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Invited review

Pain and post traumatic stress disorder – Review of clinical and experimental evidence

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ABSTRACT

Pain and Post Traumatic Stress Disorder (PTSD) are highly comorbid conditions. Patients with chronic pain have higher rates of PTSD. Likewise, patients with PTSD are often diagnosed with numerous chronic pain conditions. Despite the high pain-PTSD comorbidity, the neurobehavioral mechanisms underlying this phenomenon are incompletely understood and only recently researchers have started investigating it using experimental models. In this article, we systematically review the substantial clinical evidence on the co-occurrence of pain and PTSD, and the limited experimental evidence of pain processing in this disorder. We provide a detailed overview of the psychophysical and brain imaging experiments that compared somatosensory and pain processing in PTSD and non-PTSD populations.

Based on the presented evidence, an extensive body of literature substantiates the clinical coexistence of pain and PTSD in patients but the limited experimental data show inconsistent results highlighting the need for well-controlled future studies.

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1. Introduction

Post-traumatic stress disorder (PTSD) is a debilitating illness characterized by symptoms of re-experiencing, avoidance, emotional numbing, and hyperarousal resulting from an emotionally traumatic event with actual or perceived threat (American Psychiatric Association, 2000). It is the 5th most common psychiatric disease in the USA with a life time incidence around 7% (Kessler et al., 1995b, 2005), but it can range from 20%–50% in high risk groups including victims of motor vehicle accidents (Coffey et al., 2006; Delahanty et al., 1997; Kuch et al., 1996), sexual assault (Campbell et al., 2008; Chivers-Wilson, 2006) and persons with military combat exposure (Kessler et al., 1995a; O'Toole et al., 1998; Reeves et al., 2005). PTSD profoundly impacts the individual's life and health in general and has been associated with a number of adverse health outcomes (McFarlane, 2010) including pain (Asmundson and Katz, 2009). In this article, we will briefly review the clinical evidence suggesting high co-morbidity between chronic pain and PTSD with a more detailed focus on the psychophysical and neuroimaging studies evaluating experimental pain processing in PTSD.

1.1. Clinical evidence

Several excellent reviews have discussed the comorbidity of PTSD and chronic pain and proposed theoretical models (Asmundson and Katz, 2009; Asmundson et al., 2002; Kulich et al., 2000; Otis et al., 2003; Sharp and Harvey, 2001). We will summarize the clinical evidence in a systematic fashion.

2. Methods of literature search and selection

Searches were performed in online databases PubMed and Medline by two authors independently. The search was limited to human studies in English using the following search terms: "PTSD and chronic pain" resulting in 200 articles. After review of the abstracts and references, additional searches were done using "PTSD and Headache", "PTSD and Fibromyalgia", "PTSD and bodily pain" and "PTSD and musculoskeletal pain". Original articles reporting on one of the following were included: 1) Evaluation of PTSD in chronic pain syndromes or effects of PTSD on pain, 2) Evaluation of pain in PTSD populations or effects of pain on PTSD or 3) co-morbidity of PTSD and pain in the population studied. These search methods yielded 94 articles published between 1986 and 2010.

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3. Results

3.1. PTSD in chronic pain population and effects of PTSD on pain

A number of reports of increased prevalence of PTSD in patients with chronic pain has been published over the last 25 years (Ang et al., 2006; Asmundson et al., 2000; Benedikt and Kolb, 1986; Fishbain et al., 1986; Large, 1986; McWilliams et al., 2003; Muse, 1986; Roy-Byrne et al., 2004; Sharp, 2004; Van Loey et al., 2003b). Publications evaluating PTSD in specific clinical pain situations report on subjects with fibromyalgia (Amir et al., 1997; Arnold et al., 2006; Bradley, 2005; Buskila and Cohen, 2007; Cohen et al., 2002; Culclasure and Enzenauer, 1993; Goldenberg and Sandhu, 2002; Hudson et al., 1992; Raphael et al., 2004, 2006; Schur et al., 2007; Sherman et al., 2000; Thieme et al., 2004), headache (Chibnall and Duckro, 1994; de Leeuw et al., 2005b; Schur et al., 2007), migraine (Ifergane et al., 2009; Peterlin et al., 2008, 2010; Peterlin, 2009), orofacial pain syndromes (Aghabeigi et al., 1992; Burris et al., 2009; De Leeuw et al., 2005; de Leeuw et al., 2005a; Schur et al., 2007), accident related pain (Asmundson et al., 1998; Duckworth and Iezzi, 2005; Geisser et al., 1996; Harris et al., 2007; Hickling et al., 1992; Roth et al., 2008), back pain (Demyttenaere et al., 2007; Harris et al., 2007; Polatin et al., 1993; Schur et al., 2007), pelvic pain (Heim et al., 1998; Meltzer-Brody et al., 2007), mastalgia (Johnson et al., 2006) and complex regional pain syndrome (Lebovits et al., 1990). Furthermore, studies found increased PTSD symptoms to be related to increased pain levels, pain disability and overall pain (Beckham et al., 1997; Geisser et al., 1996). PTSD has been identified as a risk factor for chronic pain (Jenewein et al., 2009a; Miró et al., 2008), for the transition from acute to chronic pain (Kongsted et al., 2008; Shaw et al., 2010) and for pain disability (Katz et al., 2009) as well as mediator for pain in abuse victims (Wuest et al., 2009). Studies of PTSD symptom clusters provide evidence that the interrelationship among PTSD symptom clusters is different in patients with pain compared to pain free individuals (Bonin et al., 2000; Pagé et al., 2009) and identified hyperarousal as a pain mediator (Liedl et al., 2009).

3.2. Chronic pain in PTSD and effects of pain on PTSD

Pain is highly prevalent in the PTSD population (Amital et al., 2006; Avdibegovic et al., 2010; Jamil et al., 2005; Jenewein et al., 2009a; Schreiber and Galai-Gat, 1993; Seng et al., 2005; Seng et al., 2006). Pain has been found to be among the most reported physical symptom in individuals with PTSD (McFarlane et al., 1994), especially in the veteran population (Avdibegovic et al., 2010; Beckham et al., 1997; Dobie et al., 2004; Engel et al., 2000; Jakupcak et al., 2006; Shipherd et al., 2007; Uhac et al., 2006; White and Faustman, 1989). Some studies further identified pain as a predictor for the development of PTSD (Glynn et al., 2007; Norman et al., 2008; Van Loey et al., 2003a).

3.3. Comorbid PTSD and pain

A number of studies that had PTSD and pain as outcomes reported increased co-morbidity (Afari et al., 2008, 2009; Arguelles et al., 2006; Bryant et al., 1999; Glynn et al., 2007; Jenewein et al., 2009b; Kline et al., 2010; Leserman et al., 2005; Lew et al., 2009; Liebschutz et al., 2007; McWilliams et al., 2003, 2008; O'Toole et al., 1998; Sareen et al., 2005, 2007; Schur et al., 2007; Sullivan et al., 2009; Villano et al., 2007; Wuest et al., 2008). In a sample of motor vehicle accident survivors, Clapp et al found a synergistic relationship of pain and PTSD on different domains of quality of life (Clapp et al., 2008). Several studies underscore the importance of recognizing the co-prevalence of PTSD and pain for developing treatment strategies (Clapp et al., 2009; Helmer et al., 2009; Liedl and Knaevelsrud, 2008; Smeeding et al., 2010).

3.4. Experimental pain assessment in PTSD – detection thresholds, pain thresholds and response to suprathreshold stimuli

What will follow is a systematic review of the literature describing somatosensory detection thresholds, pain thresholds, as well as reported pain experience to suprathreshold stimuli in PTSD subjects, summarized in Table 1. Somatosensory detection thresholds tested include the following modalities: warm sensation, cold sensation and light touch. Thermal stimuli were delivered using a neurosensory analyzer (TSA I or II, Medoc LTD., Israel). A neurosensory analyzer is a precise, computer-controlled device capable of generating and documenting response to highly repeatable thermal stimuli. Briefly, a thermode is placed on the patient's skin to heat or cool the skin. The patients respond to the temperature stimuli by pushing a button, and the sensory threshold is recorded. Touch (mechanical) thresholds are obtained using standardized Von Frey hairs delivering increasing force when pushed onto the skin. The pain threshold is defined as "the least experience of pain which a subject can recognize" (Merskey and Bogduk, 1994). The methods used in these studies include the "method of limits" (Gescheider, 1997), where the stimulus starts out at a sub-threshold intensity and then intensifies and the "method of constant stimuli" (Gescheider, 1997), where subjects rate stimuli at random intensities as detectable or not detectable. For a suprathreshold pain experience, the intensity (sensory component) and unpleasantness (affective component) can be rated using scales including the visual analog scale (VAS) or a numeric rating scale (NRS).

4. Methods of literature search and selection

Using the method described earlier searches were performed for: 1) "PTSD" and "sensory thresholds", 2) "PTSD" and "quantitative sensory testing" 3) "PTSD" and "experimental pain" and 4) "PTSD" and "pain stimulus" as search terms. Additionally, the search included review of the reference sections of appropriate publications. These search methods yielded 25 articles published between 1987 and 2010 that were reviewed for the following criteria: 1) reports of original findings and 2) direct comparison of a primary PTSD group to non-PTSD controls. Filtering the results yielded 8 articles. Two more studies were excluded, since the sample (van der Kolk et al., 1989) overlapped with another publication (Pitman et al., 1990) and in Geuze et al. (2006) the authors did not report any of the pain related data.

5. Results

5.1. Pitman et al. (1990)

5.1.1. Group characteristics

The study compared a PTSD group (8 male subjects, mean age 40.9 years) to a combat control group (8 male subjects, mean age 39.8 years). Subjects on psychotropic medications were asked to stop them for 2 weeks prior to the experiment.

General exclusion criteria were contraindication to stopping medication, potentially interfering medical conditions (not further defined), diagnosis of organic mental, schizophrenic, paranoid, bipolar manic or other psychotic disorder and current substance dependence.

5.1.2. Testing protocol

Eight painful stimuli (5 s) at temperatures between 45 °C and 51 °C were applied to the forearm. These stimuli were first

Table 1
Experimental pain in PTSD.

Reference	Pitman et al., 1990	Orr et al., 2000	Geuze et al., 2007	Schmahl et al., 2008	Defrin et al., 2008	Kraus et al., 2009a,b
Study design						
Total N	16	33	24	76	81	30
Groups	PTSD (8) Combat Control (8)	PTSD (15) Healthy Control (18)	PTSD (12) Combat Control (12)	PTSD (16) BPD (16) BN (20) Healthy Control (24)	PTSD (32) Anxiety (29) Control (20)	PTSD (10) Combat Control (10) Healthy Control (10)
Sex	M	M/F	M	F	M/F	M
Diagnosis criteria	DSM-IV	DSM-IV	DSM-IV	DSM-IV	DSM-IV	DSM-IV
Diagnosis tools	SCID	SCID CAPS	CAPS (>50) SCID	SCID	SCID PTSD Inventory	SCID CAPS
Medication	NO (2 weeks)	NO	NO (4 weeks)	YES[b]	YES	NO
Pain co-morbidities	NO	NO	NO	NO	YES	NO
Psychiatric co-morbidities	YES	YES	YES PTSD NO Control	YES	YES	YES PTSD NO Controls
Traumatic Event	Combat	Mixed[a]	Combat	Mixed[c]	Mixed[d]	Combat
Study methods						
Stimulus Modality	Thermal heat (45/47/49/51 °C) 2 × for 5 s Before and after stress	Electrical stimulus "Highly annoying but not painful"	Thermal heat 1) fixed: 43 °C 2) individual: to produce 40/100 pain on NRS	Thermal heat and cold to threshold Before and after stress	Thermal and mechanical thresholds Supra-threshold heat	1) Thermal thresholds 2) temperature- pain response curve for:(40/42/44/46/48 °C)
Stimulus Site	Ventral forearm	2nd and 3rd finger on dominant hand	Dorsal right hand	Both hands	Both hands	Both hands
Study findings						
Sensory Thresholds	NO	PTSD < Control	NO	NO	PTSD > Anxiety/Control	Warm/cold no difference
Pain Threshold	NO	NO	NO	BPD > PTSD = BL/Control	PTSD > Anxiety/Control	Hot/cold pain PTSD = Combat Control > Control Hot pain calculated: PTSD > Combat Control > Control
Pain rating	PTSD reduced pain rating after stress	NO	PTSD < Control	NO	PTSD > Anxiety/Control	PTSD < Combat Control/Control
Conclusion	PTSD: Shows stress induced analgesia	PTSD: Increased sensitivity to electrical stimulation	PTSD: Reduced pain sensitivity	PTSD: Normal pain sensitivity and no stress induced analgesia	PTSD: reduced sensitivity at threshold, increased pain above threshold	PTSD: reduced pain sensitivity

[a] Combat (15), war related nursing (8), physical assault (2), firefighting or emergent medical technician experiences (7), motor vehicle accident (1).
[b] No pain medication.
[c] PTSD: sexual abuse (12), war-related (1), natural disaster (1), interpersonal trauma (2).
[d] PTSD: combat (21), terror victims (11).

delivered after a neutral video and repeated after a stressful video. To further evaluate the involvement of the opioid system, this was done under both control (normal saline) and naloxone conditions.

5.1.3. Findings

Under saline injection, the mean pain intensity rating, as measured by the visual analog scale (VAS) (averaged across all 4 stimuli) was 22.6 ± 6.5 for the PTSD group and 27.0 ± 4.8 for the non-PTSD group after the neutral video, which decreased to 16.0 ± 5.6 in the PTSD group and increased to 33.0 ± 6.8 in the non-PTSD group after the combat video. The authors concluded that this 6.6 point drop on the VAS for the PTSD group represented a 30% pain reduction under stressful conditions. Under naloxone condition, the mean VAS pain intensity ratings after the neutral video were 19.7 ± 4.3 in the PTSD group and 28.8 ± 4.3 in the non-PTSD group. After the combat video stressor, the ratings were 20.8 ± 5.4 for the PTSD group and 29.9 ± 5.8 in the non-PTSD group leading the authors to conclude the observed pain intensity reduction after the stressor was opioid mediated since they did not observe a significant change after injecting the opioid antagonist naloxone. The authors report the pain reduction after the stressful video was only observed for 6 of the 8 PTSD subjects and also for one of the non-PTSD subjects.

5.2. Orr et al. (2000)

5.2.1. Group characteristics

The PTSD group included veterans, firefighters, assault and accident victims. PTSD diagnosis was made using the Structured Clinical Interview (SCID) and the Clinician Administered PTSD Symptoms Scale (CAPS). Both groups (PTSD: 10 male, 5 female; non-PTSD:14 male, 4 female) included subject with other psychiatric co-morbidities, but all were free from drugs and psychoactive medications.

5.2.2. Testing protocol

Each individual received a mild electric shock via 2 electrodes attached to the second and third finger of the dominant hand. The electrical stimulation was increased until the stimulus was 'highly annoying but nor painful'. The stimulation ranged from 0.2 mA to 4 mA.

5.2.3. Findings

The mean stimulus intensity at threshold was 1.9 ± 0.7 in the PTSD group and 2.6 ± 1.1 in the non-PTSD group indicating a significantly ($p = 0.03$) lower stimulation threshold in the PTSD subjects.

5.3. Geuze et al. (2007)

5.3.1. Group characteristics

The authors compared PTSD subjects (12 male, mean age 34.5 ± 6.02 years) to non-PTSD combat exposed veterans (12, male, mean age 33.26 ± 4.24 years). General exclusion criteria were claustrophobia (the study protocol included an fMRI session), abnormal laboratory values and neurological dysfunction. A history of psychiatric illness was an exclusion criterion for the control group only.

5.3.2. Testing protocol

The authors used both a subjective pain stimulus (stimulus intensity varies between subjects to produce the same subjective pain intensity rating) and an objective pain stimulus (pain stimulus intensity is constant and pain intensity ratings vary among individuals). For the subjective stimulus, heat pain stimuli were applied to the dorsal hand for 30 s with a one minute interval between stimuli. The following temperatures were tested 4 times for each individual: 40 °C, 42 °C, 44 °C, 46 °C, 48 °C and pain intensity ratings on a 0–100 numerical rating scale (NRS) were recorded. The pain ratings were plotted against the stimulus temperatures, and the individual temperature corresponding to a 40/100 pain rating was calculated as the pain stimulus for the procedure. The objective pain stimulus was set at 43 °C.

5.3.3. Findings

For the subjective pain stimulus paradigm, the temperature was significantly higher in the PTSD group and the objective pain stimulus was rated as significantly less painful providing evidence for reduced pain sensitivity in PTSD.

5.4. Schmahl et al. (2008)

5.4.1. Group characteristics

The authors evaluated heat and cold pain thresholds in the following 4 groups: A) PTSD (16 female, mean age 32 ± 8.95 years). B) Borderline Personality Disorder subjects (16 female, mean age 29 ± 7.05 years). C) Bulimia nervosa subjects (20 female, mean age 22.15 ± 4.83). D) A healthy control group (24 female, mean age 28.33 ± 8.87).

General exclusion criteria for this study were pregnancy, schizophrenia, or bipolar −I disorder, acute depressive episode (except for PTSD group where it was allowed), substance dependence or abuse during the last 6 months before study enrollment, organic brain disease, severe medical or neurological illness and medication with analgesic properties including tricyclic antidepressants.

5.4.2. Testing protocol

Testing was performed on the dorsal surface of both hands. In addition, the authors were interested in the effects of a mental stressor (Paced Auditory Serial Addition Task) on the thresholds in all groups. For the subjects who showed increased inner tension following the stressor (increase of inner tension rating of >2 on a 11 point Likert scale), repeated thermal thresholds were taken.

5.4.3. Findings

There were no significant differences for either heat or cold pain thresholds in the PTSD group compared to healthy controls at baseline. Comparing pre-stress to post-stress results, the authors did not observe any stress induced change in heat or cold pain threshold within PTSD or between the groups.

5.5. Defrin et al. (2008)

5.5.1. Group characteristics

3 groups were compared: A) PTSD (32 total, 27 male, 5 female, mean age 44 ± 10 years), B) An anxiety disorder group (29 total, 6 male, 21 female, mean age 39 ± 11 years), C) A healthy control group (20 total, 15 males, 5 females, mean age 36 ± 9 years). General exclusion criteria were any disease causing potential neural damage like diabetes, systemic illness, skin lesions, communication difficulties and current depressive or psychotic state.

5.5.2. Testing protocol thresholds

Detection threshold testing was performed on the dorsal surface of both hands for warm sensation, cold sensation, light touch and heat pain.

5.5.3. Testing protocol pain stimuli

The authors used two paradigms. First, they applied heat pain stimuli in 1 °C increments above each individual heat pain threshold. The mean VAS pain intensity ratings in response to 6 increasingly hot stimuli were plotted against the temperature increase above threshold. The second paradigm was application of a train of 4 mechanical pain stimuli using a number 6.65 Von Frey filament and consecutive pain intensity rating of the first and 4th stimulus.

5.5.4. Findings thresholds

All thresholds were significantly higher in the PTSD group compared to both anxiety and healthy controls.

5.5.5. Findings pain stimuli

The authors showed a significant higher VAS pain score for the PTSD group for all above threshold pain ratings in comparison to the anxiety group ($p < 0.01$) and healthy controls ($p < 0.001$). For the mechanical stimuli, the VAS ratings for both first and 4th stimulus trended higher for the PTSD group against anxiety and healthy controls but did not reach significance. The authors conclude a unique sensory profile of hyposensitivity to pain accompanied by hyper-reactivity to suprathreshold pain stimuli in PTSD.

5.6. Kraus et al. (2009b)

5.6.1. Group characteristics

This study compared 3 groups: A) A PTSD group (10 male subjects, mean age 33.2 ± 4.8 years), B) Combat Control group (10 male subjects, mean age 33.6 ± 4.4 years), C) Healthy volunteers (10 male subjects, mean age 32.7 ± 3.8 years). General exclusion criteria for this study were any psychotropic medication, neurological dysfunction, chronic pain and history of alcohol or drug dependence in the last 6 months.

5.6.2. Testing protocol thresholds

Detection threshold testing was performed on the dorsal surface of both hands.

5.6.3. Testing protocol pain stimuli

The study used the same testing paradigm of 4 rounds of heat stimuli at 5 different intensities ranging from 40 °C to 48 °C for 30 s each as described in Geuze et al. (2007).

5.6.4. Findings thresholds

The authors report no significant difference for warm and cold detection. Both cold and heat pain threshold were significantly higher in the combat control and PTSD group compared to the healthy volunteers, with no significant difference between PTSD and combat controls using the method of limits. Since only 3 of the

nine PTSD subjects reached their heat or cold pain threshold at maximum stimulation, the authors applied a battery of prolonged (30 s) heat stimuli 4 times to each subject and asked the subjects to rate them as painful or not painful (method of constant stimuli). The pooled ratings were plotted as 'percent rated as painful' against the temperatures applied. Based on that function, the temperature where 50% of the ratings were painful was defined as heat pain thresholds. Using this technique, they report significantly higher heat pain thresholds for PTSD compared to combat controls and healthy volunteers.

5.6.5. Findings pain stimuli

The authors analyzed the data by categorizing the individual pain intensity ratings as either 'not painful' (NRS = 0) or 'painful (NSR > 0). They found a significantly lower incidence of painful ratings for combined stimuli in the PTSD group compared to combat controls ($p < 0.01$) and healthy controls ($p < 0.01$). The incidence of painful ratings for each individual stimulus temperature was significantly lower for PTSD compared to healthy controls for all temperatures ($p < 0.05$) and all but one ($p < 0.07$) in comparison to the combat controls suggesting reduced pain sensitivity in PTSD.

5.7. Experimental pain processing in PTSD – brain imaging studies

Studies on the neural correlates of pain processing in PTSD are only starting to emerge. Below we will present exploratory meta-analysis of functional magnetic resonance imaging (fMRI) studies for PTSD and experimental pain.

6. Literature search and selection

Articles were identified with an online citation indexing service (Medline) using "pain" and "PTSD" and "brain" as search terms. This search yielded 85 articles published online between 1990 and 2010. These search results were filtered to include only functional neuroimaging studies that published activation results as 3D coordinates (x, y, z) in stereotactic space that compared directly PTSD and non-PTSD groups. Filtering the results yielded 5 articles (Geuze et al., 2006, 2007; Kraus et al., 2009a; Mickleborough et al., 2011; Strigo et al., 2010a). The article by Geuze et al. (2006) was excluded since the sample overlapped with Geuze et al. (2007). The remaining 4 articles were then entered into the program *Ginger Ale* (www.brainmap.org). Subsequently, coordinates were transformed to Talairach space for articles that had published coordinates in the Montreal Neurological Institute (MNI) space according to the nonlinear Brett transformation (Brett, 1999) included in the *BrainMap* environment, to allow analysis relative to a single template.

7. Brief description of the selected studies

Please see Table 2 for details. Geuze et al. (2007) concluded that compared to combat controls, PTSD is associated with reduced pain (subjectively) and altered pain processing in brain areas associated with affective (increased insula, increased hippocampus, decreased amygdala) and cognitive (decreased ventrolateral PFC) pain processing. The authors proposed a stress-induced analgesia model as the possible underlying mechanism.

Kraus et al. (2009a) compared pain processing between female individuals with borderline personality disorder (BPD) with and without co-morbid PTSD. The authors observed no between-group differences in subjective pain experience, yet greater right amygdala deactivation in PTSD group during painful stimulation. The authors concluded that co-occurrence of PTSD alters neural processes related to pain in patients with BPD and suggested that reduced pain sensitivity that is often observed in BPD and was reported in PTSD may be associated with decreased amygdala activation.

Strigo et al. (2010b) compared pain processing between female individuals with PTSD related to intimate partner violence (IPV) and nontraumatized healthy comparison women. The authors concluded that PTSD is associated with altered subjective and neural response to pain. Specifically, they showed that PTSD subjects have increased initial brain response (insula, prefrontal cortex) and subsequent subjective attenuation to brief temperature stimulation. This abnormal subjective attenuation to brief temperature stimulation was accompanied by initial increase followed by a decrease in right anterior insula activation and was related to avoidance symptoms. Stress-induced analgesia was proposed as one of the possible underlying mechanisms.

Mickleborough et al. (2011) compared pain processing between individuals who developed PTSD and who did not develop PTSD following exposure to various traumatic events after subjecting these individuals to either traumatic or neutral scripts. The authors concluded that reduced subjective pain experience and abnormally increased pain-related brain activation within head of caudate in PTSD individuals are related to trauma, i.e., these differences are seeing following trauma provocation and are not present at baseline. A stress-induced analgesia model was proposed as the underlying mechanism.

7.1. Meta-analysis: activation likelihood estimation (ALE)

ALE maps were created as described by Turkeltaub et al. (2002) using a full-width half-maximum (FWHM) of 10 mm. Statistical significance was determined using a permutation test of randomly generated foci. No assumptions were made concerning the distribution or spatial separation of these random foci. Five thousand permutations were computed using the same FWHM value and the same number of foci used in computing the ALE values. The test was corrected for multiple comparisons using the false discovery rate (FDR) method (Genovese et al., 2006; Laird et al., 2005). All data processing was carried out using a Java version of Ginger Ale (www.brainmap.org). Whole-brain maps of the ALE values were imported into MRIcron (www.sph.sc.edu/comd/rorden/mricron/) for data visualization and overlaid onto an anatomical template generated by spatially normalizing the International Consortium for Brain Mapping (ICBM) template to Talairach space (Kochunov et al., 2002).

7.2. Meta-analysis results

Table 3 and Fig. 1 summarize the activation loci that showed significant differences in PTSD versus non-PTSD group. The biggest cluster that showed increased activation in PTSD vs. non-PTSD was in the right anterior insular cortex, while biggest cluster that showed decreased activation in PTSD vs. non-PTSD was in the right amygdala.

8. Discussion

The fact that patients with PTSD have a substantially higher rate of pain conditions and pain related problems is well documented by a large body of publications spanning over more than 25 years. Several theoretical models have been proposed including shared vulnerability (Asmundson et al., 2002), where individual factors predispose certain subjects to develop both chronic pain and PTSD when exposed to certain life events and and mutual maintenance (Sharp and Harvey, 2001), where components of PTSD maintain and exacerbate symptoms of pain and vice versa. Studies using experimental pain models in the PTSD population to probe for abnormalities in the somatosensory and cerebral system involving

Table 2
Experimental Pain in PTSD.

Reference	Orr et al., 2000	Kraus et al., 2009a,b	Strigo et al., 2010a,b	Mickleborough et al., 2011
Study design				
Total N	33	29	38	43
Groups	PTSD (15) Non-PTSD (18)	PTSD/BPD (12) BPD (17)	PTSD (23) Non-PTSD (15)	PTSD (17) Non-PTSD (26)
Sex	M/F	F	F	MF
Diagnosis criteria	DSM-IV	DSM-IV	DSM-IV	DSM-IV
Diagnosis tools	SCID, CAPS			
Medication	NO	NO	NO	YES[e]
Pain co-morbidities	NO	NO	NO	NO
Other psychiatric co-morbidities	YES[a]	YES	YES	YES
Trauma Control group	NO	NO	NO	YES
Healthy Control Group	NO	NO	YES	NO
Traumatic Event	Mixed[b]	Not reported	IPV[d]	Mixed[f]
Study methods				
Stimulus Modality	Electrical stimulus "Highly annoying but not painful"	Thermal Heat (43/~46 °C)[c] 30 sec	Thermal heat (40.5/45.5/47.5 °C) 5 sec	Thermal Heat (~42/~46 °C) 25 sec following traumatic/neutral scripts
Stimulus Site	2nd and 3rd finger on dominant hand	Right hand	Left forearm	Leg
Study findings				
Pain Thresholds	NO	YES	NO	NO
Sensory Thresholds		NO	NO	YES
Other	NO	1.5 T	3 T	4 T

[a] 1/12 PTSD subjects met current diagnosis for panic disorder.
[b] Combat (15), war related nursing (8), physical assault (2), firefighting or emergent medical technician experiences (7), motor vehicle accident (1).
[c] Only reported on individually adjusted temperatures (~46 °C); 1/12 PTSD subjects met current diagnosis for panic disorder.
[d] Intimate partner violence (IPV).
[e] 3/17 PTSD subjects were medicated.
[f] Assault (5), childhood abuse (3), military trauma (2), workplace trauma (2), motor vehicle collision (1), other (4) and the distribution of the type of trauma in PTSD was different from that in the non-PTSD group (chi = 16.3; $p = 0.006$).

pain processing are just emerging. As presented in this review, the evidence is inconclusive. The findings for somatosensory detection thresholds include normal (Schmahl et al., 2010) and increased (Defrin et al., 2008; Kraus et al., 2009b) thresholds in the PTSD group. For pain thresholds, some results show an increased pain threshold (Geuze et al., 2007; Kraus et al., 2009b) indicating reduced pain sensitivity, others report a reduced pain threshold (Orr and Roth, 2000) suggesting increased pain sensitivity, while still others report no difference for the PTSD group (Schmahl et al., 2010). Studies using painful stimuli found reduced pain response in the PTSD group (Geuze et al., 2007; Kraus et al., 2009b) while another study reports an increased pain response (Defrin et al., 2008).

Several studies suggest involvement of a stress induced analgesia mechanism in PTSD subjects leading to the reduced response to an acute experimental stimulus (Geuze et al., 2006; Kraus et al., 2009b; Pitman et al., 1990; Strigo et al., 2010b), while another study failed to show stress induced changes in the PTSD group (Schmahl et al., 2010). Reasons for the observed inconsistencies of these studies probably include the many differences in test group characteristics and testing protocols. Important confounding factors include gender differences, comorbid pain and psychiatric diagnosis and medications. But the inconclusive findings from these early studies could also reflect the complexity that underlies the connection of pain and PTSD. Genetic and social environment forming individual susceptibility, intensity and nature of the underlying trauma as well as duration and severity of PTSD and its different clusters might all affect pain perception differently.

Finally, experimental pain models producing prolonged and deep pain are better models of clinical pain states than superficial heat application (Sessle, 1990), with the latter usually also failing to induce autonomic responses (Chapman et al., 1985) which might play an important role in subjects with PTSD. In conclusion for studies concerning detection thresholds and pain stimuli, there is clearly the need for further studies ideally following more unified protocols and also utilizing different pain stimulus modalities to help clarifying the underlying pathophysiology connecting pain and PTSD.

Likewise, no consistent brain imaging data are available on the experimental pain studies in PTSD. Only four studies were entered into the meta-analysis. These preliminary results should provide the groundwork for the future imaging studies on the experimental pain processing in PTSD. Even though, the imaging studies discussed were very different, all of them found altered subjective pain experience and brain response to experimental pain stimuli in individuals with PTSD. Importantly, none of the studies included subjects with comorbid chronic pain conditions, suggesting that abnormal response to experimental pain is already present in

Table 3
Experimental Pain — PTSD vs. non-PTSD Meta-analysis foci.

Brain Region	Volume (mm^3)	*X*	*Y*	*Z*
PTSD > non-PTSD				
Right Insula	80	33	16	2
Right Cuneus (BA 18)	64	3	−77	15
Left Cerebellum (Anterior Lobe)	56	−12	−66	−10
Right Inferior Occipital Gyrus (BA 19)	56	40	−70	0
Right Caudate Head	56	4	16	0
Left Posterior Cingulate (BA 31)	56	−22	−62	18
Left Insula	48	−31	−16	10
PTSD < non-PTSD				
Right Amygdala	528	23	−7	−14
Left Middle Temporal Gyrus (BA 20)	80	−52	−38	−3
Right Cuneus (BA 17)	80	5	−80	10
Right Cerebellum (Posterior Lobe)	56	4	−42	−34
	56	6	−80	−22

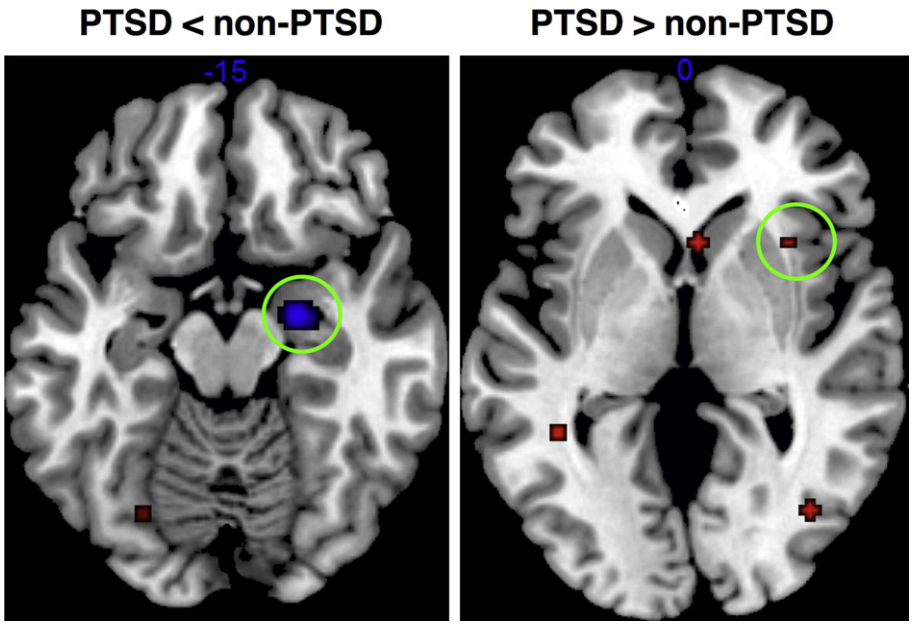

Fig. 1. Experimental pain – PTSD vs. non-PTSD meta-analysis foci. Clusters where PTSD > non-PTSD are shown in red and PTSD < non-PTSD are shown in blue (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

individuals with PTSD even before they develop comorbid chronic pain. A stress-induced analgesia model was proposed as a potential underlying mechanism in all of the above studies. Furthermore, this proposed mechanism was consistent across studies that differed on sample gender, sample trauma experience, and when compared with both traumatized and non-traumatized controls.

8.1. Amygdala

This deactivation cluster was powered by Geuze et al. (2007) and Kraus et al. (2009a) PTSD is an aversive reaction to a life-threatening, emotionally salient event (Breslau and Kessler, 2001). The majority of those who experience such an event have a substantial stress response (North et al., 1999) that is characterized by activation in the physiological and neuroendocrine systems (Bremner et al., 1997, 2003a,b; Geracioti et al., 2006; Liberzon et al., 1999). Such stress responses are associated with hyperactivation in the amygdala (Etkin and Wager, 2007). However, abnormal amygdala activation in functional imaging paradigms in PTSD has not been as consistent as that in other anxiety groups (Etkin and Wager, 2007). In fact, while a number of studies have shown amygdala hyperactivation in individuals with combat-related PTSD versus healthy controls with no history of PTSD or combat exposure (Bryant et al., 2008; Bryant, 2005; Protopopescu et al., 2005; Williams et al., 2006), fewer studies have shown amygdala hyperactivation in individuals with combat-related PTSD versus individuals with combat exposure but not PTSD (Shin et al., 2001; Yang et al., 2004). Other studies have shown amygdala hyperactivation in individuals with combat exposure but not PTSD relative to individuals with no history of combat exposure or PTSD (Chen, 2009). Taken together, these findings suggest that the experience of emotional trauma in and of itself may relate to significant differences in the functioning of emotional processing circuits.

The role of amygdala in nociception is multifaceted. Prior research implicated amygdala descending endogenous pain control (Bourgeais et al., 2001; Fields, 2000; Gauriau and Bernard, 2002; Heinricher and McGaraughty, 1999; Helmstetter, 1992; Manning and Mayer, 1995a,b; Manning et al., 2003; Manning, 1998; Millan, 1999; Rhudy and Meagher, 2000). More recent evidence suggests that the amygdala can both facilitate and block nociceptive behaviors (Neugebauer, 2007). Specifically, amygdala-insula connections are thought to mediate the amygdala's pro-nociceptive role (Jasmin et al., 2003). In human imaging studies, amygdala is not considered a part of the "pain matrix" (Tracey and Mantyh, 2007), thus amygdala activation to painful stimulation is not often investigated or reported. Amygdala activation in imaging studies is highly dependent on task (Strigo et al., 2010b), temporal resolution of the data collection and selected analysis methods. Even though there is a general lack of investigation regarding the amygdala in pain, we have identified 23 studies that show differential activation in the amygdala, 18 showing an increase and 6 showing a decrease (see Table 4). Taken in conjunction this would suggest that negative emotions (fear, stress) that produce stress-induced analgesia initially activates amygdala and subsequently reduces pain behaviors by activating amygdala-linked endogenous pain-inhibitory pathways. However chronic negative emotions (anxiety disorders and depression) can increase pain behaviors by activating amygdala-linked pain-facilitating pathways. As avoidance and dissociation are hallmark symptoms of PTSD during stress, deactivation of saliency related brain regions, such as the amygdala, might be a driving factor behind a secondary decrease in amygdala activation that temporally coincides with an analgesic response. Therefore, amygdala deactivation in PTSD as observed in Geuze et al. (2007) during experimental pain may be a dynamic process that relates to state-avoidance and dissociation.

8.2. Anterior insula

This activation cluster was powered by Strigo et al. (2010a,b), although this region was also observed in Geuze et al. (2007) The role of the anterior insula cortex in pain and anxiety cannot be overstated. Increased anterior insula activation is commonly observed in anxiety and PTSD (Etkin and Wager, 2007; Hopper et al., 2007; Simmons et al., 2008; Simon et al., 2006) and practically in all brain imaging studies of experimental and clinical pain (Craig, 2002, 2009; Schweinhardt et al., 2006). Neuroanatomical

Table 4
Amygdala response during brain imaging of experimental pain.

Article	Painful stimulus/method	Amygdala
(Hsieh et al., 1996)	Ethanol injection/PET	⇑[a]
(Derbyshire et al., 1997)	Laser stimulation/PET	⇓
(Becerra et al., 1999)	Heat stimulation (thermode)/fMRI	⇓
(Becerra et al., 2001)	Heat stimulation (thermode) /fMRI	⇓ ⇑[b]
(Schneider et al., 2001)	Vascular Pain/fMRI	⇑
(Bornhovd et al., 2002)	Laser stimulation/fMRI	⇑
(Bingel et al., 2002)	Laser stimulation/fMRI	⇑
(Petrovic et al., 2004)	Cold pressor/PET	⇓
(Lu et al., 2004)	GFD/fMRI	⇑
(Mohr et al., 2005)	Heat stimulation (thermode)/fMRI	⇑
(Kulkarni et al., 2005)	Laser stimulation/PET	⇑
(Seymour et al., 2005)	Heat stimulation (thermode)/fMRI	⇑
(Bingel et al., 2006)	Laser stimulation/fMRI	⇑
(Simon et al., 2006)	Facial expressions of pain /fMRI	⇑
(Choi et al., 2006)	Anticipation of heat (water bath) /fMRI	⇑
(Berman et al., 2008)	CRD /fMRI	⇓
(Van Oudenhove et al., 2009)	GFD /PET	⇓
(Said Yekta et al., 2009)	Virtual dental pain /fMRI	⇑
(von Leupoldt et al., 2009)	Heat (thermode) /fMRI	⇑
(Mobascher et al., 2009)	Laser stimulation /fMRI	⇑
(Dube et al., 2009)	Heat (thermode) /fMRI	⇑
(Yoshino et al., 2010)	Electrical stimulation /fMRI	⇑
(Strigo et al., 2010a)	Anticipation of heat (thermode) /fMRI	⇑

[a] Subthreshold activation; PET – positron emission tomography; fMRI – functional Magnetic Resonance Imaging; GFD – gastric fundus distention; CRD – colorectal distention.

[b] Becerrra et al., 2001 showed subthreshold decrease in amygdala activation during late phase and increased sublenticular extended amygdala (SLEA) activation during early phase of temperature stimulation.

and functional brain imaging studies suggest that the anterior insula is involved not only in pain and anxiety processing but also in integration of current interoceptive, cognitive and emotional experiences, as well as in mounting affective (Paulus and Stein, 2006) and autonomic (Critchley, 2005) responses. Related evidence indicates that the anterior insula is a neural substrate for emotional salience (Seeley et al., 2007), emotional awareness and subjective feelings states (Craig, 2002, 2008, 2009). This evidence converges with elegant anatomical research, which describes the connections between the anterior and middle insula and the frontal lobes and limbic system (Augustine, 1996). These findings are consistent with a recent model which explains the critical involvement of the anterior insula in anxiety states and anxiety disorders (Paulus and Stein, 2006), which are characterized by altered emotional and interoceptive processing. Therefore, increased activation within anterior insula in PTSD during experimental pain processing suggests increased subjective emotional reactivity to temperature stimuli in this disorder. Future studies need to examine determine the degree to which this activation is a dynamic or static process.

Although limited, the presented evidence strongly points to a model of maladaptive coping with acute pain model in PTSD, i.e., coping by avoidance and/or dissociation as proposed by Strigo et al. (2010a,b). In other words, exposure to aversive experiences, such as experimental pain, makes individuals with PTSD avoid or dissociate from these aversive experiences, which can lead to subjective numbing (reduced subjective pain experience) and reduced brain response. Strigo et al. (2010a,b) found that both the degree of the reduction in subjective pain experience and right anterior insula activation related to the degree of avoidance symptoms (as measured by Clinical Administered PTSD Scale (CAPS)) in women with PTSD. Such a mechanism (avoidance/dissociation and even depersonalization/derealization) may compensate for greater emotional distress associated with pain experience. In fact, Strigo et al. (2010a,b) found that the initial brain response to experimental pain within the insula was increased in PTSD versus non-PTSD group, suggesting greater initial distress. Other imaging studies indirectly support this model. In Geuze et al. (2007) scores on the Dissociative State Questionnaire increased in PTSD subjects and decreased in the non-PTSD subjects from the beginning to the end of the scanning session. In Mickleborough et al. (2011), subjective pain experience (both the perceived intensity and emotional unpleasantness) was reduced in PTSD group only following exposure to a trauma-related script but was not different at baseline or following the neutral script (Mickleborough et al., 2011). This model is consistent with mutual maintenance model by Sharp and Harvey (2001) where pain serves as a reminder of the traumatic event and thus may bring on line avoidant or dissociative reactions. Therefore, in order to assess a true brain response to experimental pain in PTSD it is imperative to control for such avoidance/dissociation reactions when developing experimental paradigms. The use of masked facial expressions has shown success in demonstrating increased amygdala response in PTSD to fear (Rauch et al., 2000). As masking experimental pain stimulus is not possible, future experimental pain paradigms should try to: 1) decrease predictability of painful stimulation by employing random stimulus presentation, 2) employ pain stimulation of mild intensities, as more extreme intensities would enhance avoidance/dissociation response, and 3) combine painful stimulation with a concomitant attentional task, such as continuous performance task (CPT) (Strigo et al., 2010b), where performance on the task becomes a primary goal for a subject.

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