$ ). Taken together, these results suggest that, in both groups, high-temperature stimulation induced significantly greater levels of pain than low-temperature stimulation. However, in controls, the difference between low and high temperature stimulation was greater higher than it was in PTSD patients. For both low and high temperatures, there was no significant difference in pain ratings between healthy controls and those with PTSD.

### Skin conductance during conditioned stimuli (CS)

Figure 4 demonstrates skin conduction changes that occurred during each conditioned stimulus. Three seconds after the CS+ presentation began, skin conductance began to rise, stabilizing to some degree between 5 and 8 seconds. To calculate skin conduction changes in each trial, we subtracted mean skin conductance readings recorded between 5 and 8 seconds from the corresponding mean from between 0 and 3 seconds. Table 2 shows skin conduction changes for each

type of conditioned stimuli (CS- versus CS+). On mixed model analysis, we detected no significant main effect of group on skin conduction change ( $F=1.22$ ,  $df=1$ ,  $36.0$ ,  $p=0.277$ ), while the main effect of CS type was significant ( $F=5.54$ ,  $df=1$ ,  $277.4$ ,  $p=0.019$ ). However, in the absence of a significant interaction effect between group and the type of CS ( $F=0.64$ ,  $df=1$ ,  $277.4$ ,  $p=0.425$ ,  $R^2=0.8\%$ ), we failed to identify any different pattern of responses to CS presentation between the two subject groups.

### **Pain stimuli and awareness of the conditioned versus unconditioned stimulus relationship**

At the end of the conditioning experiment, only 11 of the 19 (58%) PTSD subjects reported that they were either *completely* or *fairly certain* that the CS<sub>high</sub> signal was paired with the higher temperature stimulus (US<sub>high</sub>), and were thus designated aware (see Figure 3 for the learning curves). In healthy controls, 15 of 21 (71%) became aware of the meaning behind the conditioned signals. This difference in the rate of awareness (71% versus 58%) was not significant (Fisher's exact test,  $p=0.51$ ). There was no association between awareness and PTSD severity (total score of CAPS) among those with PTSD ( $t=-0.74$ ,  $df=17$ ,  $p=0.47$ ).

### **DISCUSSION**

In this study, we found that fear conditioning that was generated using a painful unconditioned stimulus was impaired in patients with PTSD. In other words, with respect to their level of fear, they were unable to differentiate between a visual stimulus that was 'safe' (always followed by a low-temperature, non-painful stimulus) and one that was 'unsafe' (half the time followed by a level of heat that caused significant pain). Rather than this abnormality resulting from differences in their perception of the heat stimulus, it was believed to be likely caused by their impaired capacity to inhibit fear.

Fear learning theories provide a theoretical framework for investigating reactions to threats. They assume that fear conditioning is based on the information value of cues that predict danger. Fear and anxiety responses are thought to be based on one's level of expectancy that some aversive event will follow (26). Deficits in fear learning contribute to perceived unpredictability, a crucial contributor to contextual fear, sustained anxiety and hypervigilance (12). As we have shown, such deficits also contribute to increased pain perception (13).

The causes of perceived unpredictability have not yet been fully elucidated. It has been demonstrated that subjects with anxious personalities need more time to differentiate between a non-safe and safe conditioned stimulus than healthy controls do (6). This slower learning rate has been

found at various levels, including cognitive, behavioral and physiological (skin conductance). Fear-learning deficits have been identified, biased towards an increased general expectancy of aversive events. In explicit cue fear-conditioning experiments, impaired learning of safety cues has been shown to increase one's perception of unpredictability, physiological correlates of anxiety, and behavioral avoidance (10). Such a learning deficit could be a vulnerability factor that is shared by PTSD and comorbid pain.

Fear-learning deficits have been implicated in PTSD for well over a decade (11, 24). These deficits have been categorized into both associative and non-associative forms. Through associative learning, neutral stimuli like objects, places and people become associated with a traumatic event. Consequently, these neutral stimuli have the capacity to trigger and maintain fear and anxiety long after the traumatic event is over. In PTSD, this type of learning is thought to contribute to the symptoms of re-experiencing, avoidance, and hypervigilance. Abnormal non-associative fear learning causes excessive unspecific anxious responses to novel, intense and threat-related stimuli in the environment. This type of learning might contribute to hyperarousal symptoms in PTSD.

In our study, we confirmed several aspects of the PTSD fear-learning deficit theory. The generally higher fear levels reported by PTSD subjects may reflect a general increase in anxiety reactions resulting from non-associative fear-learning deficits. The lack of differentiation between the level of fear experienced after a safe versus unsafe conditioned stimulus is the strongest argument for a deficit in fear-learning. Several mechanisms might underlie our findings, including deficient fear inhibition, overgeneralization, and increased contextual conditioning. The skin conduction data provide preliminary evidence of fear-learning deficits at a physiological level. Qualitatively, we demonstrated that there was an initial period of recognition between safe and unsafe stimuli. However, as the trials progressed, this degree of recognition became increasingly impaired. Our data are consistent with a growing body of research suggesting 1) that learning deficits are a consequence of the trauma, and 2) that these learning deficits are well-positioned to account for several core symptoms of PTSD, such as re-experiencing, avoidance and hyper-arousal (24). Nevertheless, learning models appear ill-suited to explain the the full clinical picture of PTSD, including symptoms related to guilt, shame, dissociation, and anger.

We also identified indications that fear-learning deficits may be directly related to altered pain perception in PTSD patients. This altered perception was not due to the generally abnormal pain threshold observed in PTSD, which is consistent with previous work (27). Awareness of associations

between conditioned and unconditioned stimuli potentially influenced the results of our study, suggesting that non-conscious, physiological fear-related processes play important roles in PTSD. Fear-learning helps an individual to predict pain, and the resultant fear of pain might, in turn, cause them to find ways to avoid or reduce causes of such pain. Fear-learning deficits tend to generalize fear, leading to increased anxiety and, hence, increased pain sensitivity (31). Fear-learning deficits, therefore, could exacerbate pain problems in individuals with PTSD, because they lead to an over-association of cues to pain and prevent safety-learning in the context of pain. For example, frequent unexplained somatic symptoms — like chest pain, nausea and headaches — may be incorrectly associated with past physical trauma. As a result, harmless bodily symptoms may be reinforced and attached to catastrophic thoughts. This can generate a vicious cycle wherein an increased focus on painful symptoms increases trauma-related and general health anxiety, which then enhances the intensity of somatic symptoms. Regarding the mutual maintenance theory of chronic pain in PTSD (21, 35), fear-learning deficits may contribute to persistent pain behaviors beyond the healing of an injury, because the interpretation of recovery as a safe context is impaired and, as such, coping strategies and health behaviors are insufficiently reinforced. In particular, ambiguous signals from health professionals, usually an important source of reinforcement, may be misinterpreted as negative or even catastrophic cues.

The strengths of our study include the relatively close matching between the two groups in gender, age, and group size. PTSD patients were significantly less educated than controls; however, there was no relationship between level of education and level of awareness in the PTSD group (Fisher's exact test,  $p=0.61$ ). Our conditioning experiment — which involved both a painful and non-painful (low-temperature) unconditioned stimulus after a safe conditioned stimulus — had been used previously by Ploghaus et al. (30) to study the relationship between fear and pain perception. Using the same experiment in our own previous study, we demonstrated potentially pathogenic associations between fear and pain in individuals with fibromyalgia (13). Given the strong association between PTSD and pain, this experiment, which utilized a painful unconditioned stimulus that allowed us to assess pain perception, seemed to qualify for the investigation of the pathophysiology of PTSD.

Despite its strengths, the current study has several methodological limitations. As in all fear-conditioning studies in humans, the intensity of the unconditioned stimulus was relatively minor and not comparable to the magnitude of aversive events that cause PTSD. Since we did not apply a conditional discrimination paradigm with true safety signals (no pairing with the unconditioned

stimulus) and reinforced stimuli as developed by Jovanovic et al. (18), the relevance of our findings is limited with respect to impaired safety signal theories for PTSD (16). However, such a paradigm would have been inappropriate to test our *a priori* question regarding whether or not elevated fear increases pain sensation. Further, the PTSD group was much more depressed and less educated than our healthy controls, and many in the group were taking antidepressants. These factors might have affected learning. In addition, our samples were rather small, particularly the sample of individuals with PTSD and comorbid chronic pain (just 6 of 19); therefore, we were unable to perform any meaningful comparison between PTSD patients with and without comorbid chronic pain. The relatively low sample size might also explain the non-significant difference in conditioned-unconditioned stimuli congruency awareness between the two groups. However, previous research found such awareness to be unrelated to one's ability to inhibit fear (17). For all these reasons, the results of our study need to be replicated in larger samples.

In summary, deficits learning fear in response to a painful unconditioned stimulus might hold promise as a specific, albeit still largely unstudied, psychopathological marker of pain in patients with PTSD. Consistent with our previous study involving patients with fibromyalgia, the non-conscious ability to differentiate between a cue predicting some risk of painful thermal stimulation and a 'safe' cue was impaired in subjects with PTSD. In the context of the safe cue, this impairment led to relatively increased fear and pain. Our findings might contribute to a better understanding of the pathogenesis of the chronic pain that commonly coexists with PTSD, as well as to the development of novel behavioral and/or pharmacological therapeutic approaches targeting fear learning and fear inhibition.

### Author Contributions

All authors contributed significantly to this manuscript.

- Conception and design: Josef Jenewein, Jeannine Erni, Hanspeter Moergeli, Christoph Mueller-Pfeiffer, Christian Grillon, Ulrich Schnyder, Gregor Hasler
- Data acquisition: Jeannine Erni, Josef Jenewein, Hanspeter Moergeli, Lutz Wittmann, Katayun Hassanpour, Christian Grillon, Gregor Hasler
- Analysis and interpretation of data: Josef Jenewein, Jeannine Erni, Hanspeter Moergeli, Annina Seiler, Christian Grillon, Ulrich Schnyder, Gregor Hasler
- Drafting the article or revising it critically for important intellectual content: Josef Jenewein, Jeannine Erni, Hanspeter Moergeli, Lutz Wittmann, Katayun Hassanpour, Christoph Mueller-Pfeiffer, Annina Seiler, Christian Grillon, Ulrich Schnyder, Gregor Hasler
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All authors discussed the results and commented on the manuscript.

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# TABLES

**Table 1:** Demographic and clinical characteristics of subjects with PTSD (n=19)

and healthy controls (n=21)

Variable	PTSD		Healthy controls		p <sup>a</sup>
	Mean	SD	Mean	SD	
Age	39.05	11.57	41.29	12.62	0.57
<i>State-Trait Anxiety Inventory</i>					
State	57.11	9.42	35.90	8.77	<.001
Trait	58.84	10.77	34.52	8.12	<.001
<i>Beck Depression Inventory</i>	25.53	10.36	4.38	3.32	<.001
	N	%	N	%	
Gender (female) %		47.4		47.6	n.s.
Education					<.05
Not completed	7	36.8	1	4.8	
Apprenticeship	6	31.6	10	38.1	
College/university	6	31.6	10	57.1	
<i>Occupational invalidity<sup>b</sup></i>					<.05
No	12	63.2	20	95.2	
Yes (complete or partial)	7	36.8	1	4.8	
<i>Any psychiatric diagnosis<sup>c</sup></i>	18	94.7	0	0.0	<.001
Major depressive disorder	4	21.1	0	0.0	
Any anxiety disorder	0	0.0	0	0.0	
Panic disorder	3	15.8	0	0.0	
Agoraphobia	0	0.0	0	0.0	
PTSD	18	94.7	0	0.0	
Pain disorder	6	31.6	0	0.0	
<i>Medication</i>					n.s.
Antidepressants	8	42.1	0	0.0	
Anxiolytics	0	0.0	0	0.0	
Opioids	1	5.3	0	0.0	

<sup>a</sup> Chi-square test, Fisher's exact test when appropriate

<sup>b</sup> Compensation by the insurance

<sup>c</sup> Multiple diagnoses possible

**Table 2:** Pain, fear and skin conductance change in PTSD patients (n=19) and healthy controls (n=21)

Variable	PTSD		Healthy controls		Statistics	
	Mean	SD	Mean	SD	F; df	p
<i>Fear</i>						
CS-	46.4	29.0	19.7	11.9	17.6; 1, 38.2	< 0.001
CS+ <sub>low</sub>	49.8	27.5	31.1	18.4	8.9; 1, 41.6	0.005
CS+ <sub>high</sub>	55.6	28.0	38.4	21.4	6.2; 1, 45.3	0.016
<i>Pain</i>						
CS-	43.1	26.1	30.9	18.2	1.9; 1, 28.9	0.182
CS+ <sub>low</sub>	45.1	24.7	36.7	19.4	1.1; 1, 31.6	0.297
CS+ <sub>high</sub>	70.6	22.8	67.7	23.7	0.4; 1, 38.8	0.513
<i>SC change (μS)</i>						
CS-	-0.074	0.257	-0.048	0.246	0.6; 1, 45.5	0.449
CS+	-0.001	0.277	0.044	0.375	1.7; 1, 45.8	0.194

Note: SC=skin conductance, SD=standard deviation, CS=conditioned stimulus

## Highlights

- Fear learning deficits in the link between chronic pain and posttraumatic stress disorder (PTSD) is proposed.
- Subjects with PTSD and healthy controls were included in a fear learning experiment.
- PTSD subjects with co-morbid pain did not show safety learning.
- Deficits in safety learning may increase fear and, consequently, pain sensation.