

Supplementary Webappendix

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Predetermined review protocol:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018083779

Appendix A: Characteristics of included studies

Table S1: Characteristics of included studies

| Study | Assessed outcomes | Assessment tools | Covariates | Pain comorbidities | Kind of trauma | N of PTSD (f / m) | N of controls (f / m) | Characteristics of study population and authors' Conclusion |
|--------------------|--|--|--|--|---|-------------------|-----------------------|---|
| Strigo 2018 | Pain intensity and unpleasantness (to supra threshold heat stimuli) | Low and high heat pain stimuli applied to left volar forearm | PTSD (CAPS) Depression (BDI) Anxiety (STAI) Somatization (PHQ-15) Resilience (CE-RISD) | Pain-free | Combat related trauma with traumatic brain injury | 26 (0/26) | 20 (0/20) | This study compared pain perception and corresponding brain response to experimental pain stimuli in males with combat-related trauma and mild traumatic brain injury with and without PTSD. No differences in the subjective experience of pain were found. Interestingly, brain Imaging indicated decreased activation within bilateral anterior insulas and specific alterations in functional connectivity in those with comorbid PTSD. |
| Strigo 2010 | Pain intensity (to supra threshold heat stimuli) | 2 heat pain stimuli (first and second run) applied to left volar forearm | PTSD (CAPS) Depression (BDI) Anxiety (STAI) Dissociation (DES-T) Resilience (CE-RISD) | Pain-free | Intimate partner violence | 23 (23/0) | 15 (15/0) | This study compared subjects with PTSD after exposure to intimate partner violence with non-traumatized control women. The PTSD group did not differ in their pain intensity ratings to supra threshold heat pain stimuli compared to PTSD-free healthy controls. However, there was a change in ratings between the ratings of the first heat pain stimulus series and the second series in that the average temperature ratings decreased in women with intimate partner violence-related PTSD, whereas the ratings were stable in the control group. The authors therefore suggest a subjective attenuation to repeated temperature stimuli in intimate partner violence-related PTSD. |
| Mickleborough 2011 | Heat pain threshold, Pain intensity (to supra threshold heat stimuli, neutral condition), Pain intensity (to supra threshold heat stimuli, trauma condition) | heat pain stimuli applied to the leg (lateral malleolus above ankle) | PTSD (CAPS) Depression (BDI) Dissociation (DES-T) | Pain-free | mixed | 17 (9/8) | 26 (11/15) | In this study, trauma exposed subjects with and without PTSD were compared. PTSD subjects showed no differences in heat pain thresholds compared to age- and sex matched controls. Pain intensity ratings of painful heat stimuli applied in the context of a brain imaging paradigm (neutral vs. trauma scripts) did not significantly differ between PTSD and control subjects under control conditions. Notably, under trauma/stress condition, PTSD subjects significantly reduced pain intensity ratings indicating stronger stress-induced analgesia. |
| Kraus 2009 | Pain intensity | individual temperature applied to the hand that was equal to a pain rating of 40 % | | Pain-free | unclear | 12 (12/0) | 17 (17/0) | Pain sensitivity was assessed by determining the individual temperature corresponding to a subjective pain rating of 40%. No difference in pain sensitivity was found between both groups of patients. |
| Harvold 2018 | Heat pain threshold (°C) | Heat pain threshold (°C) | | Pain and psychological comorbidities present in all participants | Accident-related | 14 (13/1) | 20 (17/3) | The PTSD-pain group was characterized by lower heat pain threshold compared to the PTSD-free pain group. Interestingly, in this study attentional avoidance of pain cues was associated with increased heat pain sensitivity and (clinical) pain intensity. Moreover, the Pain/PTSD group demonstrated attentional bias away from trauma and pain cues (avoidance), whereas the Pain/No-PTSD group demonstrated attentional bias toward pain cues (vigilance). Attentional avoidance of pain cues was associated with increased pain intensity and heat pain sensitivity. |
| Gomez-Perez 2013 | Pain threshold, pain tolerance and pain | Cold pressor test applied to the hand | Depression (CES) | ??? | mixed | 42 (42/0) | 40 (40/0) | Screening university students for trauma and PTSD, this study compared women with trauma exposure and PTSD with women with trauma exposure without PTSD and trauma-free women. Using the |

| | | | | | | | | |
|---------------|--|--|--|---------------------------------------|---------------------------|--|--|---|
| | intensity (intensity and unpleasantness) | | | | | | | cold pressure test, no differences in pain threshold, pain tolerance and pain intensity were found between the three groups. |
| Diener 2012 | Pain threshold, pain tolerance, pain intensity | Pressure to the left index finger | PTSD (PDS) Depression (yes/no) | Pain-free | unclear | 14 (9/5) | 14 (8/6) | PTSD subjects showed significant lower pain thresholds compared to non PTSD subjects. in comparison to PTSD-free subjects, PTSD-patients showed significantly more analgesia in terms of an increase of pain threshold and tolerance and a decrease in pain ratings after a stressor. As this study focused on brain imaging data, no exact values of the pain data were reported. Based on the behavioral data, the authors conclude that there is an enhanced stress reactivity and accompanying reduced pain perception in PTSD-patients in contrast to traumatized participants without PTSD. |
| Defrin 2017 | Heat pain threshold, heat pain tolerance, pain intensity (cold pressor) temporal summation (mechanical), conditioned pain modulation | Heat pain stimuli, cold pressor, mechanical | PTSD (PTSD inventory) Number of painful areas | mixed | torture | 12 (0/12) (chronic PTSD/group 1) | 14 (0/14) (PTSD-resilient/group 3) | On the basis of a longitudinal data on PTSD symptomatology, this study compared subjects with chronic PTSD (group 1) and delayed onset PTSD (group 2) with PTSD resilient (group 3) and healthy controls (group 4). They found no difference in heat pain threshold and heat pain tolerance, but lack of conditioned pain modulation and increased temporal summation in the two PTSD groups compared to the two PTSD-free groups (resilient and healthy controls). |
| Jenewein 2016 | Pain threshold, pain intensity, (temperature at VAS 50/100) and VAS ratings at baseline (without conditioning) | Heat pain stimuli applied to the thenar of the hand | Depression, (BDI) Anxiety (STAI) | unclear | unclear | 19 (9/10) | 21 (10/11) | Applying painful heat stimuli in the context of a fear-conditioning experiment, this study found no differences between subjects with and without PTSD at baseline. Interestingly, however, fear conditioning that was generated using a painful stimulus was impaired in patients with PTSD in that, 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, nonpainful stimulus) and one that was 'unsafe' (half the time followed by a level of heat that caused significant pain). |
| Kraus 2009 | Pain threshold (heat and cold pain), pain intensity to heat stimuli, plus a second measure of heat pain threshold (temperature, where 50% incidence of painful sensations) | Heat and cold stimuli applied to the dorsum of the hand | --- | Pain-free | Combat-related (veterans) | 10 (0/10) (veterans with PTSD) | 10 (0/10) (PTSD-free veterans) | In this study, no differences in pain thresholds could be seen between veterans with and without PTSD (however, both groups showed significantly higher thresholds compared to healthy controls), but PTSD subjects showed less pain intensity compared to both veterans without PTSD and healthy controls. |
| Pitman 1990 | Pain intensity | Heat pain stimuli applied to the ventral aspect of the forearm | --- | unclear | Combat-related (veterans) | 8 (0/8) | 8 (0/8) | Comparing Vietnam veterans with and without PTSD, subjects with PTSD showed lower pain ratings on fixed heat stimuli than the PTSD-free controls. Interestingly, in the placebo condition, the subjects with PTSD showed a 30% decrease in reported pain intensity ratings of standardized heat stimuli after the combat videotape. No decrease in pain ratings occurred in the subjects with PTSD in the naloxone condition. The subjects without PTSD did not show a decrease in pain ratings in either condition. The results are consistent with the induction of opioid-mediated stress-induced analgesia in the patients with PTSD. |
| Sterling 2006 | Pain thresholds (pressure, heat and cold) | Cervical spine and upper limb (as well as a bilateral lower limb control area) | --- | Neck pain present in all participants | whiplash | 10 (7/3) (whiplash exposed with PTSD) | 52 (34/18) (PTSD-free whiplash exposed) | In this study which was part of a prospective longitudinal investigation of whiplash injury, the PTSD group showed significant lower heat pain thresholds and higher cold pain thresholds compared to the PTSD-free control group. Moreover, the PTSD group reported lower pressure pain thresholds in one (upper limb/median nerve site) out of six test areas (cervical spine, and upper limb/ulnar and radial nerve site) compared to the PTSD-free control group. Notably, the association between mechanical and thermal hyperalgesia and PTSD symptoms was mediated by the levels of pain and disability. |

| | | | | | | | | |
|--------------------|---|---|--|---------------------------------------|----------------------------|---------------------------------------|--|---|
| Dunne-Proctor 2016 | Pain thresholds (cold, pressure pain) | Cervical spine (cold pain threshold and cervical pressure pain threshold at the hight at C2 and C5) plus upper limb (ventral surface of the proximal forearm), plus lower limb (muscle belly of the anterior tibialis muscle) | --- | Neck pain present in all participants | Motor-accident-related | 33 (??) | 39 (??) | Comparing chronic whiplash patients with and without PTSD, they found lower pain thresholds for cold and pressure pain thresholds for the PTSD group compared with the PTSD-free group suggesting a generalized hyperalgesic effects in PTSD subjects. Interestingly, exposure to Trauma-related cues lead to a hyperalgesic response in cold pain threshold (and mixed effects in pressure pain thresholds) indicating a kind of paradox reaction to stress. |
| Defrin 2008 | Heat pain threshold, pain intensity, temporal summation | Heat pain applied to the dorsal surface of the hand | --- | mixed | combat- and terror-related | 32 (5/27) | 27 (21/6) (clinical group with anxiety disorder) | Comparing subjects with combat- and terror-related PTSD with PTSD-free subjects with anxiety disorder and healthy controls, they found that pain thresholds of subjects with PTSD were significantly higher than those of subjects with anxiety and healthy controls, but they perceived suprathreshold stimuli as being much intense than the other two groups. The authors suggest that subjects with PTSD exhibit an intense and widespread chronic pain and a unique sensory profile of hyposensitivity to pain accompanied by hyperreactivity to suprathreshold noxious stimuli. |
| Lerman 2016 | Pain thresholds, pain intensity, temporal summation | Capsaicin pain, pressure and heat pain thresholds were assessed on quadriceps muscle. | PTSD (CAPS) Depression (BDI) Pain anxiety (PASS) Pain catastrophizing | Pain-free | Combat-related (veterans) | 10 (0/10) | 11 (0/11) | PTSD group and PTSD-free control group did not differ significantly in baseline heat or cold pain threshold or in pressure pain threshold. However, there was a significant group difference in the pain ratings after capsaicin injection in that participants with PTSD experienced enhanced pain after the capsaicin injection. Interestingly, pain intensity ratings decreased in the PTSD-free control group, but not for the participants with PTSD. Moreover, assessment of temporal summation indicated that the increase in pain intensity ratings following repeated application of pressure stimuli was significantly greater in the participants with PTSD when compared to the PTSD-free control group." |
| Orr 1998 | Pain tolerance (cold pressor) | cold pressor test applied to the hand | PTSD (IES) Somatization (SCL-90) | unclear | Combat-related (veterans) | 20 (0/20) | 15 (0/15) | Comparing combat veterans with and without PTSD, this study found higher pain tolerance in the PTSD group. |
| Schmahl 2010 | Pain thresholds (cold and heat) | Cold and heat pain stimuli applied to the dorsum of the hand | Depression (BDI) | unclear | Mixed (mostly sexual) | 16 (16/0) (Borderline with PTSD) | 16 (16/0) (Borderline without PTSD) | Comparing female borderline patients with PTSD with borderline patients without PTSD, and healthy controls, no differences in heat and cold pain thresholds were found between borderline patients with PTSD and healthy controls, whereas borderline patients without PTSD showed reduced pain sensitivity compared to both borderline patients with PTSD and healthy controls. |
| Mostoufi 2014 | Pain threshold; pain tolerance | Cold pressor test | Depression (PHQ-9) PTSD (PTSD checklist) | Pain-free | | 16 (8/8) | 12 (7/5) (anxiety without PTSD) | Comparing participants with PTSD with participants with anxiety disorder and healthy controls, PTSD subjects showed lower pain thresholds but higher pain tolerance levels compared to the other groups in the cold pressor test. |
| Vaegter 2017 | Pain threshold, pain tolerance, temporal summation, conditioned pain modulation | Hand (warm detection threshold) and leg (pressure pain, temporal summation, conditioned) | Depression (PHQ-9) Anxiety (GAD-7) Pain Catastrophising (PCS) | Back pain present in all participants | Accident-related | 44 (23/21) (spinal pain with PTSD) | 64 (35/29) (spinal pain without PTSD) | In this study, patients with accident-related back pain with PTSD were compared with those without PTSD. Pain patients with PTSD showed higher level of clinical pain and psychological comorbidities (anxiety, depression, pain catastrophising) and reduced pressure pain tolerance. No differences were found for warm and pressure pain thresholds, temporal summation and conditioned pain modulation. Interestingly, the association between PTSD and pain intensity was mediated by pain |

| | | | | | | | | |
|-------------|--|---|--|---------|---------------------------|-----------|------------|--|
| | | pain modulation) | Fear of Movement (TSK) | | | | | catastrophizing, whereas fear of movement mediated the association with pressure pain tolerance. |
| | | | | | | | | " |
| Geuze 2007 | Pain sensitivity (intensity for heat pain) | Heat pain applied to the dorsal hand | --- | unclear | Combat-related (veterans) | 12 (0/12) | 12 (0/12) | Comparing veterans with PTSD and without PTSD, patients with PTSD rated a fixed temperature as significantly less painful than control veterans without PTSD |
| Defrin 2015 | Pain threshold (heat and pressure), pain intensity | Heat and pressure pain applied to the dorsal hand | Anxiety Anxiety sensitivity Pain catastrophizing Dissociation | mixed | Combat related | 32 (4/28) | 43 (10/43) | Patients with PTSD had higher pain thresholds and higher pain ratings to suprathreshold stimuli than control individuals. Further statistical analyses revealed that anxiety sensitivity and dissociation significantly predicted 29% of the variance of heat pain thresholds. More specifically, anxiety sensitivity was inversely associated with pain threshold and dissociation was positively associated with pain thresholds; namely, the lower the level of anxiety sensitivity and the higher the level of dissociation, the higher the pain thresholds. Pain catastrophizing and anxiety did not make significant contributions to the explained variance of the pain thresholds. |

CPT: cold pressor test; m: male; f: female; N: number; y: years (range of age), *M*: mean age;
 Risk of bias: The quality scoring was divided into three sections (patient sampling/pain assessments used/analysis). Each article was then graded as a low risk of bias (80% or above for all three sections), moderate risk of bias (50% or above for all three sections) or high risk of bias (scored less than 50% for any one section) study (for further information see text).

Appendix B: Assessment of risk of bias

A modification of the Newcastle-Ottawa Scale (NOS) was used for judging the risk of bias of the included studies. The NOS is a priori standardised checklist of predefined criteria for assessing the quality of non-randomized cohort studies in meta-analyses: It assess the quality of non-randomized studies with its design, content and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results.

According to the Newcastle-Ottawa Scale, the quality scoring was divided into three sections:

- Selection (including three items): 1) Representativeness of the PTSD cohort, 2) Selection of the PTSD-free control cohort, 3) Ascertainment of exposure/PTSD diagnosis;
- Comparability (including two items): 4a) Comparability of cohorts by controlling for age and gender, 4b) Comparability of cohorts by controlling for point at the test side;
- Outcome (including two items): 5a) Blinded assessment of outcomes, 5b) Assessment of outcomes in the same body area for both samples.
- An additional star was awarded if 6) no obvious methodological flaws (e.g. high drop out rate) were identified

Its content validity and inter-rater reliability have been established. Its criterion validity with comparisons to more comprehensive but cumbersome scales and its intra-rater reliability are currently being examined. An assessment plan has been formulated for evaluating its construct validity with consideration of the theoretical relationship of the NOS to external criteria and the internal structure of the NOS components. Before the registration of the final protocol, three articles were assessed and data extraction carried out by JT and HBV to establish the consistency in the procedure and to adapt the data extraction form and the scoring system to the needs of this review. Data extraction was carried out using a standardized data extraction form and included the study characteristics and risk of bias assessment (NOS), outcome measures (e.g. stimulus type, stimulation location) and results of the studies. Following independent data extraction and quality assessment the completed forms were compared and any discrepancies were resolved by discussion. Remaining disagreements were referred to a third party for

adjudication. The checklist has been slightly adapted to the specific needs of this review. In particular, assessment considered, if 1.) there was a blind outcome assessment, 2.) testing was carried out in an either painful or pain free area BUT THE SAME for both samples, and 3.) no other obvious methodological flaws could be identified (e.g. high drop out rate).

Table S2: Risk of bias assessment of included studies

| Study | 1.) Representativeness of the PTSD cohort | 2) Selection of the PTSD- free control cohort | 3) Ascertainment of exposure/PTSD diagnosis | 4a) Comparability of cohorts by controlling for age and gender | 4b) Comparability of cohorts by controlling for paint at the test side | 5a) Blinded assessment of outcomes | 5b) Assessment of outcomes in the same body area for both samples | 6) No obvious methodological flaws (e.g high drop out rate) |
|-----------------------------|---|---|---|---|---|--|---|---|
| Strigo 2018 | low | low | low | low | unclear | low | low | low |
| Strigo 2010 | low | high | low | low | low | low | low | low |
| Mickleborough 2011 | low | low | low | low | low | high | low | low |
| Kraus 2009 (combat) | low | low | low | low | unclear | unclear | low | low |
| Harvold 2018 | low | low | high | low | unclear | unclear | low | low |
| Gomez-Perez 2013 | high | low | high | low | low | low | low | low |
| Diener 2012 | low | low | low | low | low | high | low | low |
| Defrin 2017 | low | low | high | low | high | low | low | low |
| Jenewein 2016 | low | high | low | low | low | high | low | low |
| Kraus 2009b (borderline) | low | low | low | low | low | low | low | low |
| Pitman 1990 | low | low | low | low | unclear | low | low | unclear* |
| Sterling 2006 | low | low | high | high | high | low | low | high |

| | | | | | | | | |
|-----------------------|-----|------|------|------|---------|---------|-----|-----|
| Dunne-Proctor 2016 | low | low | low | low | high | high | low | low |
| Defrin 2008 | low | low | low | high | high | high | low | low |
| Lerman 2016 | low | low | low | low | low | unclear | low | low |
| Orr 1998 | low | low | low | low | low | low | low | low |
| Schmahl 2010 | low | low | low | low | low | low | low | low |
| Mostoufi 2014 | low | low | low | low | unclear | low | low | low |
| Vaegter 2017 | low | low | high | low | unclear | unclear | low | low |
| Geuze 2007 | low | low | low | low | low | low | low | low |
| Defrin 2015 | low | high | low | high | high | high | low | low |

*: unclear whether double publication/overlap with the van Kolk paper (1989)

Appendix C: List of database searched und search strategies used

| # | Data base | Search |
|----------|--|----------|
| 1 | Medline | n = 782 |
| 2 | EMBASE | n = 1317 |
| 3 | PsycINFO | n = 500 |
| 4 | Web of Science | n = 3612 |
| 5 | CINHAL | n = 393 |
| 6 | Additional Searches*: (Checking reference lists, contacting experts of the field) | n = 2 |
| Σ | All | n = 6606 |

Medline

| | | |
|-----------|--|------------|
| Search | Most Recent Queries | 01/16/2018 |
| <u>#3</u> | #1 + #2 | 782 |
| <u>#2</u> | ("pain threshold"[ALL] OR "pain thresholds"[ALL] OR "pain tolerance*"[ALL] OR "pain tolerances"[ALL] OR "pain sensitivity*"[ALL] OR "pain sensitivities*"[ALL] OR "temporal summation"[ALL] OR "wind*up"[ALL] OR "conditioned pain modulation"[ALL] OR "endogenous pain modulation"[ALL] OR "diffuse noxious inhibitory control"[ALL] OR "dnic"[ALL] OR "cold*pressor"[ALL] OR "cold*pressure"[ALL] OR "somatosensory function"[ALL] OR "sensory function"[ALL]) | 24036 |
| <u>#1</u> | ("Trauma and Stressor Related Disorders"[Mesh] OR "ptsd"[ALL] OR "posttraumatic*stress"[ALL] OR "stress disorder*"[ALL] OR "combat disorder*"[ALL] OR "veterans"[ALL] OR "trauma"[All Fields] OR ptss[All Fields] OR pts[All Fields] OR pss[All Fields] OR "asd"[All Fields] OR "post-traumatic stress*"[All Fields] OR "posttraumatic stress*"[All Fields] OR "post traumatic stress*"[All Fields] OR "acute stress"[All Fields]) | 457.491 |

Embase

| | | |
|--------|---------------------|------------|
| Search | Most Recent Queries | 12/07/2017 |
| #3 | #1 + #2 | 1317 |

| | | |
|----|---|--------|
| #2 | ("pain threshold*" or "pain tolerance*" or "pain intensity*" or "pain sensitivity*" or "temporal summation*" or "wind*up" or "conditioned pain modulation" or "endogenous pain modulation" or "diffuse noxious inhibitory control*" or "dnic" or "cold*pressor" or "cold*pressure" or "somatosensory function" or "sensory function").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] | 52215 |
| #1 | ("Trauma and Stress* Related Disorders" or "ptsd*" or "posttraumatic*stress" or "stress disorder*" or "combat disorder*" or "veterans" or "trauma").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] | 354895 |

PsycInfo/PsycIndex

| | | |
|--------|--|------------|
| Search | Most Recent Queries | 01/16/2018 |
| #3 | #1 + #2 | 500 |
| #2 | (pain threshold OR pain thresholds OR pain tolerance* OR pain tolerances OR pain sensitivity* OR pain sensitivities* OR temporal summation OR wind*up OR conditioned pain modulation OR endogenous pain modulation OR diffuse noxious inhibitory control OR dnic OR cold*pressor OR cold*pressure OR somatosensory function OR sensory function) | 13.026 |
| #1 | (trauma related disorders OR stress related disorder OR ptsd* OR posttraumatic*stress OR stress disorder* OR combat disorder* OR veteran* OR trauma OR ptss OR pts OR pss OR asd OR post-traumatic stress* OR posttraumatic stress* OR post traumatic stress* OR acute stress) | 157.605 |

Web of Science

| | | |
|--------|---|------------|
| Search | Most Recent Queries | 01/16/2018 |
| #3 | #1 + #2 | 3.612 |
| #2 | TS=(pain threshold OR pain thresholds OR pain tolerance* OR pain tolerances OR pain sensitivity* OR pain sensitivities* OR temporal summation OR wind*up OR conditioned pain modulation OR endogenous pain modulation OR diffuse noxious inhibitory control OR dnic OR cold*pressor OR cold*pressure OR somatosensory function OR sensory function) | 83.993 |

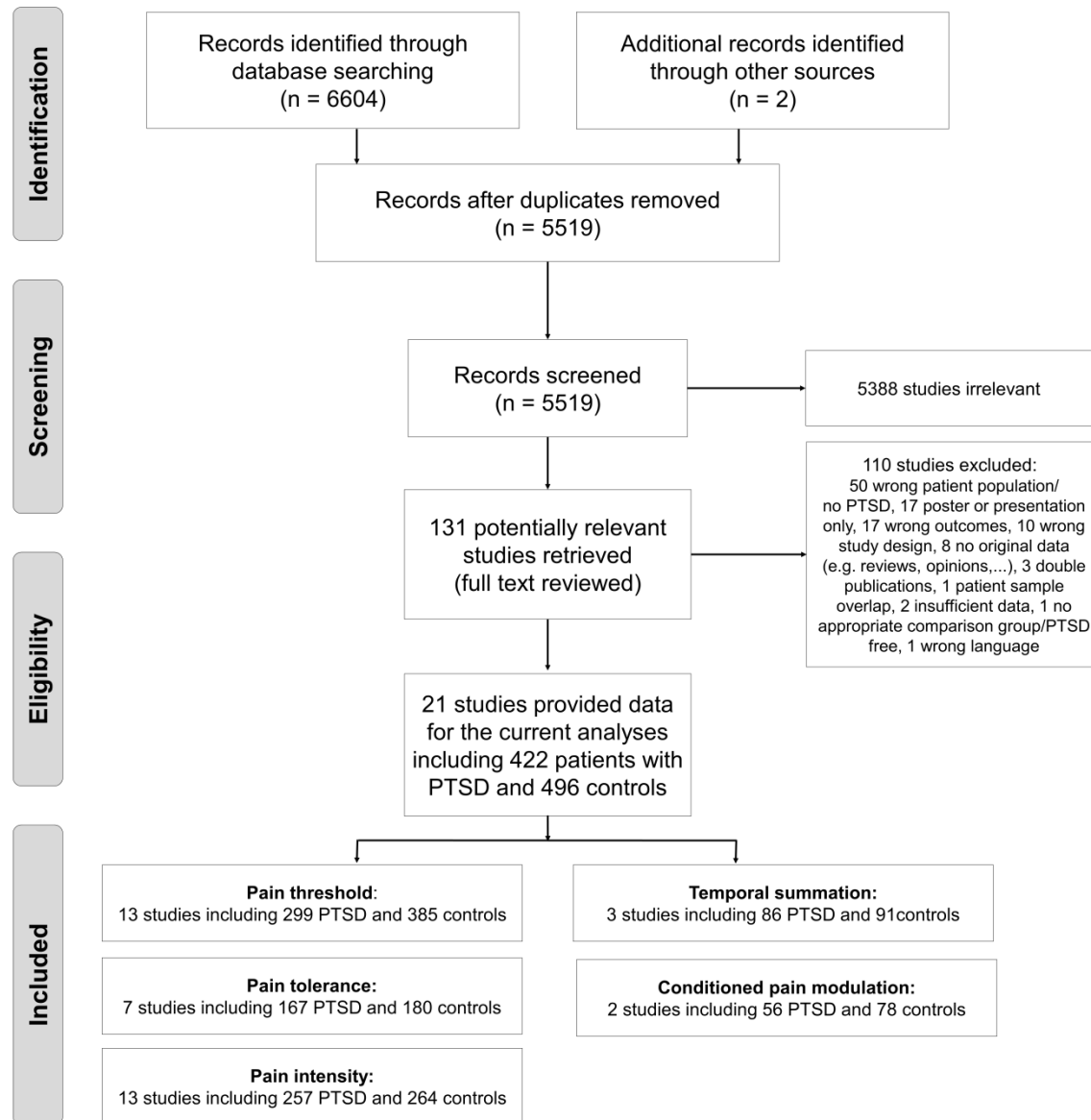
| | | |
|-----------|---|----------------|
| <u>#1</u> | TS=(trauma related disorders OR stress related disorder OR ptsd* OR posttraumatic*stress OR stress disorder* OR combat disorder* OR veteran* OR trauma OR ptss OR pts OR pss OR asd OR post-traumatic stress* OR posttraumatic stress* OR post traumatic stress* OR acute stress) | 426.414 |
|-----------|---|----------------|

CINHAL

| | | |
|-----------|--|----------------|
| Search | Most Recent Queries | 01/16/2018 |
| <u>#3</u> | #1 + #2 | 393 |
| <u>#2</u> | (pain threshold OR pain thresholds OR pain tolerance* OR pain tolerances OR pain sensitivity* OR pain sensitivities* OR temporal summation OR wind*up OR conditioned pain modulation OR endogenous pain modulation OR diffuse noxious inhibitory control OR dnic OR cold*pressor OR cold*pressure OR somatosensory function OR sensory function) | 5.280 |
| <u>#1</u> | (trauma related disorders OR stress related disorder OR ptsd* OR posttraumatic*stress OR stress disorder* OR combat disorder* OR veteran* OR trauma OR ptss OR pts OR pss OR asd OR post-traumatic stress* OR posttraumatic stress* OR post traumatic stress* OR acute stress) | 126.004 |

Appendix D: PRISMA Flowchart

Fig. S1: PRISMA Flow Diagram



Study selection process. Twenty-one studies met inclusion criteria. Note, we excluded single outcome measures of two studies due to the following conceptual flaws: For Defrin et al., 2017, we included only those pain perception measures (pain tolerance and CPM) that were not described in the Defrin et al., 2008 study because of the large overlap of the study samples between these two studies. Further, the pain intensity ratings reported in the Mostoufi et al., 2014 study were excluded

because this study assessed pain intensity rating only at baseline (starting the cold pressure immersion) as well as at the time of the pain threshold and pain tolerance assessment. Thus, pain intensity measures were potentially strongly biased by these outcomes. Finally, 21 studies including 422 subjects with PTSD (201 women, 221 men) and 496 PTSD-free controls (267 women, 229 men) provided data for our meta-analysis

Appendix E: Additional subgroup analyses

Pain thresholds: Stratifying for the pain induction method, subgroup analyses showed significant lower (i.e. more sensitive) cold pain thresholds in subjects with PTSD compared to controls in terms of a 'hyperalgesic effect' of medium effect size (Hedges' $g = 0.57$, CI_{95} 0.33 to 0.82; $I^2 = 89.3\%$; $n = 6$). No significant differences were seen for heat pain thresholds (Hedges' $g = -0.22$, CI_{95} -0.64 to 0.20; $I^2 = 98.2\%$; $n = 9$) and pressure pain thresholds (Hedges' $g = -0.37$, CI_{95} -0.87 to 0.12; $I^2 = 98.5\%$; $n = 6$) between subjects with and without PTSD.

Subgroup analyses stratifying for control groups showed significant higher pain thresholds in subjects with PTSD in terms of a 'hypoalgesic effect' of small effect, if healthy controls were used for comparisons (Hedges' $g = 0.36$, CI_{95} 0.05 to 0.67; $I^2 = 94.6\%$; $n = 3$), and significant lower pain thresholds in subjects with PTSD in terms of a 'hyperalgesic effect' of small effect were seen, if trauma-exposed controls were used for comparisons (Hedges' $g = -0.38$, CI_{95} -0.69 to -0.07; $I^2 = 87.0\%$; $n = 5$). No effect was seen if subjects suffering from anxiety disorder were used as controls (Hedges' $g = 0.42$, CI_{95} -0.74 to 1.57; $I^2 = 98.0\%$; $n = 2$). However, this analysis included only 2 studies.

Pain tolerances: Stratifying for the pain induction method subgroup analyses showed significant higher cold pain tolerance during cold pressor task (Hedges' $g = -0.41$, CI_{95} -0.58 to -0.24; $I^2 = 41.0\%$; $n = 2$) and reduced pain tolerance levels for pressure pain in subjects with PTSD compared to controls (Hedges' $g = 0.46$, CI_{95} 0.38 to 0.55; $I^2 = 0\%$; $n = 3$). No significant differences were seen for heat pain tolerance (Hedges' $g = -0.11$, CI_{95} -0.31 to 0.10; $I^2 = 32.7\%$; $n = 2$) between subjects with and without PTSD.

Subgroup stratification for differences in the control groups did not reveal any significant differences in pain tolerance between subjects with and without PTSD

Table S3: Exploratory subgroup analyses stratified for type of psychological trauma

| Outcome title | Number of studies | Number of subjects (PTSD/controls) | Effect size (Hedges' g) 95%-confidence interval | Test for overall effect p-value | Heterogeneity I ² (%); Tau ² |
|---|-------------------|---------------------------------------|---|------------------------------------|---|
| Pain threshold measures Positive values indicate an hypoalgesic effect. | | | | | |
| Combat-related | 3 | 74/81 | 0.68 [0.36, 1.01] | z=4.53, p=0.000 | 90.4; 0.000 |
| Accident-related | 4 | 101/175 | -0.41 [-0.60, -0.23] | z=4.33, p=0.000 | 81.1; 0.000 |
| Mixed trauma | 4 | 82/93 | -0.09 [-0.56, 0.38] | z= 0.36, p=0.718 | 95.9; 0.000 |
| Pain tolerance measures Positive values indicate an hypoalgesic effect. | | | | | |
| Mixed trauma | 3 | 49/47 | -0.05 [-0.54, 0.44] | z=0.20, p=0.838 | 91.0; 0.000 |
| Pain intensity measures (Positive values indicate an hyperalgesic effect) | | | | | |
| Combat-related | 6 | 104/111 | -0.29 [-0.87, 0.30] | z=0.96, p=0.339 | 97.3; 0.000 |

Exploratory subgroup analyses were performed for kind of psychological trauma, to identify possible moderators of heterogeneity. Effect sizes were calculated as Hedges' g. A DerSimonian-Laird random effects model was used to calculate pooled estimates with 95% confidence intervals (95% CI). Heterogeneity among the studies was described using the I² statistic.