Neural mechanisms underlying the conditioned pain modulation response

Narrative Review

PAIN®

Neural mechanisms underlying the conditioned pain modulation response: a narrative review of neuroimaging studies

Hadas Nahman-Averbuch[a,*], Inge Timmers[b,c]

Abstract

Processing spatially distributed nociceptive information is critical for survival. The conditioned pain modulation (CPM) response has become a common psychophysical test to examine pain modulation capabilities related to spatial filtering of nociceptive information. Neuroimaging studies have been conducted to elucidate the neural mechanisms underlying the CPM response in health and chronic pain states, yet their findings have not been critically reviewed and synthesized before. This narrative review presents a simplified overview of MRI methodology in relation to CPM assessments and summarizes the findings of neuroimaging studies on the CPM response. The summary includes functional MRI studies assessing CPM responses during scanning as well as functional and structural MRI studies correlating indices with CPM responses assessed outside of the scanner. The findings are discussed in relation to the suggested mechanisms for the CPM response. A better understanding of neural mechanisms underlying spatial processing of nociceptive information could advance both pain research and clinical use of the CPM response as a marker or a treatment target.

Keywords: Spatial filtering, Conditioned pain modulation, Neuroimaging, MRI, Nociception

1. Introduction

Processing spatially distributed nociceptive information is critical for survival. It can be imperative to focus on the more damaging and severe impact and to attend to the most imminent potential cause for harm. In animals, a phenomenon in which one noxious stimulus can inhibit and reduce the neural response of another spatially remote noxious stimulus was identified and termed diffuse noxious inhibitory control (DNIC).[24–26] In this situation, the inhibition creates a larger contrast between the 2 sets of engaged spinal cord neurons, enabling the system to focus more resources toward the more intense noxious stimulus.[23]

In humans, the conditioned pain modulation (CPM) paradigm was developed to assess the "pain inhibits pain" phenomenon and is one of the most common psychophysical tests to assess spatial processing and filtering of nociceptive processing. One of the earlier studies conducted in humans was published in 1945. In this study, an increase in pain thresholds in the tooth of the participant was found after spraying ethyl chloride on the leg.[41] Numerous studies have used this paradigm, which was also termed heterotopic noxious conditioning stimulation, DNIC-like effect, or counterirritation. In this review, we will use the term CPM, which was proposed in 2010.[62]

In the CPM paradigm, and similar to the paradigm applied in animals, one noxious stimulus (ie, the conditioning stimulus [CS]) is used to inhibit and reduce the pain intensity evoked by another noxious stimulus that is applied to a remote area of the body (ie, the test stimulus [TS]). Thus, an inhibitory or efficient CPM response would be reflected in the reduction of pain sensitivity to the TS in the presence of the CS (ie, TS + CS compared with TS_{only}) and indicates an antinociceptive profile. In some cases, however, the simultaneous application of the CS may lead to no change in TS sensitivity (no CPM response) or even to a facilitatory effect in which an increase in pain sensitivity of the TS is observed when it is applied together with the CS. No change or a faciliatory CPM response might indicate a pronociceptive profile.[65]

As a psychophysical test in humans, CPM is widely used to understand the mechanisms of chronic pain syndromes. Individuals with chronic pain typically express a less efficient CPM response compared with healthy control participants.[27,60,61] In addition, CPM has been used as a predictor for clinical outcomes, such as the development of chronic pain,[63] medication usage after surgery,[16] and the response to pain interventions,[13,66] including behavioral interventions.[38] Recently, based on the CPM inhibitory effect, a device to reduce the intensity of migraine headaches was developed.[64,67]

Understanding the mechanisms underlying spatial filtering of nociceptive processing is imperative. However, despite its wide usage, the mechanisms underlying CPM responses are not clear. DNIC, local spinal inhibition, attention modulation of pain distraction, and pain habituation are some of the suggested

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Division of Clinical and Translational Research, Department of Anesthesiology, Washington University Pain Center, Washington University in St. Louis School of Medicine, St. Louis, MO, United States, [b] Department of Rehabilitation Medicine, Maastricht University, Maastricht, the Netherlands, [c] Department of Medical and Clinical Psychology, Tilburg University, Tilburg, the Netherlands

**Corresponding Author. Address: Department of Anesthesiology, Washington University in St. Louis School of Medicine, 660 South Euclid Ave, St. Louis, MO, United States. Tel.: 314.273.5099. E-mail address:hadas@wustl.edu (H. Nahman-Averbuch).*

PAIN 00 (2022) 1–22

http://dx.doi.org/10.1097/j.pain.0000000000002716

mechanisms.[2,10,12,14,28,34] To better understand the contribution of spinal, brainstem, and midbrain mechanisms to the CPM response in humans, a series of lesion studies was conducted. These studies examined the CPM response in tetraplegic patients,[46] patients with thalamic lesions, and patients with Wallenberg syndrome (n = 3).[11] These studies demonstrated that an intact cervical spinal cord and ipsilateral medullary structure are needed to evoke an inhibitory CPM response, while lemniscal and spinothalamic pathways are not.

Later, neuroimaging studies have been conducted to better understand the neural mechanisms underlying CPM to advance our understanding of mechanisms related to spatial filtering of nociceptive information. Conditioned pain modulation has been studied using many different neuroimaging techniques that furthermore differ in their properties and hence, interpretation. For instance, acquiring functional MRI (fMRI) data while performing the CPM paradigm (ie, inside the scanner) is quite distinct from performing the CPM paradigm outside of the scanner and correlating its result with resting-state fMRI or structural MR indices. Findings from such studies have not been thoroughly and critically reviewed and synthesized before. A better understanding of the brain areas that are involved in spatial filtering of nociceptive information could advance both pain research and clinical use of the CPM response as a marker and a treatment target. Thus, the aim of this review is to first present and discuss the different ways CPM is used in combination with neuroimaging and summarize the findings on (1) brain activation and CPM, (2) functional connectivity (FC) in relation to CPM, and (3) brain structure and CPM. Finally, we interpret these findings in relation to the suggested mechanisms of the CPM response.

2. Methods

An electronic PubMed search was conducted using the keywords "conditioned pain modulation" OR "counterirritation" OR "diffuse noxious inhibitory control" OR "heterotopic noxious conditioning stimulations" AND "imaging." The references of the selected articles were searched as well. Studies were required to (1) be in English, (2) involve human participants, and (3) examine CPM as the effect of a CS on a TS. Studies that assessed CPM during an fMRI scan or that correlated pain modulation capabilities of the CPM response with brain structure or function were included. Studies that assessed CPM during an fMRI scan were required to compare brain function during TS alone (TS_{only}) or in combination with a neutral CS (TS + $CS_{neutral}$) vs in combination with a CS (TS + CS). The search yielded 96 articles; of which, 15 articles presenting 11 studies were included in this review. Two independent investigators (N.-A.H. and I.T.) conducted the search, assessed the relevancy of each article, and extracted data from the studies on the sample, the CPM paradigm, the MRI scanning and analysis, and results. If needed, authors were contacted for additional information or clarification of the results.

3. Brain activation and conditioned pain modulation

3.1. Methodology of assessing brain function during conditioned pain modulation

In this type of studies, the CPM response is tested when the participants are in the scanner. The CPM paradigm inside the scanner could be quite similar to the CPM paradigm outside the scanner, although there may be some methodological differences, owing to the type of stimuli that can be used (ie, as stimuli in the scanner require MRI-compatible devices) and the method of pain ratings (ie, the use of some rating scales during the scan may be challenging because of the loud noise during scanning and the need to avoid head movement).

There is a need for at least 2 types of stimuli: TS delivered alone (or a TS combined with a neutral CS) and TS in combination with a (noxious) CS. The 2 types of stimuli can be presented in separate runs or in the same run. A comparison between the brain response to the TS across the 2 runs is typically conducted to identify the brain regions that are specifically involved in the CPM response.

The conducted contrast (TS + CS vs TS_{only} or TS_{only} vs TS + CS) is important because it will influence the direction of findings (positively or negatively signed). Another important factor when interpreting the findings is whether the blood oxygen level–dependent response to the specific condition was an activation or deactivation compared with baseline, and hence whether the subsequent between-condition contrast reflects a reduced activation or an increased deactivation in case of a negatively signed effect after contrasting TS + CS vs TS_{only} (**Fig. 1**). In this review, findings are discussed in reference to the TS + CS scan, eg, comparing TS + CS vs TS_{only}, and where possible condition-level contrasts are described as well. In addition to analyzing changes in brain activation during the CPM paradigm, analyses may be aimed at identifying brain activation related to the extent of the CPM responses (eg, the correlation between changes in pain ratings during TS + CS vs TS_{only} and changes in brain activation during TS + CS vs TS_{only}).

3.2. Brain activation during conditioned pain modulation

Six papers/studies examined brain activation while acquiring functional MR images, with varying TS/CS stimuli, CPM paradigms, and analysis strategies. The full details of the studies can be found in **Table 1**.

About 15 years ago, Song et al. published one of the first studies that examined brain activation during the CPM response in a group of healthy participants (n = 12) and patients with irritable bowel syndrome (IBS, n = 12). They used a TS of rectal distention and a CS of cold-water immersion of the foot. In healthy participants, they found reduced activation to the TS during CPM (ie, less activation during TS + CS than during TS_{only}) in several regions, including the anterior insula, postcentral gyrus (referred to by the authors as secondary somatosensory cortex [SII]), putamen, inferior frontal gyrus (IFG), and thalamus, while the caudate was less deactivated. On the other hand, the superior temporal gyrus (STG) was more activated (ie, increased activation) during TS + CS compared with during TS_{only}, while primary somatosensory cortex (SI) was more deactivated. Patients with IBS did not show an inhibitory CPM response (ie, no reduction in pain ratings of the TS during the TS + CS compared with TS_{only}), which was contrary to healthy participants. In the patients, the IFG and thalamus were also less activated during TS + CS than during TS_{only}, and the caudate was less deactivated. Reversely, the inferior parietal lobe and STG were more activated during TS + CS than during TS_{only}, while the precuneus was more deactivated.[53] Thus, patients and healthy participants showed limited similarities in neural response of some areas such as the IFG and thalamus but also differences in CPM responses as well as the overall neural correlates of CPM.

In a later study, Piché et al. examined the cerebral and cerebrospinal mechanisms involved in the modulation of pain and spinal nociception. In this study, which included 12 healthy volunteers, the TS was an electrical stimulus, and the associated

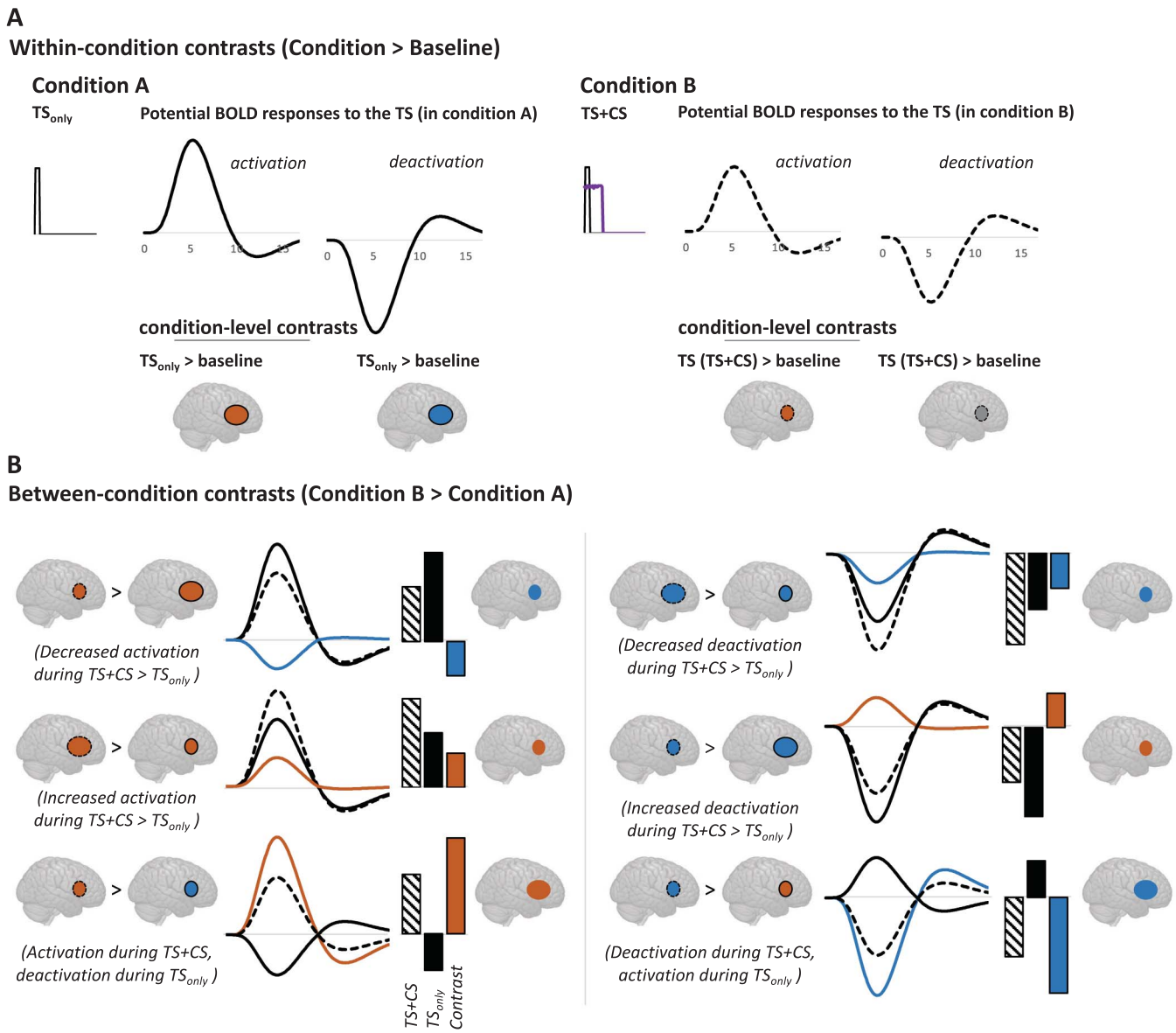

Figure 1. Schematic overview of potential conditioned pain modulation conditions, within-condition and between-condition contrasts, and corresponding blood oxygen level–dependent (BOLD) responses. (A) Condition A presents the TS delivered alone (TS_{only}, see stimulus in black). Potential BOLD responses to the TS_{only} are shown (solid line), which are either activation or deactivation compared with baseline. Condition B presents the TS when it is applied together with the CS (TS + CS, see TS stimulus in black and CS stimulus in purple). Potential BOLD responses to the TS + CS are shown (dashed line), which may also be activation or deactivation when compared with baseline. Of note, BOLD responses to the TS stimulus are modeled (and not the CS). (B) Potential scenarios for the between-condition contrasts (Condition B > Condition A or TS + CS > TS_{only}). The presentation of the results depends on whether the difference between conditions is expressed as a positive or negative sign, which furthermore depends on the specific contrast (TS + CS > TS_{only} or TS_{only} > TS + CS). An orange bar indicates a net increase in BOLD response for the TS + CS > TS_{only} contrast, while a blue bar indicates a net decrease in BOLD response. Solid black lines and bars: BOLD response to the TS during the TS_{only} paradigm; dashed black lines and bars: BOLD response to the TS during the TS + CS paradigm. Note that different contrasts can yield a similar net result (eg, decreased activation during TS + CS > TS_{only} and decreased deactivation during TS + CS > TS_{only}), illustrating the importance of presenting the results of the within-condition contrasts too. BOLD, blood-oxygen-level-dependent; CS, conditioning stimulus; TS, test stimulus.

motor response (ie, the RIII reflex amplitude) was measured in addition to pain ratings. The CS was the immersion of the foot in cold water. Reduced activation to the TS during CPM (ie, less activation during TS + CS than during TS_{only}) was found. In particular, less activation was found during CPM in all regions of interest (ROIs), which included bilateral thalamus, primary SI, precentral gyrus (primary motor cortex), anterior cingulate cortex (ACC), mid cingulate cortex (MCC), supplementary motor area (SMA), the left (contralateral) SII, posterior insula (pINS), and prefrontal cortex (PFC) as well as the right ipsilateral anterior INS and parahippocampal gyrus. For the pain ratings of the electrical stimuli, CPM response was calculated as the change in pain ratings of TS during the TS + CS. In addition, the reflex amplitude was used to calculate another CPM response. Both indices of CPM responses were correlated with brain activations. While a significant inhibitory CPM response was found for pain ratings of the TS, no change in RIII amplitude during TS + CS compared with TS_{only} was found, indicating no significant CPM response of RIII reflex. Correlations with brain activations showed that higher reductions in pain ratings, which indicates more efficient CPM responses, were correlated with larger reductions in brain activation (TS + CS > TS_{only}) in the contralateral SI, posterior

Table 1

Summary of studies examining brain function (activation and connectivity) and conditioned pain modulation

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
Bogdanov et al., 2015	24 healthy volunteers (24 f, aged 31.3, SD not presented)	*TS*: Laser heat stimuli (to the dorsum of the left hand) *$CS_{painful}$*: cold water immersion (to right leg at 2 ± 2°C for 120 seconds) using icebags *$CS_{neutral}$*: lukewarm water immersion (right leg, 35°C for 120 seconds) *CPM paradigm*: TS + CS (parallel) during scanning *CPM calculation*: TS + $CS_{neutral}$ vs TS + $CS_{painful}$	**fMRI during CPM** *Main effect conditions:* $CS_{painful}$ > baseline $CS_{neutral}$ > baseline $CS_{painful}$ > $CS_{neutral}$ TS + $CS_{neutral}$ > baseline *CPM effect:* TS + $CS_{neutral}$ > TS + $CS_{painful}$ Correlation with behavioral CPM response (*physiological CPM*) *Thresholding:* *Whole-brain search:* $P < 0.05$ FWE-corrected (CDT $P < 0.001$) *Directed ROI search*: small volume correction, $P < 0.05$ few corrected (CDT $P < 0.001$) in mask consisting of 19 "pain matrix" regions	**Behavioral CPM effect (in scanner)** No significant CPM response in pain ratings (*on individual level, inhibitory, facilitatory, and absence of CPM responses were observed)* **fMRI activation results—TS + $CS_{neutral}$ > TS + $CS_{painful}$** No significant findings **fMRI activation results—correlation** *Whole-brain search:* Behavioral CPM response correlated with CPM brain activation in anterior insula/premotor cortex, posterior insula/SII, lateral OFC, fusiform gyrus/parahippocampal gyrus *Directed ROI search:* posterior insula/SII	Study separated early and sustained cold pain responses (early: prior to TS)
Coppieters et al., 2021 *(larger study, same as Coppieters et al., 2017, 2018)*	37 patients with CWAD (37f, age median 38, 21-59) 38 patients with CINP (38f, age median 36, 18-62) 32 healthy controls (32f, age median 24, 18-62)	*TS*: pressure pain threshold (PPT) at quadriceps muscle of most painful side *CS*: cold water immersion (hand, contralateral side to PPT; at 12 ± 1°C for 120 seconds) *CPM paradigm*: TS + CS (parallel) on a separate day *CPM calculation*: TS_{only} vs TS + CS Continuous as well as categorical CPM effect was defined	**Resting-state fMRI** *ROI-to-ROI analysis:* 40 ROIs based on previous work (precuneus, PCC, left and right insula, left and right amygdala, ACC, mPFC, left and right hippocampus, left and right thalamus, left and right pallidum, left and right temporal pole, left and right superior parietal cortex, left and right precentral gyrus, left and right STG anterior and posterior division, left and right SMG anterior and posterior division, left and right frontal operculum, left and right MFG, left and right OFC, left and right postcentral gyrus, left and right SFG, and left and right frontal pole) *Contrasts:* Group differences in rsFC (post hoc correlations with CPM responses) A priori correlations with CPM responses *Thresholding:* p-FDR < 0.05 at cluster-level, followed by $P < 0.05$ uncorrected at connection level	**Behavioral CPM effect (outside scanner, different day)** Whether TS_{only} > TS + CS was significant is not reported. CPM response was significantly lower in patients with CWAD compared with controls and to CNIP Inhibitory CPM effect was observed in 65.5% of patients with CWAD, 83.3% of patients with CNIP and 92.6% of controls **fMRI resting-state functional connectivity—correlation with CPM effect** *Group difference connections:* 3 connections showed a main effect of group (rsFC was enhanced in amygdala-frontal operculum, amygdala-OFC, pallidum-frontal operculum). Of these, 1 connection (amygdala-frontal operculum) showed a correlation with CPM responses (enhanced rsFC correlated with decreased efficiency of CPM across all patients) *A priori correlations with CPM responses:* No significant findings	Study included other psychophysiological tests as well (including pressure pain thresholds)

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
Harper et al., 2018	15 patients with fibromyalgia (15f, 40.7 ± 10.2) 14 healthy controls (14f, aged 40.7 ± 11.5)	*TS:* noxious pressure (right thumbnail) at 40-50 intensity (NRS 0-100) for 30 seconds *CS:* noxious pressure (left thumbnail) at 40-50 intensity (NRS 0-100) for 60 seconds *CPM paradigm:* TS + CS (parallel), pain ratings every 10 seconds *CPM calculation:* TS_{only} vs TS + CS (3 pain ratings for each)	**Resting-state fMRI** *Seed to whole-brain analysis:* PAG seed derived from VBM analysis *Contrasts:* Correlations with CPM effect across entire sample Correlations with CPM effect separately per group Interaction analysis to compare correlations with CPM effect across groups (in clusters showing different group patterns) *Thresholding:* Whole-brain analyses using cluster-level corrections *FWE-P* < 0.05 (initial threshold *P* < 0.001) Small volume correction in ROIs (pgACC, RVM; 6 mm spheres) at cluster level *FWE-P* < 0.05	**Behavioral CPM effect (outside scanner)** *Controls:* No significant CPM response (but shift towards inhibitory CPM effect over time) *Patients:* Significant (faciliatory) CPM response *Patients vs Controls:* Significant difference at time 3 (but no main effect of group across times) **fMRI resting-state functional connectivity—correlation with CPM effect** *Whole group:* Greater rsFC between the PAG (seed) and left mid insula (whole brain) and pgACC (ROI) was correlated with greater CPM response. *Controls:* Greater rsFC between the PAG (seed) and LC (dPons) was correlated with greater CPM response. *Patients:* No significant correlations *Patients vs controls:* No differences in rsFC of PAG Significant interaction in PAG with RVM/pons (ROI) rsFC correlation with CPM effect (greater PAG rsFC correlated with more inhibition in controls, but with more facilitation in patients)	CPM was assessed within 72 hs prior to neuroimaging. Also performed a VBM analysis, showing difference in GMV in PAG across groups (subsequently took PAG as seed). Also performed mediation analyses.

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
Kisler et al., 2018 *(larger study, same as Argaman et al., 2020)*	39 patients with migraine (32 f, aged 29.5 ± 7.6) 35 healthy volunteers (30 f, aged 27.1 ± 4.6) *(final sample after exclusions)*	*TS*: heat stimulus at left volar forearm (30 seconds at 47°C) *CS*: cold water immersion (right foot, 76 seconds at 9-12°C) *CPM paradigm*: TS + CS (parallel) during scanning *CPM calculation*: TS vs TS + CS *For rs-fMRI*: CPM performed outside of scanner—one week prior to MRI (same procedure)	**fMRI during CPM** *Whole-brain search* *Main effect conditions:* TS_{only} > baseline TS + CS > baseline *CPM effect:* TS + CS > TS_{only} TS + CS < TS_{only} Correlations with behavioral CPM effect *CPM groupings:* Median split on behavioral CPM effect to get a responder and nonresponder group *Thresholding:* $P < 0.05$ FWE-corrected (voxel-level), $k > 10$	**Behavioral CPM effect (in scanner)** *Healthy*: Significant (inhibitory) CPM response in pain ratings *Migraine*: No significant CPM response *(although no group x condition interaction)* **fMRI activation results—TS_{only} vs TS + CS** *Healthy:* *Increased activation* during CPM (TS + CS > TS_{only}) in postcentral gyrus (extending into precentral gyrus, medial frontal, SMA), ITG, precuneus (extending into cuneus, PCC), MTG (extending into angular gyrus), SFG, STG, MFG, parahippocampal gyrus *Reduced deactivation* during CPM in medial frontal/ACC, precuneus/PCC *Migraine:* *Increased activation* during CPM (TS + CS > TS_{only}) in postcentral gyrus (extending into precentral, medial frontal, precuneus), fusiform gyrus (extending into parahippocampal gyrus, cerebellum), MTG, STG, lingual gyrus, parahippocampal gyrus (extending into lingual), precentral gyrus, SFG, cuneus, and hippocampus *Reduced deactivation* during CPM in medial frontal/ACC, precuneus/PCC *Decreased activation* during CPM (TS + CS < TS_{only}) in bilateral thalamus, cerebellum, and IFG	Pain ratings for TS were assessed continuously and then averaged Participants with mean pain ratings of less than 4 for the TS were excluded from the study CPM paradigm was repeated 3 times. Results are mean of all CPM repetitions Participants with TS average rating ≤ 4 were excluded Also included temporal summation of pain (TSOP) procedure Note that behavioral CPM effect is different outside the scanner compared with inside the scanner rsFC correlations with CPM were not tested directly (only group differences in this correlation)

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
				Healthy vs migraine: No group differences in brain activation during CPM; no interaction between group and condition *CPM responder groups:* *Participants were divided into CPM responder and nonresponder groups:* No CPM group × participants group interaction; no main effect of CPM group or participants group **fMRI activation results—correlation** No correlations between behavioral CPM response and brain activation in each group	
Argaman et al., 2020 *(larger study, same as Kisler et al., 2018)*	*From same sample:* 32 patients with migraine (27f, median age 26, 23-44) 23 healthy controls (20f, median age 26, 20-39) *(final sample after exclusions)*		**fMRI during rest** *Group ICA* to identify default mode/DMN, salience/SN, and executive control/ECN network *Seed-based analysis (SBA):* seeds in regions involved in TSOP and/or CPM based on literature (ascending pathway: SI hand, SI face, thalamus, pIns; descending pathway: amygdala, pgACC, aIns, vmPFC, lateral OFC) *Contrasts*: Group differences in rsFC Differences in relationship CPM and rsFC across groups (interaction effect) *Thresholding*: $P < 0.05$ FDR-corrected permutation-based (CDT $P < 0.001$) + additional Bonferroni correction in SBA for # ROIs (8 in ascending, 10 in descending)	**Behavioral CPM effect (outside scanner)** *Healthy.* Significant (inhibitory) CPM response in pain ratings *Migraine*. Significant (inhibitory) CPM response in pain ratings (no group differences in TS_{only}, TS + CS, TS_{only} > TS + CS) **fMRI resting-state functional connectivity—group differences in correlation with CPM effect** *gICA*: no interactions between group and correlation with CPM effect in rsFC of DMN, SN, ECN *SBA*: interaction between group and CPM effect in rsFC pgACC seed with PCC/precuneus; vmPFC seed with PCC/precuneus; aIns seed with angular gyus/AG (last did not survive Bonferoni correction) For controls, greater CPM response was related to greater rsFC of pgACC-PCC and vmPFC-PCC rsFC, and lower aIns-AG rsFC	

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
				For migraineurs, no correlation CPM response and pgACC-PCC, greater CPM response was related to lower vmPFC-PCC rsFC and greater aIns-AG rsFC *(no group main effects were found in either analyses)*	
Nahman-Averbuch et al., 2014	13 healthy volunteers (8 f, aged 25.6 ± 2.8)	*TS*: heat stimuli to lower left leg (30 seconds at 49°C, using thermode) *CS*: cold water immersion (right foot, at 10-12°C for 87 seconds) *CPM paradigm*: TS + CS (parallel) during scanning *CPM calculation*: TS vs TS + CS	**fMRI during CPM** *Whole-brain search* *CPM effect:* TS + CS > TS_{only} *Main effect conditions:* TS_{only} > baseline TS + CS > baseline (presented in figure) *Thresholding:* z > 2.3 and cluster significance threshold of $P < 0.05$	**Behavioral CPM effect (in scanner)** Significant (inhibitory) CPM response in pain ratings **fMRI activation results—TS_{only} vs TS + CS** *Increased deactivation* (reduced activation) during CPM (TS + CS > TS_{only}) in PCC, precuneus, superior parietal lobe, and brainstem (including pons) *Increased activation* during CPM in SII, premotor cortex, IPL, lateral occipital cortex *Reduced deactivations* during CPM in frontal pole, SFG, IFG, SI, STG	CPM paradigm was repeated 3 times. Only the first CPM repetition was analyzed The study also examined offset analgesia (OA) in between the TS_{only} and TS + CS runs
Piché et al., 2009	12 healthy volunteers (10 f, aged 26.7 ± 4.7)	*TS*: electrical stimuli to sural nerve (at 120% of the RIII-reflex threshold)—presented prior and after TS + CS ($TS_{baseline}$ and $TS_{recovery}$, respectively) *CS*: cold water immersion of (contralateral) foot for 2 minutes at 4°C *CPM paradigm*: TS + CS (parallel) during scanning *CPM calculation*: $TS_{baseline}$ vs TS + CS *(for both pain ratings and RIII reflex amplitude)*	**fMRI during CPM** *Main effect conditions:* $TS_{baseline}$ > baseline TS + CS > baseline *CPM effect:* TS + CS > $TS_{baseline}$ Correlation with 2 behavioral CPM effects *Directed ROI search (for TS + CS vs. TS contrast)*, including thalamus, SI, SII, SMA, the anterior and posterior INS, MCC, ACC, the amygdala, PHG, OFC, PFC *Directed ROI search (for correlations with CPM response)*, including PAG, SI, SII, and motor cortex cingulate cortex, anterior insula, entorhinal cortex, OFC, and amygdala *Thresholding:* *p-corr* < 0.05 in search volume (corresponds to *p-uncorr* < 0.0009)	**Behavioral CPM effect (in scanner)** *Pain ratings*: Significant (inhibitory) CPM response *RIII reflex*: No significant CPM response **fMRI activation results—TS_{only} vs TS + CS** *TS + CS > TS_{only}* Reduced activation during CPM in all ROIs: bilateral thalamus, SI, precentral gyrus (PrCG), ACC, MCC, and SMA; left (contralateral SII), pINS, and PFC; and right ipsilateral aINS and parahippocampal gyrus **fMRI activation results—correlation** *Correlations of CPM of pain ratings:* Stronger CPM response correlated with larger decreases (TS + CS > TS_{only}) in contralateral SI, PCC, and amygdala; ipsilateral PFC and OFC; and bilateral ACC and MCC	The study also tested maintenance of CPM during recovery period The study also examined other relationships across activation or connectivity patterns of the different scans (not mentioned in this review) Included 3 control scans (only TS) prior to TS + CS scan to examine habituation

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
			In addition, a more permissive threshold: *p- uncorr* < 0.005	*Correlations with CPM of RIII reflex:* Stronger CPM response correlated with larger decreases in (TS + CS > TS_{only}) contralateral SMA, aINS, PFC, and OFC and bilateral SMA **fMRI functional connectivity—coactivation with seed regions (no contrast TS + CS vs. TS_{only})** *Coactivation with OFC—CPM of pain ratings*: Coactivation between the OFC (seed) and the PCC, ACC, sACC, anterior insula, amygdala, parahippocampal gyrus, mPFC, and OFC *Coactivation with PAG—CPM of RIII reflex*: Coactivation between the PAG (seed) and the SI, paracentral lobule, SMA and pre-SMA, ACC, PCC, parahippocampal gyrus, PFC, thalamus, pons, and RVM	
Song et al., 2006	12 patients with IBS (12 f, aged M ± SE: 23 ± 0.4) 12 healthy volunteers (12 f, aged M ± SE: 23 ± 0.9)	*TS:* rectal distention (inflated to pain detection threshold plus 20% for 30 seconds) *CS*: foot cold water immersion (4°C) for 30 seconds *CPM paradigm*. TS + CS (parallel) during scanning *CPM calculation*. TS_{only} vs TS + CS	**fMRI during CPM** *Whole-brain search* *Main effects condition:* TS_{only} > baseline TS + CS > baseline Separately for both groups. *CPM effect:* TS_{only} > TS + CS TS + CS > TS_{only} Separately for both groups *Thresholding:* Random-effect analysis (group-level) at *P* < 0.001, uncorrected	**Behavioral CPM effect (in scanner)** *Healthy:* Significant (inhibitory) CPM response in pain ratings *IBS:* No significant CPM response **fMRI activation results—TS_{only} vs TS + CS** *Healthy:* *TS_{only} minus TS + CS:* Activations in anterior insula, postcentral gyrus (SII), putamen, inferior frontal gyrus, thalamus. Deactivation in caudate head *TS + CS minus TS_{only}:* Activations in the superior temporal gyrus. Deactivation in parietal lobule (SI) *IBS:* *TS_{only} minus TS + CS:* Activations in inferior frontal gyrus, thalamus. Deactivation in caudate head *TS + CS minus TS_{only}:* Activations in the superior temporal gyrus and inferior parietal lobule Deactivation in the precuneus	Included a sham TS condition too (to examine anticipation) Participants received a cue 1 second prior to the stimuli (same cue for all stimuli; TS, CS + TS, sham TS)

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
Sprenger et al., 2011	20 healthy volunteers (0 f, aged M ± SEM: 25.8 ± 0.1, age is based on initial n = 22)	*TS*: heat stimuli (applied to the left lower arm) at 47.5°C for 10 seconds using thermode *$CS_{painful}$*: cold water immersion (applied to the right leg) at 0°C using ice bags *$CS_{neutral}$*: lukewarm water immersion (applied to right leg) at 25°C using water bags *CPM paradigm*: TS + CS (parallel) during scanning *CPM calculation*: TS + $CS_{neutral}$ vs TS + $CS_{painful}$. Separate for saline and naloxone + contrasting the 2 CPM effects	**fMRI during CPM** *Directed ROI search*, including SI, SII, pACC, sACC, aMCC, insula, OFC, dlPFC, amygdala, thalamus, hypothalamus, midbrain, pons, and medulla *CPM contrast:* TS + $CS_{neutral}$ > TS + $CS_{painful}$ Correlation with behavioral CPM response Separate for saline and naloxone + contrasting the 2 CPM effects/ correlations *PPI analysis*: subgenual ACC (aACC) taken as seed (6 mm sphere on peak voxel of fMRI effect) Both tonic ($CS_{painful}$ vs $CS_{neutral}$) and phasic (TS + $CS_{neutral}$ vs TS + $CS_{painful}$) effects were examined *Thresholding*: small-volume random field approach; $P < 0.05$, FWE-corrected	**Behavioral CPM effect (in scanner)** Significant (inhibitory) CPM response in pain ratings during saline and naloxone Relative reduction of CPM effect during naloxone because of increase in pain rating for $CS_{painful}$ compared with during saline (but formal test not significant) **fMRI activation results—TS + $CS_{neutral}$ vs TS + $CS_{painful}$** *Saline:* *TS + $CS_{neutral}$ > TS + $CS_{painful}$* Reduced activation during CPM in right (contralateral) thalamus, bilateral SII, anterior and posterior insula, aMCC, PCC, bilateral amygdala, and medulla *Naloxone:* Not presented *Saline > Naloxone TS + $CS_{neutral}$ > TS + $CS_{painful}$* Effects observed during saline are reduced during naloxone in SII, amygdala, PAG/midbrain, and OFC **fMRI activation results—correlation** *Saline*: Greater behavioral CPM response was related to greater reduction in activation (TS + $CS_{neutral}$ > TS + $CS_{painful}$) in right thalamus, left insula, dlPFC, dorsal parts of medulla *Naloxone*: Not presented *Saline > Naloxone*: Positive correlations observed during saline are diminished during naloxone in the dlPFC and medulla **fMRI functional connectivity (PPI) - TS + $CS_{neutral}$ vs TS + $CS_{painful}$** *Saline*: Greater functional connectivity between the sACC (seed) and PAG/midbrain, left amygdala, hypothalamus, and medulla during TS + $CS_{painful}$ (compared with TS + $CS_{neutral}$)	Also tested a correlation between brain activation during CS and the CPM response (referred to as tonic changes in brain activation or connectivity)

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
				Naloxone: Not presented *Saline > Naloxone*: These correlations were diminished during naloxone (except for sACC-medulla) **fMRI functional connectivity (PPI)—correlation with CPM effect** *Positive correlation:* Greater functional connectivity between sACC (seed) and PAG/hypothalamus/medulla correlated with greater behavioral CPM responses during saline (but not during naloxone)	
Wilder-Smith et al., 2004	10 healthy volunteers (10 f, age M = 31 years (24-38 y) 10 patients with IBS (5 constipated IBS-C and 5 with diarrhea IBS-D) (10 f, IBS-C age M = 35 y (25-45 y), IBS-D age M = 40 y (24-57 y)	*TS:* rectal distention (inflated to pain detection threshold plus 20% for 48 seconds) *CS:* foot cold water immersion (4°C) *CPM paradigm*: TS + CS (parallel) during scanning *CPM calculation*: TS vs TS + CS	**fMRI during CPM** *ROI analysis (individually delineated)*: S1, M1, amygdala/hippocampus, anterior and posterior cingulum, anterior and posterior insula, PAG, supramarginal gyrus (SII), OFC, inferior dlPFC, superior dlPFC, anterior, posterior, medial, and lateral quadrants of the thalamus, and the occipital visual cortex (control area) *Main effects condition*: TS_{only} > baseline TS + CS > baseline Group differences *Thresholding*: z > 3, Bonferroni correction for # of ROIs (for voxel-based visualization: z > 5)	**Behavioral CPM effect (in scanner)** Significant inhibitory CPM response in healthy controls but not in IBS-C and IBS-D **fMRI activation results ROIs—TS_{only}, TS + CS** *TS_{only} > baseline* *Healthy controls:* activations in bilateral anterior and posterior cingulate, inferior and superior dlPFC, anterior and posterior insula, lateral and medial thalamus, S1, SII; and deactivations in right OFC *IBS-C:* activations in left posterior cingulate, left inferior dlPFC, right anterior insula, left S1, bilateral SII; and deactivations in bilateral OFC and amygdala/hippocampus *IBS-D*: activations in bilateral anterior insula, right anterior and lateral thalamus, bilateral medial thalamus, right SII; and deactivation in left OFC *TS + CS > baseline* *Healthy controlss:* activations in bilateral anterior and posterior cingulate, inferior and superior dlPFC, SI; and deactivations in bilateral anterior insula, left posterior insula, right medial thalamus, and PAG *IBS-C*: activations in right posterior cingulate, bilateral inferior and superior dlPFC, lateral, anterior and medial thalamus, OFC and amygdala/hippocampus	Group differences were also formally tested No comparison between TS_{only} and TS + CS

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
				IBS-D: deactivations in right anterior insula	
Youssef et al. 2016a (NeuroImage) *(larger study, same as Youssef et al., 2016b)*	54 healthy volunteers (32 f, aged M ± SEM: 23.1 ± 0.6)	*TS*: heat stimuli (applied to the lip, at temperature between 44 and 49°C generating pain rating of 6/10 for 15 seconds) using thermode *CS*: injection of 1 mL of hypertonic saline into the right tibialis anterior muscle (lower leg) *CPM paradigm*: TS + CS (parallel) during scanning *CPM calculation*: TS (first 4) vs TS + CS (last 4 stimuli)	**fMRI during CPM** **Brainstem analysis** *Directed ROI search*, including SRD, SpVc and dlPons (spherical, 3 mm radius) *Main effect condition:* TS_{only} > baseline *CPM contrast*: TS_{only} vs TS + CS Separately in the CPM and noCPM group Correlations with behavioral CPM in significant clusters *Thresholding*: Initial $P < 0.001$; then small volume corrections for ROIs ($P < 0.05$)	**Behavioral CPM effect (in scanner)** Overall CPM effects not reported *CPM group*: Significant (inhibitory) CPM effect *noCPM group*: no CPM effect **fMRI activation results brainstem—TS + CS** *CPM group vs noCPM group in TS + CS activation*: Greater activation in noCPM group compared with CPM group in ipsilateral SpVc, PB nucleus (ipsilateral and contralateral), SRD and ipsilateral trigeminal nerve (*visually, TS_{only} > TS + CS in CPM group; but this is not formally tested*) **fMRI activation results brainstem—correlation** *Tested in clusters with CPM vs noCPM group difference*: Positive correlations between behavioral CPM response (reduction in pain) and reductions in brain activation during CPM (TS_{only} > TS + CS) in SRD, SpVc, and PB nucleus	No formal comparison TS_{only} and TS + CS for the CPM effect, but only comparison between CPM and noCPM groups during TS + CS (only comparison with TS_{only} in some follow-up analyses) The study found no difference in activation TS > baseline contrast across CPM and noCPM groups, but did find difference in FC between SRD and right OFC across groups

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	fMRI analysis and reporting	Reported findings	Comments
Youssef et al. 2016b (Human Brain mapping) (*larger study, same as Youssef et al., 2016a)*		*CPM grouping.* If mean TS + CS (first 2/4) < mean + 2 SD TS (first 4) (inhibitory): CPM group (n = 23) If not (no inhibition): noCPM group (n = 31) *CPM ability.* % change in mean pain rating during TS + CS (last 4) with mean of TS (first 4)	**fMRI during CPM** **Whole-brain analysis** *Whole-brain analysis* (using GM mask) *Main effect conditions:* TS > baseline (*p-FDR* < 0.05) CS > baseline (*p-FDR* < 0.05) TS + CS in the CPM and noCPM group (*p-FDR* < 0.05) (in follow-up analyses: TS_{only} vs TS + CS, $P < 0.05$ for *t* test) Correlation CPM ability with brain response to TS + CS (initial $P < 001$, then small volume correction $P <$ 0.05, including clusters in brainstem, medial prefrontal and orbitofrontal) Functional connectivity analysis between SRD and rest of brain; differences in FC are compared across CPM and noCPM group. Post-hoc, TS_{only} vs TS + CS is examined in identified regions	**fMRI activation results cortex—TS + CS** *CPM group vs noCPM group in TS + CS activation.* Greater activation in noCPM group compared with CPM group in SI, SII, MI, insula, dlPFC, dmPFC, posterior insula, MCC, PCC, precuneus, putamen, caudate nucleus, cerebellum, parietal association cortex, amygdala and OFC **fMRI activation results cortex—correlation** *Correlation CPM ability and TS + CS brain activation.* Positive correlations between CPM ability and increases in right SI, SII, dlPFC, amygdala, MCC, PCC, nucleus accumbens, putamen, insula, and OFC, and bilateral parietal association cortex Negative correlations between CPM ability and signal intensity increases in the left mPFC **fMRI functional connectivity brainstem-cortex** *CPM group vs noCPM group in FC during TS + CS.* Greater FC in noCPM compared with CPM group in SRD with insula, dlPFC, dmPFC, MCC, parietal association cortices. Greater FC in CPM group compared with noCPM group in SRD with precuneus and OFC *TS_{only} vs TS + CS in regions with group difference (direction not reported).* In noCPM group: bilateral insula, dlFC, right dmPFC, left parietal association cortex In CPM group: right dmPFC, right parietal association cortex, left OFC	

a/pIns, anterior/posterior insula; ACC, anterior cingulate cortex; AG, angular gyrus; aMCC, anterior MCC; CDT, cluster-defining threshold; CINP, chronic idiopathic neck pain; CPM, conditioned pain modulation; CS, conditioned stimulus; CWAD, chronic whiplash-associated disorders; dlPons, dorsolateral pons; dm/dlPFC, dorsomedial/lateral prefrontal cortex; dmPFC, dorsomedial PFC; DMN, default mode network; ECN, executive control network; f, female; FC, functional connectivity; FDR, false discovery rate; FWE, family-wise error; GM, grey matter; IBS, irritable bowel syndrome; ICA, independent component analysis; IPL, inferior parietal lobe; ITG, inferior temporal gyrus; LC, locus ceruleus; M, mean; MFG, middle frontal gyrus; MI, primary motor cortex; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; NRS, numerical rating scale; OFC, orbitofrontal cortex; PAG, periaqueductal grey; PB, parabrachial nucleus; PCC, posterior cingulate cortex; pgACC, pregenual anterior cingulate cortex; PPT, pressure pain threshold; ROI, region of interest; rsFC, resting-state functional connectivity; RVM, rostral ventral medulla; sACC, subgenual ACC; SD, standard deviation; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; SBA, seed-based analysis; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SN, salience network; SpVc, caudalis subdivision of spinal trigeminal nucleus; SRD, subnucleus reticularis dorsalis; STG, superior temporal gyrus; TS, test stimulus; TSOP, temporal summation of pain; VBM, voxel-based morphometry; vm/vl PFC, ventromedial/lateral prefrontal cortex.

cingulate cortex (PCC), amygdala, ipsilateral PFC, orbitofrontal cortex (OFC), and bilateral ACC and MCC. Greater reductions in RIII amplitude (ie, greater CPM responses) correlated with greater reductions in brain responses (TS + CS > TS_{only}) in contralateral SMA, aINS, PFC, and OFC and bilateral SMA.[44]

A study by Sprenger et al. elaborated on these findings and examined the effect of naloxone, a mu opioid antagonist, on the CPM response in 20 healthy participants. Heat stimuli were used as a TS and cold-water immersion as a painful CS, in addition to a stimulus of lukewarm water immersion, which served as neutral CS. Significant CPM responses were found during both saline and naloxone administration. During saline administration, reductions in brain activation (less activation during TS + $CS_{painful}$ than during TS + $CS_{neutral}$) were found in the contralateral thalamus, bilateral SII, anterior and pINS, amygdala, PCC, anterior MCC, and the medulla. The observed effects were reduced during naloxone in OFC, periaqueductal grey (PAG)/midbrain, SII, and amygdala.[54] The correlation between changes in brain activation during CPM and the CPM response was also examined. A significant positive relationship was found between the CPM responses and changes in brain activation (reductions during TS + $CS_{painful}$ compared with TS + $CS_{neutral}$) in the thalamus, insula, dorsolateral PFC (dlPFC), and dorsal parts of the medulla. It was found that during naloxone, these observed correlations were diminished in the insula, dlPFC, and medulla.[54] Although naloxone did not affect the CPM response, changes in brain activation during CPM were noted, which might indicate some involvement of opioid mechanisms.[54]

Bogdanov et al. also included a painful CS, and a neutral CS, and found no significant changes (increases or decreases) in brain activation during CPM (TS + $CS_{painful}$ > TS + $CS_{neutral}$) in 24 healthy participants. They did identify large variability in CPM responses across participants, with some individuals showing an inhibitory CPM response, while others showed no response or a facilitatory response. This large variability could explain the lack of changes in brain activation. When the CPM responses were correlated with changes in brain activations during CPM, significant correlations were found in the anterior insula/premotor cortex, pINS/SII, lateral OFC, and fusiform gyrus/parahippocampal gyrus.[4]

Another study in 13 healthy volunteers used heat stimuli as TS and cold-water immersion as CS and found reduced brain activation during CPM (ie, less activation during TS + CS than during TS_{only}) in the thalamus and occipital cortex. Increased deactivations (which will also be observed as reduced brain activation, see **Fig. 1**) were observed in the PCC, precuneus, superior parietal lobe, and brainstem (including pons). In contrast, increased activations during TS + CS compared with the TS_{only} were found in the SII, premotor cortex, inferior parietal lobule, and lateral occipital cortex, as well as reduced deactivations in the frontal pole, and superior and IFG, SI, and STG.[37] No correlation analyses with the CPM response were performed. In a later study that used a similar CPM paradigm, brain responses during CPM

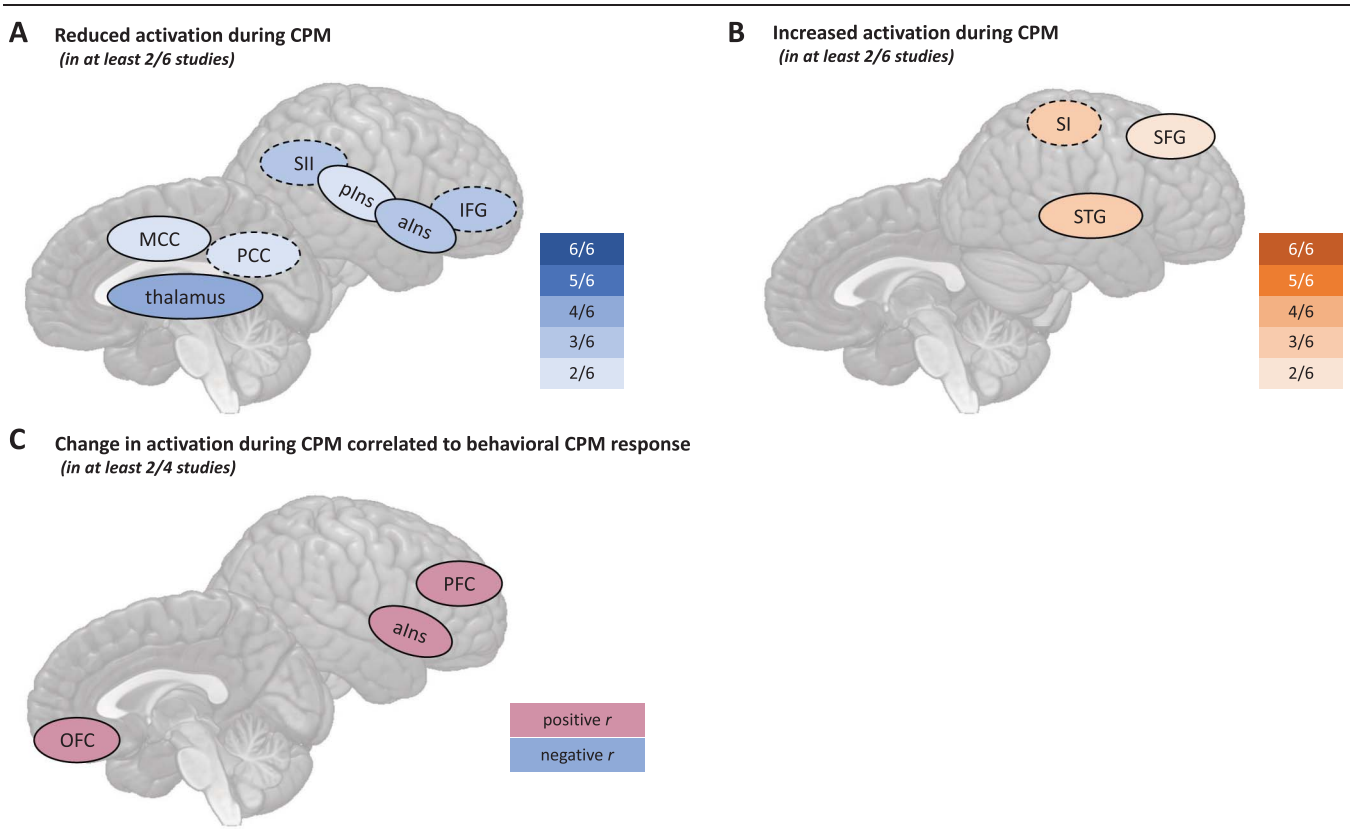

Figure 2. Descriptive overview of brain regions implicated in the conditioned pain modulation effect. Presented are brain regions that were differentially activated when comparing TS + CS with TS_{only} in at least 2 of 6 studies. The color indicates how often a region was reported across studies (the darker, the more often it was observed). (A) Regions showing reduced activations (or increased deactivations) during CPM (ie, less activation to the TS during TS + CS than during TS_{only}). (B) Regions showing increased activation (or reduced deactivations) during CPM. The dotted border lines indicate that both reduced activations as well as increased activations during CPM have been reported across studies, while solid lines indicate that all reported effects point in the same direction. (C) Regions in which there were significant correlations between changes in brain activation during the CPM paradigm and the CPM response. Note that this is a descriptive summary; thus, not the result of a formal meta-analysis. CS, conditioning stimulus; CPM, conditioned pain modulation; TS, test stimulus.

were examined in individuals with migraine (n = 39) as well as healthy participants (n = 35). In healthy participants, an increased activation during TS + CS than during TS_{only} was found in the postcentral gyrus (extending into precentral, SMA, medial frontal), inferior temporal gyrus, medial frontal cortex (extending into ACC), middle temporal gyrus (extending into angular gyrus [AG]), middle and superior frontal gyrus (SFG), STG, and parahippocampal gyrus. In addition, reduced deactivation was observed in the precuneus/PCC and medial frontal cortex/ACC. In participants with migraine, findings were quite similar, including increased activation during CPM (TS + CS > TS_{only}) in postcentral gyrus (extending into precentral, medial frontal), fusiform gyrus (extending into parahippocampal gyrus, cerebellum), middle temporal gyrus, STG, lingual gyrus, and hippocampus. Similarly, there was a reduced deactivation in precuneus/PCC. In addition, there was a decreased activation during CPM (TS_{only} > TS + CS) in the thalamus, cerebellum, and IFG. The groups did not significantly differ in brain activation during CPM. When the CPM responses were included in the model, no correlations were found between the CPM response and brain activations in both groups. In addition, when participants were divided into CPM responder and nonresponder groups, based on their behavioral CPM response, no group differences in brain activations were found either.[21]

3.2.1. In summary

Figure 2 summarizes these findings descriptively by presenting the brain regions that have been observed across the different studies as being involved in the CPM response (n = 6) in healthy participants. The thalamus, MCC, PCC, anterior and pINS, SII, and IFG show reduced activation (ie, either reduced activation or increased deactivation) to the TS during CPM, with the thalamus being the region that is most often reported (in 4/6 studies). In contrast, the SI, SFG, and STG mostly show greater activation (ie, either increased activation or reduced deactivation) during CPM, with the SI and STG being the regions that are observed the most (in 3 of 6 studies). Most studies did not distinguish between the causes for increased/decreased activation, and hence, we could not separate increased activations from reduced deactivations and vice versa. Of note, not all regions showed a consistent pattern across studies, as SI, SII, and PCC showed increases in activation during CPM in some studies but decreases in others. Interestingly, when examining correlations with the CPM responses (performed in n = 4 studies; **Fig. 2C**), the PFC and OFC showed up in addition to the anterior insula (all in 2/4 studies), while these areas were not observed when merely contrasting TS + CS with TS_{only}.

3.3. Other brain activation studies

Other studies did not meet all criteria for this fMRI studies; however, they focused on key areas such as the brainstem and should be mentioned. These studies used a different approach and assessed TS-related brain activation only during TS_{only} and/or during TS + CS but without a formal contrast between TS_{only} and TS + CS (**Table 1**). Thus, these findings are presented separately because they do not represent the CPM response.

In one of the first CPM studies of Wilder-Smith et al. in 2004, TS-related brain activation during TS_{only} and during TS + CS was examined (in multiple ROIs) in 10 patients with IBS and 10 healthy controls. During TS + CS, in healthy controls, the bilateral cingulate (anterior and posterior), prefrontal and postcentral (SI) areas were activated compared with baseline, while the insula (anterior and posterior), right thalamus, and PAG were deactivated compared with baseline. In patients, different patterns emerged with more asymmetry as well as additional activations in OFC and amygdala/hippocampus. During TS_{only}, in healthy controls, bilateral activation was observed in the anterior and posterior cingulate, prefrontal, anterior and pINS, and lateral and medial thalamus, SI, and SII, while deactivations were observed in OFC. In patients, different patterns emerged again, with a lack of activation in several regions and increased deactivations in amygdala/hippocampus.[59] However, as was stated above, no formal comparisons between TS + CS and TS_{only} were provided.

Youssef et al. based their fMRI analysis on the behavioral CPM response. Healthy participants (n = 54) were divided into a CPM group (if they showed a reduction in pain ratings in TS + CS compared with TS_{only}) and a noCPM group (if they did not show a reduction in pain ratings in TS + CS compared with TS_{only}). The brain response to the TS during the TS + CS was compared across these 2 groups. Thus, instead of comparing the TS-related brain activation during the TS + CS vs the TS-related brain activation during the TS_{only}, this analysis focused on brain areas that show different TS-related activation/deactivation only during the TS + CS paradigm across those participants who had a behavioral CPM response vs those who did not and without taking into account potential differences in TS-related brain activation during the TS_{only}. The interpretation is therefore different, and it is more challenging to compare the results to other studies. This analysis also focused only on a small volume, including 3 ROI in the brainstem (ie, caudalis subdivision of spinal trigeminal nucleus/SpVc, dorsolateral pons/dlPons, and the subnucleus reticularis dorsalis (SRD); of which, it should be noted that the latter is not defined in the human brainstem atlas[42]). In the CPM group, reduced TS-related brain activation during the TS + CS paradigm was found in the SpVc, SRD, and parabrachial nucleus (compared with the noCPM group). No differences were found in the PAG or the region of medullary raphe nuclei. In addition, the authors found positive correlations between the behavioral CPM response and brain response to TS + CS in the SRD, SpVc, and parabrachial nucleus.[70]

In a second article, the authors performed a whole-brain analysis on the same data set using a similar approach. During the TS + CS paradigm, the CPM group compared with the noCPM group, demonstrated reduced TS-related brain activation in bilateral SI, insula cortex, precuneus, parietal association cortex, PCC, MCC, cerebellar cortex, putamen and the right caudate nucleus, SII, motor cortex, amygdala, OFC, dorsomedial PFC (dmPFC), and dlPFC. There were no brain areas that showed increases in activation during the TS + CS paradigm in the CPM group compared with the noCPM group. Similar to the previous analysis, correlations between the CPM response and signal intensity changes were also tested. Greater CPM responses correlated with increases in the TS-related brain activation during the TS + CS paradigm in the right SI, SII, dlPFC, amygdala, MCC, PCC, nucleus accumbens, putamen, insula, and OFC, and bilateral parietal association cortex. In addition, greater CPM responses also correlated with TS-related reductions in brain activation during the TS + CS paradigm in the left medial PFC.[69]

Although these studies did not perform a formal comparison between the TS-related brain activation during the TS_{only} and TS + CS paradigms, the findings seem to be roughly in line with the summary of the studies that did perform this contrast—albeit seemingly more extensive. However, because the contrast was

not performed, it is not possible to relate the *change* in brain function to the *change* in pain perception.

3.4. Functional connectivity in relation to conditioned pain modulation

3.4.1. Methodology of assessing functional connectivity in relation to conditioned pain modulation

Functional connectivity examines temporal relationships between different brain areas. FC can be examined during a task to examine if the task changes the temporal relationships between brain areas. A more common approach is to examine FC during rest (resting-state FC [rsFC]). Usually, in rsFC studies, the CPM response is performed outside the scanner and then is correlated with rsFC data.

Only 6 articles (of which 5 are part of previously described studies) have investigated FC in relation to CPM (see **Table 1** for more details). Two studies performed FC analyses of fMRI data acquired during the CPM paradigm: one used psychophysiological interaction/PPI, assessing changes in FC that are specific to a condition such as TS_{only}, in comparison to rest or a different condition such as TS + CS, while the other used a coactivation approach to examine which brain regions are coactivated to specific seed regions that are implicated in the CPM response. In addition, 3 studies did not perform CPM during neuroimaging data acquisition and have instead correlated resting-state fMRI (ie, without a task) with CPM responses assessed at a different time and most likely outside the scanner. Finally, one study examined FC during only the TS + CS paradigm with no calculation of the CPM response (see "Other functional connectivity studies" section).

3.5. Functional connectivity during conditioned pain modulation

As part of a bigger study examining brain activation during CPM with saline or naloxone (described above), Sprenger et al. also examined the FC related to CPM in 20 healthy participants. PPI analyses were conducted, in which TS-related differences in FC between TS + $CS_{painful}$ vs TS + $CS_{neutral}$ were examined. The subgenual ACC (sACC) was tested as the seed region for this analysis to examine if its connection with other brain regions changed based on the condition. Greater FC of the TS during TS + $CS_{painful}$ vs TS + $CS_{neutral}$ was found during the saline condition between sACC and the PAG/midbrain, left amygdala, hypothalamus, and medulla. This connectivity of the sACC was diminished during naloxone (in all regions, except for medulla). Furthermore, the strength of the connectivity between the sACC and the PAG/midbrain, hypothalamus, and medulla positively correlated with the CPM responses during saline but not during naloxone. This indicates that greater connectivity between sACC and these regions during CPM (TS + $CS_{painful}$ vs TS + $CS_{neutral}$) was related to a greater reduction in pain sensitivity in TS + $CS_{painful}$ vs TS + $CS_{neutral}$ paradigms, or greater CPM efficiency.[54]

Also, as part of a bigger study, Piché et al. examined coactivations with seeds that their activations were related to the CPM response. For the CPM of pain perception, the OFC was chosen as a seed because its sustained activity was related to the pain perception analgesia. Coactivations were tested for the CPM paradigm (which included the TS with and without a CS). An individual regression model was built for each participant with all conditions (ie, TSs, CSs) and the OFC time course as a regressor of interest. Of note, there was no explicit contrast with the control paradigm (ie, TS_{only}). Coactivations of the OFC and the PCC, ACC, sACC, aINS, amygdala, parahippocampal gyrus, mPFC, and OFC were found. For the CPM of the RIII reflex, the PAG was chosen as a seed because its sustained activity was related to the RIII inhibition. Coactivations of the PAG and the SI, paracentral lobule, SMA and pre-SMA, ACC, PCC, parahippocampal gyrus, PFC, thalamus, pons, and rostral ventral medulla (RVM) were identified. The lack of involvement of the OFC in the modulation of spinal nociception (RIII reflex) and the lack of involvement of the PAG in the modulation of pain perception suggest distinct neural mechanisms involved in the modulation of pain and spinal nociception and that several modulation mechanisms might be involved in the CPM response.[44]

These FC analyses point toward the involvement of additional brain regions, such as the ACC, OFC, and PAG, and their interaction with areas including brainstem, amygdala, and hypothalamus—regions that did not show robust convergence in brain activation studies but might have a role in the CPM response.

3.6. Resting-state functional connectivity in relation to the conditioned pain modulation response

Other studies assessed the CPM response outside the scanner and correlated it with rsFC. Harper et al. examined CPM response in 15 participants with fibromyalgia and 14 healthy controls. There was no significant CPM response in the healthy group, while a facilitatory CPM response was found in the fibromyalgia patient group (ie, increase in pain sensitivity for TS + CS compared with TS_{only}). Resting-state FC between the PAG (seed, identified in a grey matter [GM] analysis) and the whole brain as well as with specific ROIs (pgACC and RVM) was examined. The authors included all participants together (patients and healthy) in the analysis and found that greater rsFC between the PAG and the left mid insula and pgACC correlated with greater CPM response (ie, greater inhibitory or less facilitatory response). Then, the fibromyalgia and healthy control groups were analyzed separately. In the healthy control group, greater rsFC between the PAG and LC/dPons correlated with greater CPM response. No correlations between PAG rsFC and CPM response were found in the fibromyalgia group. Furthermore, an interaction was found in which greater rsFC between the PAG and RVM/pons was related to greater CPM response (ie, more inhibition) in the healthy control group but with lower CPM response (ie, more facilitation) in the fibromyalgia group. Further analyses showed that in the healthy control group, the correlation between CPM and insula-PAG connectivity was mediated via the PAG connectivity to the LC. On the other hand, in patients, the correlation between CPM and insula-PAG connectivity was mediated via the PAG connectivity to the RVM/pons.[17]

Another rs-fMRI study focused on differences between a migraine group (n = 32) and a healthy control group (n = 23). In particular, the authors examined an interaction effect of whether the relationships between rsFC and CPM responses are different between the groups. In this study, simple relationships between rsFC and CPM were not tested. Both a group independent component analysis as well as a seed-based analysis were performed. SI, insula (anterior and posterior), thalamus, pgACC, vmPFC, amygdala, and lateral OFC were chosen as seeds. No group differences were identified in rsFC in either approach. In the group independent component analysis, no interactions between group and CPM responses were observed in the networks of interest (default mode network, salience network, executive control network). In the seed-based analysis, however, there were significant interactions between the group and CPM. These analyses found that in healthy controls, greater CPM inhibitory responses were related with (1) greater rsFC between right pgACC

and left PCC/precuneus, (2) greater rsFC between right vmPFC and PCC/precuneus, and (3) lower rsFC between left aINS and right AG. In patients with migraine, opposite patterns were found: (1) no significant correlation between CPM response and the pgACC-PCC/precuneus rsFC, (2) greater CPM inhibitory response was related with lower vmPFC-PCC/precuneus rsFC, and (3) greater CPM inhibitory response was related with greater aINS-AG rsFC.[1]

Finally, a study by Coppieters et al. focused on group differences in rsFC between 75 women with chronic neck pain and 32 healthy controls and examined whether these differences are related to CPM responses. The correlations between rsFC and CPM response across the patient group (independent of group differences) were examined. Resting-state FC between the left amygdala and left frontal operculum was stronger in patients compared with healthy controls and was also associated with less efficient CPM responses. No other correlations with CPM responses were observed. Interestingly, the observed effects were strongest in those patients with traumatic origin neck pain. These patients also had more efficient CPM responses.[7]

Because of different focus points, findings across these rsFC studies are quite heterogenous. At first sight, however, findings seem in line with findings of the studies that assessed brain function during the CPM response. It is important to note that studies that examine the relationships between rsFC and the CPM response that is tested on a different day (or same day, outside scanner) only give *indirect* insights into neural mechanisms that correlated with the CPM response. In addition, these studies suggest that different neural mechanisms may underlie CPM capabilities in individuals with chronic pain, although this could be explained by a common third factor as well.

3.7. Other functional connectivity studies

Youssef et al. also studied FC in 54 healthy participants, in addition to examining brain activation during TS + CS (not compared with TS_{only}).[69] The FC of the SRD with all voxels above the brainstem during TS + CS was examined. Then, this FC was compared between the CPM group (participants with an inhibitory CPM response) and the noCPM group (participants who did not have a CPM response). This approach is different from the other FC study, which contrasted within-subjects conditions using PPI analysis, while this study contrasted between subjects. The noCPM group had greater FC between the SRD and the bilateral insula, dlPFC, dmPFC, MCC, and the parietal association cortices compared with the CPM group, whereas the CPM group showed greater FC of SRD with precuneus and OFC compared with the noCPM group. In these identified regions, the authors then post hoc contrasted TS_{only} vs TS + CS and found differential FC between the SRD and the insula, dlPFC, dmPFC, and parietal association cortex in the noCPM group, as well as differential FC between SRD and dmPFC, parietal association cortex, and OFC in the CPM group (ie, direction not reported). Thus, indirectly, these findings imply that SRD connectivity with cortical areas might be involved in the CPM response.

4. Brain structure and conditioned pain modulation

4.1. Methodology of assessing brain structure in relation to conditioned pain modulation

Using MRI, different aspects of brain structure can be assessed. These include assessing GM properties such as density, volume, and thickness, or white matter (WM) properties (eg, using diffusion-weighted imaging), including indices for WM integrity. There were 3 articles (2 studies described above already) that assessed the correlations between these structure brain properties and the CPM response, where CPM is obtained at a different time than the MRI scan (in some cases, even on a separate day). The full details of the studies can be found in **Table 2**.

4.2. Grey matter correlations with the conditioned pain modulation response

Relationships between the CPM response and GM cortical thickness were examined in 14 patients with IBS and 14 healthy controls. The analysis was performed within a mask consisting of predefined ROIs (SI, SII, ACC, Ins, and OFC). In both groups, lower CPM responses were associated with a thicker right lateral OFC.[45]

In another study, relationships between the CPM response and GM volume were examined in 72 patients with chronic neck pain in comparison to 30 healthy controls. Twenty-eight ROIs, including the PCC, lateral PFC, SMG, and the superior parietal cortex, were inspected for correlations with the CPM response. The ROIs were chosen because they presented differences between the groups. No relationships were found between the ROIs GM volumes and the CPM responses in any of the groups.[8] In the same population, the authors performed an analysis of GM cortical thickness also using an ROI-based approach. From the 18 predefined ROIs, only the precuneus showed a group difference, but no correlations between the precuneus thickness and CPM responses were found in any of the groups.[9]

Taken together, studies examining GM have all focused on specific regions. In these regions, only the lateral OFC showed a correlation with CPM responses such that a greater CPM inhibitory effect was related to thinner OFC. Studies examining brain activation during CPM have also identified the OFC as a region showing correlations with the CPM response, such that greater activation of OFC was related to more efficient CPM response. However, other well-studied regions, such as the PCC and PFC, did not show such correlations. Interestingly, all studies examining GM are in female controls, begging the question of how this generalizes to male controls.

4.3. White matter correlations with conditioned pain modulation inhibitory response

As part of a larger study described in the previous section, WM was also examined in patients with chronic neck pain and controls using diffusion tensor imaging. The measures included fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity, all representing indirect (and nonspecific) indices of WM integrity. From the 20 ROIs that were examined, only the cingulum hippocampus and tapetum showed group differences and were therefore subjected to correlation analyses with the CPM response. In patients with chronic whiplash-associated disorder, lower CPM responses (less inhibition) were correlated with increased MD and RD in the left tapetum. These correlations were not present in the other groups of patients with chronic idiopathic neck pain and healthy controls, and no other associations were found between CPM responses and the other measures (ie, FA at the left tapetum; FA, MD, RD at the left cingulum hippocampus).[9]

Table 2

Summary of studies examining brain structure and conditioned pain modulation.

Studies	Sample (f, age M ± SD)	CPM paradigm	sMRI analysis and reporting	Reported findings	Comments
Coppieters *et al.*, 2017 *(larger study, same as Coppieters et al., 2018, 2021)*	37 patients with CWAD (37f, age median 38, 21-59) 35 patients with CINP (35f, age median 36, 19-62) 30 healthy controls (30f, age median 25, 18-62) For GM volume and cortical thickness, n = 12 additional exclusions For WM, n = 3 additional exclusions	*TS*: pressure pain threshold (PPT) at quadriceps muscle of most painful side *CS*: cold water immersion (hand, contralateral side to PPT; at 12 ± 1°C for 120 seconds) *CPM paradigm*: TS + CS (parallel) on a separate day *CPM calculation*: TS_{only} vs TS + CS	**Grey matter volume** *Software*: FreeSurfer *ROI-based*: 28 ROIs (14L, 14R) based on the literature: amygdala and thalamus, caudal ACC, rostral ACC, PCC, rostral middle frontal, medial OFC, lateral OFC, superior parietal, insula, postcentral, precuneus, pars orbitalis IFG, and supramarginal cortex (Desikan atlas) *Thresholding*: $P < 0.01$ considered significant	**Behavioral CPM effect (outside scanner, different day)** In all groups, average CPM effect was inhibitory (but ranging from facilitatory to inhibitory; whether $TS_{only} > TS + CS$ was significant is not reported CPM response was significantly lower in CWAD compared with controls **Correlation GM volume with CPM effect in regions showing group difference** Left PCC, right lateral PFC, left supramarginal cortex, and left superior parietal showed group differences and were further inspected for correlations with CPM No correlation with CPM response was found in any of the groups	Associations tested only for ROI that showed significant group differences Only females were included controls were significantly younger compared with both patient groups T2* images were inspected for lesions (none found)
Coppieters *et al*, 2018 *(larger study, same as Coppieters et al., 2017, 2021)*			**Cortical thickness** *Software*: FreeSurfer *ROI-based:* 18 (9L, 9R) regions based on literature, including caudal ACC, PCC, lateral OFC, superior parietal cortex, postcentral cortex, precuneus, IFG pars orbitalis, parahippocampal cortex and supramarginal cortex (Desikan atlas) MANCOVA including all ROIs **White matter** DTI: FA, MD, AD, and RD *Software*: ExploreDTI *ROI-based*: 20 WM regions/tracts (10L, 10R) Projection fibers: superior cerebellar peduncle, anterior corona radiata, posterior corona radiate, anterior limb of internal capsule, posterior limb of internal capsule Association fibers: cingulum cingulate gyrus, cingulum hippocampus, fornix and stria terminalis Commissural fibers: tapetum and splenium of the corpus callosum *Thresholding*: MANCOVA including all ROIs for each index. Bonferroni correction for 4 indices ($P < 0.0125$)	**Correlation GM cortical thickness with CPM effect in regions showing group difference** Precuneus showed group difference, and was further inspected for correlations with CPM No correlation with CPM response was found in any of the groups **Correlation WM DTI indices with CPM effect in regions showing group difference** Cingulum hippocampus and tapetum showed group differences in FA, MD, and RD and were further inspected for correlations with CPM *CWAD group:* CPM effect was negatively correlated with MD and RD in the left tapetum *CINP group*: no associations were found *controls*: no associations were found	

(*continued on next page*)

Table 2 (*continued*)

Studies	Sample (f, age M ± SD)	CPM paradigm	sMRI analysis and reporting	Reported findings	Comments
Piche et al., 2013	14 patients with IBS (14f, aged 31.6 ± 8.3) 14 controls (14f, aged 29.8 ± 6.9) *(controls are same sample as Piche et al., 2011)*	*TS*: electrical stimuli to sural nerve (at 120% of the RIII-reflex threshold)—presented prior and after TS + CS ($TS_{baseline}$ and $TS_{recovery}$, respectively) *CS*: ice pack to left (contralateral) forearm for 2 minutes *CPM paradigm*. TS + CS (parallel) outside of scanner, same day *CPM calculation*. $TS_{baseline}$ vs TS + CS	**GM cortical thickness** *Software*. FreeSurfer *Directed search*: vertex-wise analysis in a ROI mask (ROIs based on the literature: SI, SII, ACC, INS, and OFC; parcellation atlas) *Thresholding*. cluster-wise correction to $P < 0.05$ using Monte Carlo simulations (CDT: $P < 0.001$)	**Behavioral CPM effect (outside scanner, same day)** *controls*: significant (inhibitory) CPM effect *Patients*: no significant CPM effect **Correlation GM cortical thickness with CPM effect in** a priori **ROIs** When accounting for group, lower CPM effect (facilitation) was correlated with thicker cortex in the right lateral OFC (present in both patients and controls)	Also investigated modulation of anxiety ratings by CPM (and find increased anxiety during TS + CS in patients compared with TS_{only} but no difference in controls)

ACC, anterior cingulate cortex; AD, axial diffusivity; CDT, cluster-defining threshold; CINP, chronic idiopathic neck pain; CPM, conditioned pain modulation; CS, conditioned stimulus; CWAD, chronic whiplash-associated disorders; DTI, diffusion tensor imaging; f, female; FA, fractional anisotropy; GM, grey matter; IBS, irritable bowel syndrome; IFG, inferior frontal gyrus; INS, insula; M, mean; MD, mean diffusivity; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PPT, pressure pain threshold; RD, radial diffusivity; ROI, region of interest; SD, standard deviation; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; sMRI, structural MRI; TS, test stimulus; WM, white matter.

5. Discussion

This review summarizes the approaches and results of studies that examined the neural mechanisms related to spatial filtering of nociceptive information using the CPM paradigm in humans. Most of the studies have focused on healthy participants and aimed to identify brain activations during the CPM response. This allowed us to aggregate results across studies and to identify the most common brain areas that show increases/decreases in activation during the CPM response. On a group level, the most consistent findings were reduced activations in the thalamus and insula and increased activation in STG during the TS obtained in the TS + CS condition compared with TS_{only} condition. In addition, on an individual level, changes in activation in the anterior insula and frontal regions (PFC and OFC) were related to the efficiency of the CPM response. Other studies examined relationships between the CPM responses and functional or structural properties of the brain. These studies mainly used ROI analyses, and thus, the results are dependent on the chosen ROIs. Overall, these studies found relationships between the CPM responses and both FC (during rest or during the CPM response) as well as brain structure. Some of the relationships involved brain areas, which were also found in the brain activation studies, such as the insula and the OFC. Other brain regions such as the ACC and brainstem were found only in the connectivity/structure analyses and might be related directly or indirectly to the ability to engage inhibitory pain mechanisms activated during the CPM paradigm.

5.1. Neuroimaging as a tool to advance the understanding of the conditioned pain modulation mechanisms

The underlying mechanisms of spatial filtering of nociceptive information are not clear yet. However, it may involve several inhibitory pain modulation mechanisms such as DNIC, local spinal inhibition independent of descending inhibition, brain-related mechanisms of cognitive-attention modulation or pain distraction, pain habituation, or, more likely, a combination of these mechanisms. Neuroimaging studies could assist in identifying the mechanisms involved in the modulation and might allow distinguishing between these mechanisms. For example, distinct brain networks were found to be related to modulation of pain perception and modulation of spinal nociception (measured by the RIII reflex).[44] However, behavioral studies cannot make conclusions on specific inhibitory mechanisms and need to consider all potential inhibitory pain modulation mechanisms mentioned above.

The insula, thalamus, and SII showed a greater reduction in activation during the TS + CS compared with the TS alone. The thalamus is a relay station for somatosensory and nociceptive information.[68] The thalamus is also part of the salience network, which also includes the anterior insula and MCC. This network is involved in identifying stimuli and guiding behavior in response to these stimuli.[31,49] The SII region receives information from the thalamus and insula and is involved in somatosensory processing.[6,15,58] Because these brain regions are involved in nociceptive processing and salience, the reduction in the activation of these areas during the CPM response may indicate that lower nociceptive input reaches supraspinal areas and point toward spinal inhibition. Interestingly, during a "pain inhibits pain" paradigm in animals with transected spinal cord, inhibition of the TS-related activity (during TS + CS) in the dorsal horn neurons was still observed.[5,47] This indicates that spinal inhibitory processes (independent of supraspinal processes) can inhibit

responses to noxious stimuli and hence reduce the nociceptive information that reaches the brain from the TS when paired with a CS. Taken together, spinal inhibition can be the explanation for the reduction in activation in nociceptive processing regions during CPM. Reduced activations in the brainstem, however, were not consistently reported, possibly bcause of the difficulty in assessing this region.

An interesting finding of this review is the consistency of increased activation of the STG during the CPM paradigm. Although this area is not one of the classic pain areas, the STG is involved in spatial processing. It receives polysensory input, is involved in visual, auditory, and sensory processing and could be the site for multimodal sensory convergence.[19] In addition, a role of the STG in spatial neglect or the neglect syndrome was also found.[20] Also, in healthy participants, inhibition of the STG using rTMS resulted in difficulties attending to stimuli on the contralateral side[51] (ie, similar to what patients with neglect encounter on the side contralateral to their lesion). Although speculative, the finding that STG engaged during CPM may indicate that its role also extends to spatial processing of somatosensory, noxious stimuli.

This review also noted associations between activations in frontal regions (ie, OFC and PFC) and the CPM responses. Attention modulation might be, in some capacity, involved in the CPM response and can explain these findings. Increased activation in frontal areas and reduction in activations in the ACC, insula, and thalamus is typically found during distraction tasks.[3,29,43,48,50] Previous studies reported that when combining CPM and distraction paradigms, the resulting inhibitory pain response was greater than the inhibitory response from CPM only,[22,33] suggesting an additive effect of attention modulation on the CPM response. A comparison of brain activation during CPM vs distraction has been conducted using electroencephalography (EEG) with source localization. During pain distraction and compared with CPM, a greater increase in frontal and temporal areas, including the OFC and dlPFC and medial temporal gyrus was found.[33] On the other hand, other studies suggested a minor involvement of cognitive mechanisms of attention modulation in the CPM response,[55] and modulation of pain sensitivity by the Stroop test was found even in participants with no inhibitory CPM response.[18] Taken together, the correlation between activation of frontal regions and the CPM response may indicate a role for higher-order cognitive processes, such as distraction, in explaining individual differences in CPM responses.

Only one study assessed FC during CPM. Although more research is needed, this study pointed toward additional involvement of brain regions such as the ACC and its interaction with areas, including the brainstem, amygdala, and hypothalamus. These regions did not show robust convergence in brain activation studies but may still be important parts of the involved circuitry.

5.2. Limitations and considerations related to neuroimaging and conditioned pain modulation

There are several challenges related to acquiring and analyzing neuroimaging data and CPM. One of the main challenges is the lack of consistency in the CPM methodology. Different CPM paradigms use different stimulus modalities, measures, intensities, and locations and evoke different inhibitory responses that do not necessarily correlate with each other.[36,39,52] Because of MRI restrictions, it may not be feasible to test all types of stimuli and all body locations. In addition, it might be preferable to use heterotopic and heterosegmental locations, as was done in most, but not all of the included studies (eg, by stimulating the arm/hand and leg/foot) because it could reduce the involvement of spinal segmental mechanisms, allowing for better identification of cortical and brainstem-related mechanisms.

Also, there are different approaches for analyzing fMRI data, which are even on top of the wide variety of preprocessing and denoising pipelines. Most of the fMRI studies in this review assessed changes in the whole brain. Some studies used an ROI approach in which the analysis is focused on only one or several predefined areas. Focusing on specific areas (vs. whole-brain analysis) reduces the number of voxels that are being tested and the correction for multiple comparisons (although they are still needed). Also, different ways of thresholding the statistical maps are used (eg, no corrections, small volume corrections, cluster-level approaches), which may also introduce variation across studies. A basic understanding of neuroimaging analysis can be helpful for readers to evaluate neuroimaging studies (see review[32]). Another issue relates to imaging the brainstem. Brainstem areas may be important in pain modulation, however, neuroimaging these nuclei is more challenging. The neuroimaging sequences and analyses (eg, spatial alignment, smoothing) that may be appropriate for cortical and subcortical areas have limitations regarding imaging the relatively small brainstem nuclei. Higher-resolutions (eg, 1 mm^3 voxels) voxel-based correction for multiple comparisons and nonparametric approaches are favored for neuroimaging the brainstem.[40] In addition, higher noise because of chest motion and cardiac and respiratory pulsation can also affect the MRI signal in the brainstem.[40] Furthermore, some nuclei, such as the SRD, are defined in animals[56,57] but not in the human brainstem atlas.[42] Thus, caution is needed when interpreting results on brainstem nuclei, especially when the acquisitions and processing were not designed specifically for the brainstem.

It is important to note that when acquiring neuroimaging data during TS + CS, it is extremely challenging to differentiate between the TS-related activations and CS-related activations. A sequential CPM paradigm, in which the TS_{only} is introduced after the CS can avoid this problem. However, a sequential CPM paradigm might evoke a smaller CPM response compared with a parallel CPM paradigm in which the TS is delivered together with the CS.[35]

Another major issue concerns the interpretation of effects. To interpret the observed activations/deactivations, it is important to report main effects of conditions (eg, TS_{only} > baseline, TS + CS > baseline) in addition to the contrast across conditions (eg, TS + CS > TS_{only}). This will allow distinguishing reductions in activations from increases in deactivations and increased activations from reduced deactivations. In many of the included articles, the condition-level effects were missing, and hence, it was unclear how a certain positively or negatively signed difference came about. Ultimately, reporting such information in a more complete manner will increase the level of understanding of the results and will furthermore allow meta-analytic approaches.

In addition, while results of brain activation during the CPM paradigm indicate areas that may be involved in the CPM response, the results of the correlations between CPM responses (assessed outside the scanner) and brain structure and function indicate areas that are related to inhibitory pain mechanisms of the CPM paradigm. Although these approaches examine different questions, the findings of the correlation studies generally agreed with the results of studies assessing fMRI during CPM, indicating the involvement of the OFC, ACC, insula, and amygdala. Thus, the observed correlations may indicate that

these parameters are somehow involved in pain modulation and contribute to CPM capabilities. However, these analyses assessed correlations and not causations, and thus, interpretation of the results should be done with care.

This review summarizes the current knowledge on neural activation and correlates related to spatial filtering of nociceptive information tested using the CPM response. As can be seen in **Table 1**, many studies had a small sample size of less than 30 participants, and in some studies, even less than 15 participants were included. Thus, these results might not be reproducible.[30] Moreover, acquiring fMRI data during CPM may be quite challenging and involve the application of 2 noxious stimuli, and thus, only a few studies have been published. Because of the small number of studies and lack of access to raw data, a meta-analysis of the data was not possible. Hence, our conclusions are based on the number or % of articles that found specific activation/correlations in relation to the CPM response.

5.3. Future directions

Conditioned pain modulation has become a common psychophysical test to examine pain modulation capabilities related to spatial filtering of nociceptive information. Conditioned pain modulation is wildly used to elucidate mechanisms of chronic pain or to predict clinical outcomes. For the understanding of the neural mechanisms underlying the CPM response, there is a need for studies focusing on (1) different populations such as healthy pediatric and geriatric populations and patients with chronic pain; (2) using manipulations to better distinguish between potential mechanisms such as pain adaptation and distraction; and (3) imaging of spinal cord and brainstem areas to better identify the involvement of these structures. A better understanding of the CPM response and what is being assessed is required for drawing educated conclusions and for the development of pain interventions.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. IT is supported by the European Union's Horizon 2020 research and innovation programme (Marie Skłodowska-Curie Action, grant agreement # 841426).

Article history:
Received 18 December 2021
Received in revised form 30 March 2022
Accepted 25 April 2022
Available online 13 June 2022

References

[1] Argaman Y, Kisler LB, Granovsky Y, Coghill RC, Sprecher E, Manor D, Weissman-Fogel I. The endogenous analgesia signature in the resting brain of healthy adults and migraineurs. J Pain 2020;21:905–18.
[2] Bannister K, Kucharczyk MW, Graven-Nielsen T, Porreca F. Introducing descending control of nociception: a measure of diffuse noxious inhibitory controls in conscious animals. PAIN 2021;162:1957–59.
[3] Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. Brain 2002;125:310–19.
[4] Bogdanov VB, Vigano A, Noirhomme Q, Bogdanova OV, Guy N, Laureys S, Renshaw PF, Dallel R, Phillips C, Schoenen J. Cerebral responses and role of the prefrontal cortex in conditioned pain modulation: an fMRI study in healthy subjects. Behav Brain Res 2015;281:187–98.
[5] Cadden SW, Villanueva L, Chitour D, Le Bars D. Depression of activities of dorsal horn convergent neurones by propriospinal mechanisms triggered by noxious inputs; comparison with diffuse noxious inhibitory controls (DNIC). Brain Res 1983;275:1–11.
[6] Coghill RC. The distributed nociceptive system: a framework for understanding pain. Trends Neurosci 2020;43:780–94.
[7] Coppieters I, Cagnie B, De Pauw R, Meeus M, Timmers I. Enhanced amygdala-frontal operculum functional connectivity during rest in women with chronic neck pain: associations with impaired conditioned pain modulation. Neuroimage Clin 2021;30:102638.
[8] Coppieters I, De Pauw R, Caeyenberghs K, Danneels L, Kregel J, Pattyn A, Meeus M, Cagnie B. Decreased regional grey matter volume in women with chronic whiplash-associated disorders: relationships with cognitive deficits and disturbed pain processing. Pain Physician 2017;20: E1025–e1051.
[9] Coppieters I, De Pauw R, Caeyenberghs K, Lenoir D, DeBlaere K, Genbrugge E, Meeus M, Cagnie B. Differences in white matter structure and cortical thickness between patients with traumatic and idiopathic chronic neck pain: associations with cognition and pain modulation?. Hum Brain Mapp 2018;39:1721–42.
[10] Damien J, Colloca L, Bellei-Rodriguez CE, Marchand S. Pain modulation: from conditioned pain modulation to placebo and nocebo effects in experimental and clinical pain. Int Rev Neurobiol 2018;139:255–96.
[11] De Broucker T, Cesaro P, Willer JC, Le Bars D. Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. Brain 1990;113 ( ):1223–34.
[12] Do ATL, Enax-Krumova EK, Özgül Ö, Eitner LB, Heba S, Tegenthoff M, Maier C, Höffken O. Distraction by a cognitive task has a higher impact on electrophysiological measures compared with conditioned pain modulation. BMC Neurosci 2020;21:53.
[13] Edwards RR, Dolman AJ, Martel MO, Finan PH, Lazaridou A, Cornelius M, Wasan AD. Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. BMC Musculoskelet Disord 2016;17:284.
[14] Eitner L, Özgül Ö S, Enax-Krumova EK, Vollert J, Maier C, Höffken O. Conditioned pain modulation using painful cutaneous electrical stimulation or simply habituation?. Eur J Pain 2018;22:1281–90.
[15] Friedman DP, Murray EA. Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. J Comp Neurol 1986;252:348–73.
[16] Grosen K, Vase L, Pilegaard HK, Pfeiffer-Jensen M, Drewes AM. Conditioned pain modulation and situational pain catastrophizing as preoperative predictors of pain following chest wall surgery: a prospective observational cohort study. PLoS One 2014;9:e90185.
[17] Harper DE, Ichesco E, Schrepf A, Hampson JP, Clauw DJ, Schmidt-Wilcke T, Harris RE, Harte SE. Resting functional connectivity of the periaqueductal gray is associated with normal inhibition and pathological facilitation in conditioned pain modulation. J Pain 2018;19: 635.e631–635.e615.
[18] Hoegh M, Seminowicz DA, Graven-Nielsen T. Delayed effects of attention on pain sensitivity and conditioned pain modulation. Eur J pain (London, England) 2019;23:1850–62.
[19] Karnath HO. New insights into the functions of the superior temporal cortex. Nat Rev Neurosci 2001;2:568–76.
[20] Karnath HO, Ferber S, Himmelbach M. Spatial awareness is a function of the temporal not the posterior parietal lobe. Nature 2001;411:950–3.
[21] Kisler LB, Granovsky Y, Coghill RC, Sprecher E, Manor D, Yarnitsky D, Weissman-Fogel I. Do patients with interictal migraine modulate pain differently from healthy controls? A psychophysical and brain imaging study. PAIN 2018;159:2667–77.
[22] Ladouceur A, Tessier J, Provencher B, Rainville P, Piché M. Top-down attentional modulation of analgesia induced by heterotopic noxious counterstimulation. PAIN 2012;153:1755–62.
[23] Le Bars D, Chitour D. Do convergent neurones in the spinal dorsal horn discriminate nociceptive from non-nociceptive information?. PAIN 1983; 17:1–19.
[24] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. PAIN 1979;6:283–304.
[25] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. PAIN 1979;6:305–27.

[26] Le Bars D, Villanueva L, Bouhassira D, Willer JC. Diffuse noxious inhibitory controls (DNIC) in animals and in man. Patol Fiziol Eksp Ter 1992:55–65.
[27] Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. J Pain 2012;13:936–44.
[28] Lockwood S, Dickenson AH. What goes up must come down: insights from studies on descending controls acting on spinal pain processing. J Neural Transm (Vienna) 2020;127:541–9.
[29] Loose R, Kaufmann C, Tucha O, Auer DP, Lange KW. Neural networks of response shifting: influence of task speed and stimulus material. Brain Res 2006;1090:146–55.
[30] Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, Donohue MR, Foran W, Miller RL, Hendrickson TJ, Malone SM, Kandala S, Feczko E, Miranda-Dominguez O, Graham AM, Earl EA, Perrone AJ, Cordova M, Doyle O, Moore LA, Conan GM, Uriarte J, Snider K, Lynch BJ, Wilgenbusch JC, Pengo T, Tam A, Chen J, Newbold DJ, Zheng A, Seider NA, Van AN, Metoki A, Chauvin RJ, Laumann TO, Greene DJ, Petersen SE, Garavan H, Thompson WK, Nichols TE, Yeo BTT, Barch DM, Luna B, Fair DA, Dosenbach NUF. Reproducible brain-wide association studies require thousands of individuals. Nature 2022; 603:654–60.
[31] Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct 2010;214:655–67.
[32] Moayedi M, Salomons TV, Atlas LY. Pain neuroimaging in humans: a primer for beginners and non-imagers. J Pain 2018;19:961.e1–961.e21.
[33] Moont R, Crispel Y, Lev R, Pud D, Yarnitsky D. Temporal changes in cortical activation during distraction from pain: a comparative LORETA study with conditioned pain modulation. Brain Res 2012;1435:105–17.
[34] Moont R, Pud D, Sprecher E, Sharvit G, Yarnitsky D. "Pain inhibits pain" mechanisms: is pain modulation simply due to distraction? PAIN 2010; 150:113–20.
[35] Nahman-Averbuch H, Granovsky Y, Coghill RC, Yarnitsky D, Sprecher E, Weissman-Fogel I. Waning of "conditioned pain modulation": a novel expression of subtle pronociception in migraine. Headache 2013;53:1104–15.
[36] Nahman-Averbuch H, Leon E, Hunter BM, Ding L, Hershey AD, Powers SW, King CD, Coghill RC. Increased pain sensitivity but normal pain modulation in adolescents with migraine. PAIN 2019;160:1019–28.
[37] Nahman-Averbuch H, Martucci KT, Granovsky Y, Weissman-Fogel I, Yarnitsky D, Coghill RC. Distinct brain mechanisms support spatial vs temporal filtering of nociceptive information. PAIN 2014;155:2491–501.
[38] Nahman-Averbuch H, Schneider VJ, 2nd, Chamberlin LA, Kroon Van Diest AM, Peugh JL, Lee GR, Radhakrishnan R, Hershey AD, Powers SW, Coghill RC, King CD. Identification of neural and psychophysical predictors of headache reduction after cognitive behavioral therapy in adolescents with migraine. PAIN 2021;162:372–81.
[39] Nahman-Averbuch H, Yarnitsky D, Granovsky G, Gerber E, Dagul P, Granot M. The role of stimulation parameters on 'conditioned pain modulation' response. Scand J Pain 2013;4:10–14.
[40] Napadow V, Sclocco R, Henderson LA. Brainstem neuroimaging of nociception and pain circuitries. Pain Rep 2019;4:e745.
[41] Parsons CM, Goetzi FR. Effect of induce pain on pain threshold. Proc Soc Exp Biol Med 1945;60:327–9.
[42] Paxinos G, Huang X-F Atlas of the Human Brainstem. Academic Press, Sydney 1995.
[43] Petrovic P, Petersson KM, Ghatan PH, Stone-Elander S, Ingvar M. Pain-related cerebral activation is altered by a distracting cognitive task. PAIN 2000;85:19–30.
[44] Piche M, Arsenault M, Rainville P. Cerebral and cerebrospinal processes underlying counterirritation analgesia. J Neurosci 2009;29:14236–46.
[45] Piche M, Chen JI, Roy M, Poitras P, Bouin M, Rainville P. Thicker posterior insula is associated with disease duration in women with irritable bowel syndrome (IBS) whereas thicker orbitofrontal cortex predicts reduced pain inhibition in both IBS patients and controls. J Pain 2013;14:1217–26.
[46] Roby-Brami A, Bussel B, Willer JC, Le Bars D. An electrophysiological investigation into the pain-relieving effects of heterotopic nociceptive stimuli. Probable involvement of a supraspinal loop. Brain 1987;110 ( ):1497–508.
[47] Sandkühler J, Stelzer B, Fu QG. Characteristics of propriospinal modulation of nociceptive lumbar spinal dorsal horn neurons in the cat. Neuroscience 1993;54:957–67.
[48] Schulz E, Stankewitz A, Witkovský V, Winkler AM, Tracey I. Strategy-dependent modulation of cortical pain circuits for the attenuation of pain. Cortex 2019;113:255–66.
[49] Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349–56.
[50] Seminowicz DA, Davis KD. Interactions of pain intensity and cognitive load: the brain stays on task. Cereb Cortex (New York, NY: 1991) 2007; 17:1412–22.
[51] Shah-Basak PP, Chen P, Caulfield K, Medina J, Hamilton RH. The role of the right superior temporal gyrus in stimulus-centered spatial processing. Neuropsychologia 2018;113:6–13.
[52] Smith A, Pedler A. Conditioned pain modulation is affected by occlusion cuff conditioning stimulus intensity, but not duration. Eur J Pain 2018;22: 94–102.
[53] Song GH, Venkatraman V, Ho KY, Chee MW, Yeoh KG, Wilder-Smith CH. Cortical effects of anticipation and endogenous modulation of visceral pain assessed by functional brain MRI in irritable bowel syndrome patients and healthy controls. PAIN 2006;126:79–90.
[54] Sprenger C, Bingel U, Buchel C. Treating pain with pain: supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimulation. PAIN 2011;152:428–39.
[55] van Wijk G, Veldhuijzen DS. Perspective on diffuse noxious inhibitory controls as a model of endogenous pain modulation in clinical pain syndromes. The J pain 2010;11:408–19.
[56] Villanueva L, Bouhassira D, Bing Z, Le Bars D. Convergence of heterotopic nociceptive information onto subnucleus reticularis dorsalis neurons in the rat medulla. J Neurophysiol 1988;60:980–1009.
[57] Villanueva L, Cliffer KD, Sorkin LS, Le Bars D, Willis WD, Jr. Convergence of heterotopic nociceptive information onto neurons of caudal medullary reticular formation in monkey (Macaca fascicularis). J Neurophysiol 1990; 63:1118–27.
[58] Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med 2013;368: 1388–97.
[59] Wilder-Smith CH, Schindler D, Lovblad K, Redmond SM, Nirkko A. Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. Gut 2004;53:1595–601.
[60] Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 2010;23:611–15.
[61] Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. PAIN 2015;156(Suppl 1):S24–31.
[62] Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC testing. Eur J Pain 2010;14:339.
[63] Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. PAIN 2008;138:22–8.
[64] Yarnitsky D, Dodick DW, Grosberg BM, Burstein R, Ironi A, Harris D, Lin T, Silberstein SD. Remote electrical neuromodulation (ren) relieves acute migraine: a randomized, double-blind, placebo-controlled, multicenter trial. Headache 2019;59:1240–52.
[65] Yarnitsky D, Granot M, Granovsky Y. Pain modulation profile and pain therapy: between pro- and antinociception. PAIN 2014;155:663–5.
[66] Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. PAIN 2012;153:1193–8.
[67] Yarnitsky D, Volokh L, Ironi A, Weller B, Shor M, Shifrin A, Granovsky Y. Nonpainful remote electrical stimulation alleviates episodic migraine pain. Neurology 2017;88:1250–5.
[68] Yen CT, Lu PL. Thalamus and pain. Acta Anaesthesiol Taiwan 2013;51: 73–80.
[69] Youssef AM, Macefield VG, Henderson LA. Cortical influences on brainstem circuitry responsible for conditioned pain modulation in humans. Hum Brain Mapp 2016;37:2630–44.
[70] Youssef AM, Macefield VG, Henderson LA. Pain inhibits pain; human brainstem mechanisms. Neuroimage 2016;124:54–62.