Review article

The neural correlates of pain-related fear: A meta-analysis comparing fear conditioning studies using painful and non-painful stimuli

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A B S T R A C T

Compared to the field of anxiety research, the use of fear conditioning paradigms for studying chronic pain is relatively novel. Developments in identifying the neural correlates of pain-related fear are important for understanding the mechanisms underlying chronic pain and warrant synthesis to establish the state-of-the-art. Using effect-size signed differential mapping, this meta-analysis combined nine MRI studies and compared the overlap in these correlates of pain-related fear to those of other non-pain-related conditioned fears (55 studies). Pain-related fear was characterized by neural activation of the supramarginal gyrus, middle temporal gyrus, inferior/middle frontal gyri, frontal operculum and insula, pre-/post-central gyrus, medial frontal and (para-)cingulate cortex, hippocampus, thalamus, and putamen. There were differences with other non-pain-related conditioned fears, specifically in the inferior frontal gyrus, medial superior frontal gyrus, post-central gyrus, middle temporal gyrus, parieto-occipital sulcus, and striatum. We conclude that pain-related and non-pain-related conditioned fears recruit overlapping but distinguishable networks, with potential implications for understanding the mechanisms underlying different psychopathologies.

1. Introduction

Learning that certain cues predict pain results in pain-related fear towards these cues and motivates protective action to avoid further bodily harm (Bolles and Fanselow, 1980). Although learning to predict harm is adaptive, anomalies in these learning processes are posited to contribute to the maintenance of chronic pain (Leeuw et al., 2007; Meulders, 2019; Vlaeyen et al., 2016; Vlaeyen and Linton, 2000), a personally and societally burdensome disorder, affecting approximately 20% of adults in Europe (Breivik et al., 2006). The mechanisms proposed in contemporary biopsychosocial models of chronic pain, such as the fear-avoidance model (Vlaeyen et al., 2016; Vlaeyen and Linton, 2000), are similar to biopsychosocial models of anxiety disorders (Bouton et al., 2001). Namely, following an initial trauma, aberrant fear learning (see Duits et al., 2015 for review in anxiety disorders, Harvie et al., 2017 for review in chronic pain) results in excessive fear responses and avoidance behaviors that are not proportional to the actual threat. These fears and behaviors maintain disability, and feed back into a vicious cycle that maintains both anxiety and chronic pain disorders.

Classical fear conditioning procedures (Pavlov, 1927) have become a valuable tool for creating experimental models of various pain-related fears (De Peuter et al., 2011; Meulders, 2020; Vlaeyen et al., 2016). In these procedures, a conditioned fear response is evoked when a previously neutral cue (conditioned stimulus; CS+) has been repeatedly paired with a painful outcome (unconditioned stimulus; US). Typically, a differential paradigm is used to control for aspects of the response not due to associative learning, i.e., changes in responding due to the sensory characteristics of the CS and its onset, or habituation to the CS. The conditioned response to the CS+ is then compared to the response evoked by a control cue (CS−), which is never paired with the US. Hence, differential responses are not likely to be due to stimulus onset per se, but rather to the difference between the threatening stimulus (CS+) and the safe stimulus (CS−). To maximize the relevance for specific chronic pain populations a range of CSs have been used: movements (Meulders, 2019;
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In addition to these cued conditioning procedures, contextual procedures (Maren et al., 2013) have also been used to mimic the experience of generalized or widespread pain, by presenting unpredictable pain unpaired from an explicit cue (e.g., Biggs et al., 2017; Labrenz et al., 2016; Meulders et al., 2011), although the number of studies using these procedures in the fMRI environment is still limited. While the US is usually a painful electrocutaneous stimulus, in some studies painful rectal distensions have been used to mimic the sensations in gastrointestinal pain disorders (Gramsch et al., 2014; Icenhour et al., 2015; Kattoor et al., 2013). In contrast, when used as an experimental non-painful USs has not yet been made. Such a comparison, between the mild electrocutaneous stimulus (Lonsdorf et al., 2017). While the choice of a particular US can be made to increase the face validity of the paradigm for a particular psychopathology, the effect of “belongingness” on conditioned fear can be faster acquisition (Rescolora, 1974; Trevino, 2016), or stronger acquisition due to increased matching between CS and US (Hamm et al., 1989). However, the consequence of US type for the identified neural correlates of conditioned fear is still unknown.

Meta-analyses and systematic reviews on the neural correlates of conditioned fear have been conducted previously (Etkin and Wager, 2007; Fullana et al., 2016; Mechias et al., 2010). However, given the relative novelty of studies investigating pain-related fear, the comparison between the neural correlates of conditioned fear using painful or non-painful USs has not yet been made. In the most recent meta-analysis (Fullana et al., 2016), 27 studies were included, of which only two used a painful US. Therefore it is not surprising that whilst the effect of the sensory modality of the US (e.g., tactile, auditory, etc.) on the identified neural correlates of conditioned fear has been investigated (Fullana et al., 2016; Sehlmeyer et al., 2009), a comparison between painful and non-painful USs has not yet been made. Such a comparison, between the neural correlates of pain-related fear and other non-pain-related conditioned fears, would indicate the degree to which different ‘types’ of conditioned fear are supported by the same neural mechanisms, and would inform on the generalizability of findings across these two fields.

Therefore, to shed light on the question of whether or not pain-related fear can be distinguished on the neural level from non-pain-related fear, we conducted an effect-size signed differential mapping (ES-SDM) meta-analysis (Radua et al., 2012; Radua and Mataix-Cols, 2012) of fMRI studies that used a classical fear conditioning procedure. This method uses the statistical maps (SPMs) of each study so that data points are available at each voxel, addressing the common issue of an inflation of zero-values for many voxels (e.g., as in coordinate-based meta-analyses). In order to capture the majority of research on this topic we included studies that used a differential (i.e. both a CS+ and CS−) procedure in healthy (and pain-free) participants. The outcomes of interest from these studies were the statistical maps from a whole-brain comparison of CS+ and CS−.

Our first aim was to identify the neural correlates that are consistently associated with pain-related fear (evoked by a painful somatosensory stimulus, USPAIN). We hypothesized that the neural correlates of pain-related fear would include the same collection of regions as identified in a previous general fear conditioning meta-analysis (Fullana et al., 2016). Specifically, we expected to find positive effects (CS+ > CS−) in the anterior cingulate cortex, parietal operculum and temporoparietal junction, dorsolateral prefrontal cortex, middle frontal gyrus, and inferior and middle temporal cortex. Furthermore, as identified in previous meta-analyses (Fullana et al., 2016), we expected negative effects (CS− > CS+) in clusters in the hippocampus and retrosplenial cortex, posterior cingulate cortex, caudate, ventromedial prefrontal cortex, orbitofrontal cortex, post-central gyrus, and inferior parietal cortex. We expected both positive and negative clusters in the precuneus.

Our second aim was to compare these results found with painful somatosensory stimuli as US (USPAIN) to the neural correlates of fear reported by studies using a) non-painful somatosensory stimuli (e.g. mild shock), and/or b) non-painful non-somatosensory stimuli as USs (e.g., loud noise). We made a distinction between non-painful somatosensory (USNO-PAIN(S)) and non-painful non-somatosensory (USNO-PAIN (NS)) studies in order to control for the effect of sensory modality when comparing painful and non-painful USs. This distinction allowed us to test whether differences were present due to US sensory modality, in which case we would expect only differences between the USPAIN group and USNO-PAIN(NS) group but not between the USPAIN and USNO-PAIN(S) group. If a region showed differences in the strength of differential responses (CS+ > CS−) between studies that used a painful US compared to studies that used a non-painful US, we considered this evidence of quantitative differences in the neural response. A region that only shows differential responses to CS+ and CS− when a painful US was used and no differential responding when a non-painful US was used (or vice versa), was considered evidence of qualitative differences in the pattern of neural response.

2. Methods

2.1. Literature search

In November 2017 the databases PubMed, Web of Knowledge, and BrainMap were searched for relevant literature. In PubMed and Web of Knowledge the following search terms were used: Neuroimaging, Magnetic Resonance Imaging, Positron Emission Tomography, Fear, Aversive, Conditioning. In BrainMap, due to a different search system, the following search terms were used: ‘Experiments’ ‘Imaging modality’ ‘is’ ‘fMRI’ & ‘Experiments’ ‘Paradigm class’ ‘is’ ‘classical conditioning’ and ‘Experiments’ ‘Imaging modality’ ‘is’ ‘PET’ & ‘Experiments’ ‘Paradigm class’ ‘is’ ‘classical conditioning’. No limits or filters, such as year published or document type, were used.

2.2. Exclusion criteria

At least two raters (EB & IT/ALK) evaluated the abstracts of the retrieved studies for the following exclusion criteria:

1. Article type: Retracted articles, review, meta-analysis, editorial, or commentary;
2. Sample: Animal studies, patient studies with no healthy control group, or pharmacological studies with no placebo group;
3. Paradigm: No aversive conditioning (e.g., non-conditioning task, or appetitive conditioning);
4. Imaging: No fMRI or PET imaging (during the acquisition phase of the experiment), or no whole brain data acquisition1;
5. Conditioning parameters: No CS-, studies that used only contextual, operant, or instructed conditioning were excluded;
6. Data reported elsewhere: Duplicate data (i.e., analysis of a previously published dataset).

In case of disagreement between the two raters a decision was reached by consensus between all three raters (EB, IT, ALK). Following this the full text of each article was assessed for the same exclusion criteria by one rater (EB).

1 Data was considered as ‘whole brain’ if the authors explicitly described it as such, or if a field-of-view was reported that was typical for whole brain coverage (i.e. ≈ 192mm3 or larger). Cerebellum coverage was not required.
2.3. Outcome measures and data extraction

The outcome measure of interest was activation loci identified from a general linear model-based contrast of CS+ > CS- (if available, the contrast using only the unreinforced CS + presentations). Authors of each study deemed eligible for inclusion were contacted and asked to provide statistical parametric maps (SPMs) for the contrast CS+ > CS- (inclusion until March 2018). In cases where these data were not available, the coordinates for significant activation clusters and their corresponding statistic were recorded (EB). Similar to the approach in previous meta-analyses, if the analysis was divided into an early and late acquisition phase, results from the early phase were used (Fullana et al., 2016). Given the wide range of trial numbers across studies, the early phase was considered the most comparable. Other details of interest were grouped in four categories, including paradigm details, sample characteristics, scanning parameters, and analysis details (Supplementary Material 1). These details were recorded to assess the heterogeneity of the included studies, and to assess possible sources of bias. Studies were subdivided into one of three groups based on the type of US. Studies were assigned to the USPAIN group if the US was explicitly described as such, studies referring to a ‘mild shock’ were assigned to the USNO-PAIN (no pain / somatosensory) group. Studies using a non-painful, and non-somatosensory US (e.g., loud noise) were assigned to the USNO-PAIN(NS) group.

2.4. Meta-analytical approach

The present meta-analysis used the effect-size signed differential mapping (ES-SDM) approach (Radua et al., 2012; Radua and Mataix-Cols, 2012). This method combines an image-based and coordinate-based approach, allowing neuroimaging data to be entered in the form of either a statistical parametric map (SPM) or coordinates of significant activation clusters. Two key benefits of an image-based approach using SPMs are the reduction of inter-study heterogeneity caused by differing statistical thresholds, and the presence of a data point for each voxel. When SPMs are not available and coordinates have to be used instead, the ES-SDM method mitigates the problems associated with the coordinate-based approach by ‘reconstructing’ a whole brain activation effect-size SPM based on the reported coordinates, their corresponding statistic (z- or t-values) and the sample size.

Prior to analysis, the obtained SPMs were interpolated to a 1 mm³ resolution, and centered within a 256 mm³ bounding box, then visually inspected in BrainVoyager (BrainInnovation, Maastricht, the Netherlands (Goebel et al., 2006)) to confirm correct placement and whole brain coverage. All SPMs were provided in MNI space and therefore no spatial transformations were applied. For studies for which only coordinates were available, coordinates reported in Talairach space were transformed to MNI using the ‘icbm2tal’ transform (Lancaster et al., 2007). Activation effect-size SPMs were then created, using an anisotropic kernel whose size was dependent on the coordinate’s statistic and study sample size (40 % anisotropy and FWHM 20mm) (Radua et al., 2014).

2.4.1. Mean maps

To identify regions where there was consensus in the neural correlates of pain-related fear (USPAIN) the mean activation effect-size estimate (z-scored) was calculated, for both positive and negative effects (separately). Mean maps (positive and negative effects) were also computed for studies using non-painful / somatosensory USs (USNO-PAIN(S)) and non-painful / non-somatosensory USs (USNO-PAIN(NS)). All z-scored activation effect-size maps were thresholded for statistical significance using p < .005, cluster extent ≥ 10 voxels, and z > 1.00. These thresholds are recommended as the inclusion of non-SPM data in the meta-analysis results in a non-normal distribution of values, which means that traditional methods for multiple comparison correction are overly conservative (Radua et al., 2012). As an additional verification of the robustness of the mean maps (i.e., regions of consensus across studies) a jackknife approach was used. The mean maps were calculated N times (N = number of studies), using a leave-one-out method. The N mean maps were then overlaid and visually inspected for differences from the (whole sample) mean map.

2.4.2. Comparison maps

To assess differences in the neural correlates the non-painful US subgroups were compared to the painful US subgroup. A linear model compared the maps of two subgroups (1: USPAIN vs. USNO-PAIN(S); 2: USPAIN vs. USNO-PAIN(NS)), with the resulting maps thresholded at p < .005.

3. Results

3.1. Study characteristics

The selection of studies is summarized in Fig. 1. The inter-rater reliability was moderate (Altman, 1990), as assessed by Cohen’s kappa (Cohen, 1960) (κ = 0.60, p < .001, 79 % agreement). A total of 64 studies were included in the meta-analysis, 10 of which used a painful US. The data from two of these studies (Ridder et al., 2012) (published in one article) were combined by the original authors into one dataset, therefore the USPAIN group is henceforth labelled as n = 9.

3.2. USPAIN: the neural correlates of pain-related fear

Nine datasets were included in the meta-analysis of pain-related fear (Table 1), with a total of 390 participants (approximately 45 % female, average age 26 years).

The main effect for CS+ > CS- was calculated including all studies (Fig. 2A). The regions that showed reliable consensus across studies included a large cluster in the right hemisphere extending from the supramarginal gyrus across the middle temporal gyrus, and a second large cluster in the right inferior frontal gyrus that extended into the frontal operculum and anterior insula. A smaller cluster was also present in the right pre-central gyrus. A frontal operculum / anterior insula cluster was furthermore present in the left hemisphere, as was activation in the supramarginal gyrus, however this activation was less extended and did not include the middle temporal gyrus. Along the midline, with the cluster spreading into both the left and right medial wall, there was significant activation in the mid-cingulate and para-cingulate regions, including portions of the juxtapositional lobule. In the subcortical regions there was bilateral activation in the thalamus and the anterior putamen. Negative clusters (i.e., CS- > CS+) were found in the bilateral middle frontal gyrus, left hippocampus, and right post-central gyrus. Based on a leave-one-out jackknife analysis, the obtained results were deemed reliable, see supplementary material 2 for further details.

3.3. USNO-PAIN(NS): the neural correlates of fear evoked by non-painful somatosensory USs

Forty-one studies (total of 1352 participants; 45 % female; mean age 25 years) were eligible for inclusion in the non-painful / somatosensory US group (Table 2). The mean of the CS+ > CS- contrast maps was calculated using all forty-one studies (Fig. 2B). Regions with positive responses were found in the superior medial frontal cortex, a large
Articles identified through database search (n=1382) Articles identified from other sources (n=6)

Articles screened (n=1388) Articles included (n=138)

Studies * included (n=141)

Studies included in analysis (n=65)

USPAIN (n=10)† USNO-PAIN(NS) (n=41) USNO-PAIN(NS) (n=14)

![Diagram](image)

**Table 1**
Overview of studies using a painful US. Abbreviations: a = studies where SPMs were made available; b = analysis split into early/late acquisition; – = unknown. Inclusion criteria: ‘none’ = no specific criteria stated; ‘right-handed’ = only right-handed participants recruited; ‘hormone’ = participants selected based on gender, menstrual cycle, or oral contraceptive use. Voxel size refers to the resolution that functional data was acquired in, and the slice thickness dimension includes the size of the slice gap (if applicable). Statistical threshold refers to the threshold used to identify co-ordinates of significant activation clusters for studies where no SPMs were available.

| Study                        | N (% female) | Mean age (years) | Inclusion criteria | CS | US | # CS+ trials (reinforcement) | Voxel size (mm) / smoothing FWHM | Statistical threshold |
|------------------------------|--------------|------------------|--------------------|----|----|-----------------------------|----------------------------------|-----------------------|
| Cacciaglia et al., 2013 *    | 114 (36%)    | 22               | none               | geometric figure | painful shock (right hand) | 18 b (50%) delay 3.44–3.44 × 4 (8mm) | Not applicable               |
| Krause-Utz et al., 2016      | 26 (100 %)   | 28               | none               | geometric figure | painful shock (right hand) | 36 (50%) delay 3.44–3.44 × 4 (8mm) | P < 0.05                  |
| Ridder et al., 2012 *        | 112 (38 %)   | 22               | right-handed       | geometric figure | painful shock (right hand) | 36 (50%) delay 3.44–3.44 × 4 (10mm) | Not applicable               |
| Gramsch et al., 2014         | 24 (54 %)    | 29               | hormone            | geometric figure | rectal distension          | 5 (80%) delay 2.55–2.55 × 3.45 (8mm) | P < 0.001                |
| Kattoor et al., 2013 *       | 19 (100 %)   | 24               | hormone            | geometric figure | rectal distension          | 16 b (75%) delay 2.6–2.6 × 3 (8mm) | Not applicable               |
| Labrenz et al., 2016         | 24 (58 %)    | 26               | hormone            | Geometric figure | rectal distension          | 16 (75%) delay 2.8–2.8 × 3.6 (8mm) | Not applicable               |
| Moessnang et al., 2013 *     | 29 (52%)     | 31               | right-handed       | odor             | CO2 in nose                | 70 (60%) delay 3.1–3.1 × 3.9 (8mm) | Not applicable               |
| Eippert et al., 2012 *       | 32 (0%)      | 26               | none               | Geometric figure | painful shock (right hand) | 10 (100%) delay 2–2 × 3 (8mm) | Not applicable               |
| Birbaumer et al., 2005 *     | 10 (0%)      | 32               | none               | face (neutral)   | pressure                   | 16 (100%) delay 3 × 3 × 3 (15mm) | Not applicable               |

Cluster covered both the right and left (para-)cingulate and medial superior frontal gyrus. Positive differences (i.e., CS+ > CS-) were also apparent in the bilateral anterior insula / frontal operculum, bilateral supramarginal gyri, middle frontal gyrus / pre-central gyrus, as well as many subcortical regions, such as the thalamus, caudate, putamen, and mid-brain / periaqueductal grey. Negative responses (i.e., CS- > CS+) were present in the right post-central gyrus, bilateral middle frontal gyrus (anterior to the positive response clusters), medial prefrontal cortex, bilateral parieto-occipital sulcus, bilateral posterior cingulate / precuneus, and bilateral hippocampus.

3.4. USNO-PAIN(NS): the neural correlates of fear evoked by non-painful non-somatosenory USs

Fourteen studies (total of 308 participants; 51% female; mean age 25 years) were eligible for inclusion in the non-painful / non-somatosenory US group (Table 3).

When combining all fourteen studies, the mean response to the comparison of CS+ > CS- (Fig. 2C) showed a pattern of positive differences in the bilateral anterior insula, thalamus, pre-central gyri, and supramarginal gyri, as well as a cluster of positive responses in the right medial frontal cortex, specifically the medial portion of the superior
frontal gyrus. Negative responses were present in the bilateral parieto-occipital regions (both lateral and medial clusters), middle frontal gyri, right medial prefrontal cortex, and left posterior parahippocampus.

3.5. Differences between the neural correlates of pain-related fear and other non-pain-related conditioned fears

A comparison was made between studies in the US\textsuperscript{PAIN} group and studies in the US\textsuperscript{NO-PAIN(S)} group, to identify either quantitative and/or qualitative differences in neural correlates of conditioned fear, not confounded by differences in US modality. Significant differences in the strength of the CS\textsuperscript{+} > CS- contrast between these groups (analogous to an interaction between CS type (CS\textsuperscript{+}/CS-) and group (US\textsuperscript{PAIN}/US\textsuperscript{NO-PAIN(S)}) were observed in the right middle temporal gyrus, and the right inferior frontal gyrus (Fig. 3A), as well as in the right striatum (Fig. 3B). One negative cluster (larger negative differences in the US\textsuperscript{PAIN} group compared to positive differences in the US\textsuperscript{NO-PAIN(S)} group) was in the post-central gyrus (Fig. 3B).

To investigate if the differences between US\textsuperscript{PAIN} and US\textsuperscript{NO-PAIN(NS)} were also present when a non-somatosensory US was used, a second comparison was made between studies using a painful US and studies using a non-painful / non-somatosensory US (US\textsuperscript{PAIN} vs. US\textsuperscript{NO-PAIN(NS)}). The two clusters in the right middle temporal cortex and right inferior frontal gyrus were also present – again, larger differences between CS \textsuperscript{+} and CS- in the US\textsuperscript{PAIN} group compared to the US\textsuperscript{NO-PAIN(NS)} group. In addition, a cluster in the left parieto-occipital sulcus showed a positive difference between CS \textsuperscript{+} and CS- in the US\textsuperscript{PAIN} group, but a negative difference between CS \textsuperscript{+} and CS- in the US\textsuperscript{NO-PAIN(NS)} group. On the lateral right post-central gyrus, a similar pattern was present as in the comparison between the US\textsuperscript{PAIN} group and the US\textsuperscript{NO-PAIN(S)} group, namely, a negative difference between CS \textsuperscript{+} and CS- in the US\textsuperscript{PAIN} group, and smaller positive difference in the US\textsuperscript{NO-PAIN(NS)} group. In the right medial superior frontal gyrus, there was only a very small difference between CS + and CS- for the US\textsuperscript{PAIN} group, with a stronger positive difference for the US\textsuperscript{NO-PAIN(NS)} group. This is also visible in the mean maps for the three groups (Fig. 2), with the significant differences in the US\textsuperscript{PAIN} group being more inferior and more within the cingulate cortex than the US\textsuperscript{NO-PAIN(NS)} group, with the majority of the significant clusters being in the medial superior frontal gyrus.

4. Discussion

Building on a rich history of research on fear and anxiety, increasingly diverse fear conditioning procedures are being implemented to study the behavioral and neural responses associated with pain-related fear. Conducting an effect-size signed differential mapping (ES-SDM) meta-analysis of the existing literature (Radua et al., 2012; Radua and Mataix-Cols, 2012) revealed that pain-related fear consistently involves the supramarginal gyrus, middle temporal gyrus, inferior/middle frontal gyri, frontal operculum and insula, pre-/post-central gyri, medial frontal and (para-)cingulate cortex, hippocampus, thalamus and putamen. The comparison of these correlates with those from studies using a non-painful US indicated quantitatively different responses to conditioned pain-related fear in middle temporal gyrus, inferior frontal gyrus, striatum, and qualitatively different responses in the post-central gyrus.

4.1. The neural correlates of pain-related fear

For studies using a painful US (e.g., a painful electrocutaneous stimulus or painful interoceptive stimulus), differential responses to the CS \textsuperscript{+} and CS- were consistently present in a number of regions, including large clusters in the right and left supramarginal gyrus, in the right...
Table 2
Abbreviations: a = studies where SPMs were made available; b = analysis split into early/late acquisition; c = only contingency aware participants included in analysis; d = only contingency unaware participants included in analysis; – = unknown. Inclusion criteria: ‘none’ = no specific criteria stated; ‘right-handed’ = only right-handed participants recruited; ‘hormone’ = participants selected based on gender, menstrual cycle, or oral contraceptive use; TEC = trauma-exposed controls.
Voxel size refers to the resolution that functional data was acquired in, and the slice thickness dimension includes the size of the slice gap (if applicable). Statistical threshold refers to the threshold used to identify co-ordinates of significant activation clusters for studies where no SPMs were available.

| Study | N(% female) | Mean age (years) | Inclusion criteria | CS | US | # CS + trials (reinforcement) | Voxel size (mm) / smoothing FWHM | Statistical threshold |
|-------|-------------|------------------|--------------------|----|----|-------------------------------|----------------------------------|---------------------|
| (Åhs et al., 2015) a | 43 (51 %) | 29 | right-handed | 3D pictures (snake/spider) | mild shock (right hand) | 16 b (31%) delay 4 × 3.8 (8mm) | Not applicable |
| Delgado et al., 2008a, 2008b | 12 (50 %) | 23 | right-handed c | – | mild shock (hand) | 36 (17%) delay 3 × 3 (4mm) | Puncorrect < 0.005 |
| Dunsmoor et al., 2011 | 14 (50 %) | 22 | right-handed | face (neutral) | mild shock (right hand) | 16 (63%) delay 4 × 3.8 (8mm) | Puncorrect < 0.005 extent > 5 voxels |
| Garfinkel et al., 2014 | 14 (0%) | – | TEC | pictures (lamp) | mild shock (hand) | 16 (60%) delay 3 × 3.4 × 3 (5mm) | Prox < 0.05 |
| Hermann et al., 2016 (a) | 46 (0%) | 23 | right-handed | Pictures (lamp) | mild shock (right hand) | 16 (63%) delay 3 × 3.6 (9mm) | Prox < 0.05 |
| Hermann et al., 2012 | 78 (47 %) | 24 | genotype | Geometric figure | mild shock (left leg) | 20 (100%) delay 3 × 3.6 (9mm) | Prox < 0.05 extent > 10 voxels |
| Holt et al., 2012 | 17 (0%) | 34 | none | Pictures (lamp) | mild shock (hand) | 16 b (60%) delay 3.1 × 3.1 (5mm) | Puncorrect < 0.005 cluster size α < 0.05 |
| Jemen et al., 2008 | 11 (45 %) | 28 | right-handed | geometric figure | mild shock (left hand) | 45 (33%) delay 3.1 × 3.4 × 4 (10mm) | Puncorrect < 0.005 extent > 15 voxels |
| Klucken et al., 2015 | 100 (47 %) | 24 | right-handed | geometric figure | mild shock (left leg) | 16 (50%) delay 3 × 3.6 (8mm) | Not applicable |
| Klumpers et al., 2015 a | 99 (0%) | 22 | none | geometric figure | mild shock (hand) | 18 (30%) delay 3.3 × 3.3 (5mm) | Not applicable |
| Lange et al., 2017 a | 46 (78 %) | 21 | none | geometric figure | mild shock (left leg) | 12 (66%) delay 3 × 3.6 (6mm) | Not applicable |
| Lerner et al., 2017 a | a: 17 (29 %) b: 31 (50%) | 23 | a: none b: geometric figure | pictures (lamp) | mild shock (hand) | 16 (60%) delay 3 × 3.3 (5mm) | Not applicable |
| Leuchs et al., 2017 a | 34 (47 %) | 26 | right-handed | geometric figure | mild shock (right hand) | 20 (60%) delay 3.4 × 3.4 × 3.4 (6mm) | Not applicable |
| Lim et al., 2008 | 21 (%) | 18–34 | right-handed | face (neutral) | mild shock (right hand) | 6 (50%) delay 3.75 × 3.75 × 3.75 (6mm) | Puncorrect < 0.005 extent > 5 voxels |
| Lindner et al., 2015 | 15 (100 %) | 23 | right-handed | geometric figure | mild pressure (toe/leg) | 8 (100%) delay 2 × 2.3 (6mm) | Prox < 0.05 extent > 5 voxels |
| Lissek et al., 2014 | 20 (55 %) | 24 | none | geometric figure | mild shock (right leg) | 15 (80%) delay 1.7 × 1.7 × 3.5 (4mm) | Puncorrect < 0.001 cluster size α < 0.05 |
| MacNamara et al., 2015 a | 49 (57 %) | 25 | right-handed | pictures (lamp) | mild shock (left foot) | 40 (60%) delay 3.4 × 3.4 × 3 (8mm) | Not applicable |
| Marschner et al., 2008 | 19 (0%) | 30 | none | geometric figure | mild shock (right arm) | – (100%) delay 2 × 2.2 (8mm) | Prox < 0.05 |
| Menon et al., 2007 a | 17 (29 %) | 18–50 | none | geometric figure | mild shock (left hand) | 45 (33%) delay 3.1 × 3.1 × 4.4 (8mm) | Not applicable |
| Merz et al., 2017 a | 40 (0%) | 18–35 | right-handed | geometric figure | pictures (lamp) | mild shock (right hand) | 16 (62.5%) delay 2 × 2.37.3 (9mm) | Not applicable |
| Merz et al., 2012 a | 122 (74 %) | 23 | hormone d | geometric figure | mild shock (left leg) | 10 (100%) delay 3 × 3.6 (9mm) | Not applicable |
| Merz et al., 2013 a | 48 (50 %) | 18–35 | right-handed & hormone e | geometric figure | mild shock (right leg) | 21 b (100%) delay 3.3 × 3.6 (9mm) | Not applicable |
| Merz et al., 2014 a | 16 (0%) | 23 | right-handed & hormone e | geometric figure | mild shock (left leg) | 16 b (62.5%) delay 3 × 3.6 (9mm) | Not applicable |
| Milad et al., 2013 | 21 (52 %) | 26 | right-handed | geometric figure | mild shock (hand) | 16 (60%) delay 3.1 × 3.1 × 3 (8mm) | Prox < 0.05 extent > 10 voxels |
| Molapour et al., 2015 a | 20 (50 %) | 22 | right-handed | face (neutral) | mild shock (right hand) | 9 (100%) delay 1.7 × 1.7 × 2.3 (8mm) | Not applicable |
| Morey et al., 2015 a | 35 (29 %) | 42 | TEC | face (fearful) | mild shock (right hand) | 18 (33%) delay 3.75 × 3.75 × 3.75 (5mm) | Not applicable |
| Phelps et al., 2004 | 11 (55 %) | 18–25 | right-handed | geometric figure | face (angry) | 23 (38%) delay 3 × 3.3 (4mm) | Puncorrect < 0.01 |
| Schiller et al., 2008 | 17 (47 %) | 18–31 | right-handed | face (neutral) | mild shock (right leg) | 18 (30%) delay 3 × 3.3 (4mm) | Prox < 0.05 |
| Schunk et al., 2010 | 6 (0%) | – | right-handed | Geometric figure | mild shock (left leg) | 12 (50%) delay 4 × 4.4 (8mm) | Puncorrect < 0.001 cluster size α < 0.05 |
| Spoonmaker et al., 2010 a | 16 (0%) | 25 | right-handed & hormone | face (neutral) | mild shock (right hand) | 30 (50%) delay 6 (8mm) | Not applicable |
| Stark et al., 2006 a | 17 (53%) | 24 | right-handed & hormone | geometric figure | mild shock (left leg) | 30 (100%) delay 3 × 3.6 (9mm) | Not applicable |
| Straube et al., 2007 | 12 (83 %) | 21 | right-handed | geometric figure | mild shock (left leg) | (50%) delay 3 × 3.4 (8mm) | Puncorrect < 0.005 extent > 4 voxels |
| Tabbert et al., 2005 a | 18 (67%) | – | none | geometric figure | mild shock (left leg) | 30 (100%) delay 3 × 3.6 (9mm) | Not applicable |

(continued on next page)
hemisphere extending across the middle temporal gyrus. A second large cluster in the right and left inferior frontal gyrus extended into the frontal operculum and anterior insula. A smaller cluster was also present (bilaterally) in the right pre-central gyrus. Along the midline, with the frontal operculum and anterior insula. A smaller cluster was also present (bilaterally) in the right pre-central gyrus. Along the midline, with the frontal operculum and anterior insula. A smaller cluster was also present (bilaterally) in the right pre-central gyrus. Along the midline, with the frontal operculum and anterior insula. A smaller cluster was also present (bilaterally) in the right pre-central gyrus. Along the midline, with the frontal operculum and anterior insula. A smaller cluster was also present (bilaterally) in the right pre-central gyrus. Along the midline, with the frontal operculum and anterior insula. 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for chronic pain patients has not yet been investigated.

The anterior insula is functionally connected to the dorsal anterior cingulate cortex (Cauda et al., 2011), also referred to as the mid-cingulate cortex. It is posited to control averagely-motivated action, including behaviors and the control of facial expressions (Shackman et al., 2011). Within the context of pain-related fear conditioning, this is especially interesting given recent research that has shown dorsal anterior cingulate activity is correlated with the ‘tipping point’ between approach and avoidance behavior, relating to the probability of an aversive outcome (Schlund et al., 2016). Given the importance of avoidance behavior in maintaining chronic pain disability, this too is a key region-of-interest for studying individual differences in pain-related fear responses.

The present results also included clusters in the right temporoparietal junction, right inferior frontal gyrus, and right anterior insula which may reflect processing related to the ventral attention network (Corbetta and Shulman, 2002). This is a ‘bottom-up’ network, that interacts with, but is dissociable from, the ‘top-down’ dorsal attention network (Vossel et al., 2014). Its function is thought to be in the reorienting of attention to salient cues (Geng and Mangun, 2011; Mars et al., 2012), and consists of the right temporoparietal junction, right inferior frontal gyrus, and right anterior insula (Corbetta and Shulman, 2002; Uddin, 2014). Whilst spatially and conceptually similar to the salience network, a data-driven approach to network identification has found that these networks are separable (Power et al., 2011), and the overlap with the anterior insula (right lateralization for the ventral attention network) could be due to these regions’ role in switching between relevant networks (Uddin, 2014). The differential involvement of the ventral attention network for CS+ compared to CS− is not surprising, given the greater acquired salience of the CS+ after pairing with the US. Interestingly, previous research has shown that activation of the right temporoparietal junction and right inferior frontal gyrus is even more enhanced when a target (of high salience) stimulus is in some way unexpected (e.g., in location or frequency) (Corbetta and Shulman, 2002).

![Fig. 3. Comparisons between each of the three sub-groups. A) Regions that showed larger differences between CS+ > CS− for both comparisons between USPAIN group > USNO-PAIN(NS) group and USPAIN group > USNO-PAIN(NS) group. B) Regions that showed larger differences between CS+ > CS− for the comparison between the USPAIN > USNO-PAIN(NS) group. C) Regions that showed larger differences between CS+ > CS− for the comparison between the USPAIN > USNO-PAIN(NS) group. IFG = inferior frontal gyrus; MTG = middle temporal gyrus; PCG = post-central gyrus; mSFG = medial superior frontal gyrus; POS = parieto-occipital sulcus. Map threshold: p < 0.005, cluster extent > 10 voxels, peak height > z = 1.](image-url)
Therefore, it is possible that the degree of differential responding in this network may be dependent on the number and ratio of CS+/CS- trials.

The identified clusters in the hippocampus and retrosplenial cortex are often found as reflecting episodic memory and learning processes (Eichenbaum and Cohen, 2004; Tulving and Markowitsch, 1998), but are also commonly implicated in contextual fear conditioning (Maren et al., 2013), a procedure that has been used as a model for generalized or widespread pain conditions (Biggs et al., 2017; Labrenz et al., 2016; Meulders et al., 2011). Within cued conditioning, the hippocampus is necessary for CS-US contingency awareness, but is dissociated from the physiological response to a feared stimulus (Bechara et al., 1995). Research on the neural networks underlying episodic memory is well established, although interactions with fear networks is still less well-understood (Phelps, 2004). Typically, higher activity in the hippocampus during emotional memory encoding has been correlated with better performance at recall (LaBar and Cabeza, 2006), however the implications of these findings for interpretation of the higher responses for the CS- compared to the CS+ during fear acquisition is unclear. One caveat to consider is that the hippocampus and retrosplenial cortex may show different patterns of BOLD response (i.e. activation or deactivation) depending on the current task. These regions have been shown to have a pattern of deactivation at rest, consistent with their function as part of the default mode network (Greicius et al., 2009), and therefore this is especially a region where inspection of the obtained BOLD signal would be informative.

The present results also included clusters in the middle temporal gyrus, which visual neuroscience studies have shown is relevant for the recognition of bodies and body parts (Kalfas et al., 2017; Schwoebel and Moayedi, 2017) and response to fearful faces (Straube et al., 2010; Yang et al., 2012). As none of the USPAIN studies included in this meta-analysis used fearful faces, bodies or body parts as CS, it is unlikely that the responses are due to the type of CS. Instead, it may be that the middle temporal gyrus is implicated in the formation and maintenance of the structural body image, i.e. a topological map of locations derived primarily from visual input that defines body part boundaries and proximity relationships (Buxbaum and Coslett, 2001; Schwoebel and Coslett, 2005). A similar region has also been suggested as the neurophysiological correlate of ‘prosthesis embodiment’ (van den Heiligenberg et al., 2018). Interpreted in that sense, the region’s involvement in pain-related fear might indicate that a structural body image is activated which helps to localize the anticipated pain on the body. A similar process may also be related to the negative response (i.e. CS+ > CS-) observed in the post-central gyrus (primary somatosensory cortex). Research has shown that the anticipation of a tactile (not necessarily painful) stimulus leads to a down-regulation of the ipsilateral side (Drevets et al., 1995; Schäfer et al., 2012; Staines et al., 2002; Van Ede et al., 2014).

Whilst positive differential responses (i.e. CS+ > CS-) are largely expected, for the ventromedial prefrontal cortex (vmPFC) it was expected that this region would show negative differential activity (i.e. CS- > CS+) due to its role in the inhibition of the fear response to the CS- (Fullana et al., 2015; Greenberg et al., 2013; Milad et al., 2007). In line with this hypothesis, a region in the left orbitofrontal/inferior medial prefrontal cortex, consistent with the vmPFC, showed a reliable negative differential response in the USPAIN studies. The vmPFC is thought to reduce fear responses via inhibitory connections with the amygdala (Phelps et al., 2004).

An unexpected finding was the negative differential responses in the left middle frontal gyrus (often referred to as the dorsolateral prefrontal cortex [dPFC]), which showed a positive response in the meta-analysis by Fullana et al. (2015). The dPFC is a core part of the dorsolateral attention network (Seeley et al., 2007), and is typically associated with higher order executive functioning, such as the maintenance of ‘task-sets’, a state representation necessary to link stimuli to optimal responses to achieve a goal in a given context (Ochsner and Gross, 2005; Wagner et al., 2001). In the context of a pain-related fear response, evidence from imagery and placebo literature points to a function of expectation formation for the imminent painful US. For instance, the dPFC has been shown to be active during imagery tasks prompted using pain-related words (Richter et al., 2010), and shows increased functional connectivity with the anterior insula during pain imagery (Mochizuki et al., 2013). However, evidence from the placebo literature is mixed. In a study by Eisenbruch et al. (2012), placebo-induced expectations of reduced pain intensity were correlated with decreased activity in this area, whilst Eippert et al. (2009) found that placebo-induced pain relief was associated with stronger dPFC responses. Further research is needed to identify the source of these differences, which would shed light on our own unexpected finding of stronger responses in the dPFC to the CS- compared to the CS+. Moreover, the function of the dPFC in pain-related fear is especially important considering evidence that the dPFC is involved in the regulation of fear responses via its connections with the vmPFC and onward connections to the amygdala (Delgado et al., 2008), making the dPFC a core putative target for modulation of pain-related fear responses (Seminowicz and Moayedi, 2017).

In sum, the neural correlates of pain-related fear include many regions considered as part of the core fear network. Based on the current evidence, it would appear that the ventral attention network including the right temporoparietal junction and inferior frontal gyrus is consistently recruited during pain-related fear, as well as the salience network related to behavioral and autonomic regulation, encompassing the bilateral insula and medial frontal cortex. The prefrontal regions such as dPFC and vmPFC are regularly found as neural correlates a number of higher-order aspects of cognitive functioning. The negative differential response in dPFC might be associated with expected pain relief, but defining the circumstances under which this occurs requires further research. The negative differential response in the vmPFC is in line with our hypotheses, given this region’s role in the inhibition of the fear response when it is not required. The function of the cluster in the middle temporal gyrus is less clear, however one hypothesis is that it is involved in the recognition of perceptual features of the visual CSs and their emotional associations, via connections with the amygdala. Alternatively, it could also be linked to activation of structural body representations in relation to anticipated pain on a specific body part.

4.2. Pain-related fear compared to other non-pain-related conditioned fears

The direct comparison within the current meta-analysis of the neural correlates of conditioned fear induced by painful versus non-painful USs allowed us to investigate potential differences between pain-related and other conditioned fears. We made a distinction between non-painful somatosensory USs (i.e., mild shock; the USNO-PAIN(NS) group) and non-painful non-somatosensory USs (i.e., loud noise; the USNO-PAIN(NS) group). This distinction allowed us to test to what extent the neural correlates of pain-related fear are dependent on (1) US sensory modality – in which case a correlate would be qualitatively differently involved for the USPAIN vs. USNO-PAIN(NS) studies but would show similar involvement for the USPAIN and USNO-PAIN(NS) studies – (2) US intensity – in which case a specific region would show quantitatively different responses in the USPAIN compared to the USNO-PAIN(NS) and/or USNO-PAIN(N) studies – and finally (3) a pain-specific effect – in which case a correlate would show a qualitative difference between the USPAIN and USNO-PAIN(NS) studies, as well between USPAIN and USNO-PAIN(NS).

These comparisons revealed three patterns of differences. First, the USPAIN studies evoked stronger responses than USNO-PAIN(NS) studies in three regions: the right inferior frontal gyrus, the right middle temporal gyrus, and the right striatum, indicative of quantitative differences potentially due to US intensity. Second, there was no differential activity in the USPAIN group, but strong differences in the USNO-PAIN(NS) group, in the medial superior frontal gyrus, indicative of qualitative differences potentially due to US sensory modality. Third, the response evoked was
of opposing directions in two regions. First, the right post-central gyrus showed negative differences [CS+ > CS-] in the USPAIN group vs. positive responses [CS+ > CS-] in the USNO-PAIN(NS) and USNO-PAIN(NS) group, indicative of pain-specific qualitative differences (i.e., not only due to US sensory modality). Second, the left parieto-occipital sulcus showed positive differences [CS+ > CS-] in the USPAIN group vs. negative responses [CS- > CS+] in the USNO-PAIN(NS) group, indicative of qualitative differences potentially due to US sensory modality.

The first pattern of responses (i.e. increased differences in the USPAIN group) is in line with the hypothesis that the primary difference between pain-related fear and other conditioned fears is due to the intensity of the unconditioned stimulus (i.e., a quantitative difference). Given the posited function of these regions in the pain-related fear network, this could be due to a stronger capture of attention (inferior frontal gyrus) (Corbetta and Shulman, 2002; Seeley et al., 2007), increased activation of the structural body image related to the location of the expected pain or aversive stimulus (middle temporal gyrus) (Buxbaum and Coslett, 2001; Kalfas et al., 2017; Schoebel and Coslett, 2005), and the encoding of a greater differential value of the CS + and CS- in the striatum (Delgado et al., 2008; Menon et al., 2007; Seymour et al., 2007).

The second pattern of responses, that is, no differential responding between CS+ and CS- for the USPAIN studies, but strong differences in the USNO-PAIN(NS) studies, was in the medial superior frontal gyrus. This source of this difference is apparent from the mean maps for the two groups, the response clusters on the medial wall tend to be more inferior for the USPAIN studies, compared to the USNO-PAIN(NS) studies. The superior frontal gyrus is typically associated with working memory processes (Boisgueheneuc et al., 2006; McCarthy et al., 1994; Petrides et al., 1993), and the medial portion has been shown to be recruited predominantly during working memory tasks with a high load (Rypma et al., 1999). Therefore, the differences observed in this meta-analysis may reflect a higher demand on working memory processes for the differentiation between CS + and CS- when a non-painful US is used. This difference in response between the USPAIN and USNO-PAIN(NS) group suggests that there are qualitative differences between the neural correlates of these conditioned fears, however, given that this difference was only present when compared to non-somatosensory USs this could also be related to the modality of the US.

The third pattern of differences was characterized by opposing signs for the mean effect in the USPAIN studies compared to the USNO-PAIN(NS) studies. In the right post-central gyrus (primary somatosensory cortex) this included negative responses (i.e. CS+ < CS-) when a painful US was used, with positive responses (CS+ > CS-) when a non-painful (both somatosensory and non-somatosensory) US was used. Interpretation of this difference is limited by the heterogeneity in US location – it is unclear whether the responses are ipsilateral to the US. Among the USPAIN studies, when an electrocutaneous stimulus was used as US it was administered to the right arm, and therefore the negative response could reflect down-regulation of the ipsilateral side in anticipation of the painful US (Drevets et al., 1995; Schäfer et al., 2012; Staines et al., 2002; Van Ede et al., 2014). At present, the results suggest that there are qualitative differences in the neural correlates of pain-related fear in the post-central gyrus, although further investigation is required to assess the degree to which this is influenced by anticipatory responses for a tactile US (irrespective of intensity), or whether this is unique to pain-related fear. An opposing sign of response was also found in the left parieto-occipital sulcus, although the opposite pattern was present: negative responses (CS+ < CS-) in the USPAIN studies, with positive responses (CS+ > CS-) in the USNO-PAIN(NS) studies. The parieto-occipital sulcus is typically associated with higher-order visuo-spatial processing and working memory (Hutchison et al., 2015). It is also functionally connected to a number of the identified neural correlates, such as the cingulate cortex, middle temporal gyrus, and superior frontal gyrus (Hutchison et al., 2015). One possible interpretation of the present findings is that the differences between the USPAIN and USNO-PAIN studies in the parieto-occipital sulcus are due to differential recruitment of this visuo-spatial network. This would be further evidence of some qualitative differences in the neural correlates of pain-related fears.

The observed differences in neural correlates between the USPAIN and USNO-PAIN studies provide evidence for both distinct neural correlates underlying pain-related fear, as well as stronger differential responses in the core fear neural correlates when a painful US is used. Particularly, the primary somatosensory cortex, medial superior frontal gyrus, and parieto-occipital sulcus appear to respond differently to pain-related fear compared to other conditioned fears, suggesting that there are differences in the neural mechanisms underlying different ‘types’ of conditioned fears.

4.3. Considerations and future directions

There are a number of considerations that are relevant when interpreting these results. First, this meta-analysis used positive and negative t-statistics from the contrast CS+ > CS- as the primary data. The contrast is computed as the difference between the CS + and CS- beta values divided by their standard error. The betas correspond to the optimal weights assigned to the CS + and CS- predictors in the GLM fitting procedure. A positive (negative) beta indicates an increased (decreased) activation compared to baseline. It is important to note that whereas a positive CS+ > CS- t-value could result from a larger increase in activation in response to CS + than CS-, it might just as well result from a larger decrease in activation for CS- compared to a null response for CS+. In addition, the beta values in a particular study are influenced by the experimental baseline used in that study and possible co-linearity with other predictors included in the GLM. Given that we did not have the betas for the single predictors to inspect, nor event-related BOLD time courses, it is important to be cautious in interpreting the mean contrast maps. The t-statistic for the contrasts simply reflects whether the beta value for the CS + is more positive than the beta value for the CS-. While such a ‘negative’ effect (CS- > CS+) could be caused by a more positive BOLD response to the CS- compared to the CS+, e.g., related to a sense of relief, it could also be caused by a less negative BOLD response to the CS- compared to the CS+, e.g., related to an inhibitory response to the CS+ that is not present for the CS-. However, without the underlying BOLD responses such conclusions remain highly speculative and so we have limited the interpretations we make here.

Second, there may be a bias present in the coordinate-based data used in this meta-analysis when recorded from the publication. Only coordinates reported from whole-brain corrected thresholds were used. In case a small volume correction was applied to a priori regions-of-interest, these regions were only used if they were also explicitly reported to be present after the more stringent whole brain correction. However, this may not always have been the case, and therefore the analysis could be biased away from findings responses in the more commonly used regions-of-interest (e.g., amygdala, hippocampus, insula). Still, the identification of robust responses in the insula and in some cases in the hippocampus makes it unlikely that such a bias affected the current meta-analysis. Furthermore, the inclusion of data from full SPMs would also mitigate these effects.

A third consideration relates to the homogeneity of the studies included in the analysis, such as the inclusion of data from trauma-exposed controls, or studies using trace conditioning. As a consequence, the present results show regions where there is consensus despite differences between studies. Although there is evidence from previous meta-analyses and reviews (Fullana et al., 2016; Schlimeyer et al., 2009) that many of these factors influence the identified neural correlates, e.g. trace and delay conditioning (Knight et al., 2004), reinforcement rate, and number of trials, the present sub-group comparisons demonstrated that the exclusion of these studies did not affect the main results. Therefore, in the present meta-analysis, such differences are either not apparent, or very small, likely because of the high variance due to inter-study differences.
Fourth, we used a dichotomous classification of pain US and non-pain US based on the description of the experience of the US provided by the researchers. In line with the IASP definition of pain (Merskey and Bogduk, 1994), subjective self-report of pain is currently the standard for pain calibration procedures. Hence, we also accept this description for experimental studies of pain as it captures the operationalization of pain that we were interested in investigating. However, a potentially interesting avenue of future research could lie in the development and implementation of standardized calibration procedures across studies that could eventually allow a parametric examination of the shift in neural correlates as a function of increasing self-reported pain intensity.

Fifth, there are differences in the number of studies included in each group, with the USpain group containing the least number of studies. Consequently, further investigation of study heterogeneity is not feasible. As more studies are conducted on pain-related fear it will be possible, and highly beneficial, to address remaining questions: do the neural correlates of pain-related fear differ depending on pain modality? Are these neural correlates recruited for all CS types (e.g., visual, auditory, somatosensory, etc.)? Are there differences in interoceptive vs. exteroceptive USs (Koenen et al., 2017)? Furthermore, in this meta-analysis we focused on studies of experimental cue learning, however once the field of research has grown and more studies are conducted a broader approach including observational and instructed learning, as well as contextual fear (as an experimental model of generalized or widespread pain experiences) would be invaluable. Studies of other conditioned fears have already demonstrated the recruitment of different networks depending on the type of learning (i.e., instructed vs. experiential) (Mechias et al., 2010), and contextual compared to cue learning (Maren et al., 2013). While more research is still needed before meta-analyses of analogous networks for pain-related fear is possible, this is certainly an interesting direction for the field as it moves forward.

4.4. Conclusions

The present synthesis of fear conditioning studies using a painful (as opposed to non-painful) unconditioned stimulus demonstrated that the reliable neural correlates of pain-related fear include the supramarginal gyrus, middle temporal gyrus, inferior frontal gyrus, frontal operculum, anterior insula, pre-central gyrus, medial frontal cortex, (para-)cingulate cortex, juxtapositional lobule, thalamus and putamen. Furthermore, correlates that showed stronger responses to the CS- than CS+ were found in the bilateral middle frontal gyrus, left hippocampus, and right post-central gyrus. These neural correlates form a putative network for pain-related fear in non-chronic pain patients. However, comparing responses in this network between chronic pain patients and healthy controls could shed light on how pain-related fear influences the neural processing of subsequent nociceptive – or non-nociceptive – stimulation, helping us to better understand the perceptual changes that accompany many chronic pain conditions. Furthermore, understanding the relationship between this network and motor networks could be a pathway to understanding the behavioral responses accompany pain-related fear.

Comparing the present meta-analysis on pain-related fear to previous meta-analyses including all types of conditioned fears showed a number of overlapping responses. However, a direct comparison within the current meta-analysis also revealed both qualitatively, as well as qualitatively, different CS+ vs. CS- responses depending on which US type was used for conditioning. Together, these results suggest that there are regions that respond proportional to the anticipated US aversiveness (e.g., inferior frontal gyrus, middle temporal gyrus, striatum), possibly related to enhanced attention and salience, as well as regions that respond differentially depending on the nature (pain/non-pain) of the expected US (e.g., medial superior frontal gyrus, primary somatosensory cortex and parieto-occipital sulcus). The practical implication of these findings is that, when investigating the neural mechanisms of conditioned fear, the choice of US is not trivial. Future research would be valuable to understand whether these differences occur also in with other conditioning procedures, i.e., contextual fear conditioning as an experimental model for generalized anxiety and widespread pain conditions, and during the reduction of fear related to extinction procedures. Exposure-based therapies for chronic pain are largely efficacious (Den Hollander et al., 2016), but an improved understanding of underlying (neural) mechanisms, using experimental models such as extinction, could considerably aid efforts to improve these therapies.

Given the differences in the observed neural correlates of pain-related fear to previous research, we conclude that until these differences are better understood, caution is warranted when generalizing the findings obtained with basic fear conditioning paradigms to pain-related fear. However, we have identified a number of regions-of-interest that warrant further investigation, to shed light on the degree to which different conditioned fears (in both the lab and in psychopathology) share common neural mechanisms.

Declaration of Competing Interest

The authors report no conflict of interest. The authors would like to thank Judith Eck and Andreas Bressler for their help with data extraction and analysis, as well as the many authors that shared data.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.09.016.

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