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The effects of different types of pain modulation on social emotions and behaviour—a systematic literature review

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Abstract

Changes to one's pain processing system through external or cognitive influences may influence how we interact with other people. To investigate the causal effects of different pain modulations on social emotions and behaviour, we conducted a pre-registered PRISMA-guided systematic literature review. Our main aim was to investigate how directly or indirectly interfering with pain perception through (psycho)pharmacological manipulations affects our abilities to perceive, process, and react to positive and negative emotions (including pain) in other individuals. We included and synthesized 50 of 2060 screened studies. Included studies investigated the effects of opioids, opioid antagonists, acetaminophen, capsaicin, cannabinoids, ketamine, alcohol, placebo analgesia, and hypnotic analgesia. Overall risk of bias was low in 23, medium in 12, and high in 14 studies, while only 24% of studies checked whether their employed manipulation reduced first-hand pain (which it did in all of these). In summary, studies report inconsistent results, with findings generally showing small effects in both directions, ie, an increase or decrease of social emotions or abilities. The strongest and most consistent effect was observed for placebo analgesia decreasing empathy for pain. These results can be attributed to study heterogeneity, pharmacological effects, modes of action, as well as dosage differences. This review thus shows that we are far away from understanding the intricacies of different (psycho)pharmacological pain manipulations and their effects on social emotions and behaviour. To advance as a field and better understand the mechanisms of this interplay, we need well-powered studies, large-scale replications, and systematic meta-analyses.

Keywords: Pain modulation, Placebo analgesia, Nocebo hyperalgesia, Opioid, Prosocial behaviour, Empathy, Emotion recognition

1. Introduction

Pain is a fundamental sensory and affective experience, but also a deeply social one. Observing others in pain strongly shapes how we perceive, evaluate, and respond to our social environment, and appropriate reactions to others' suffering are a cornerstone of human interaction.[36,45,68,78] A growing body of work suggests that how we process our own pain is intricately linked to how we understand and respond to the emotions of others. As such, pain represents an ideal model for studying the interplay between first-hand affective experiences and social cognition. The notion that pain and social cognition are closely intertwined is built on a long tradition of research in social and affective neuroscience, with early imaging work demonstrating that observing others in pain engages parts of the same affective network that underlies the first-hand experience of pain.[35,68] Such findings are in line with simulation and shared representation theories of empathy,[13,20] which propose that understanding others' emotions relies on partial reactivation of one's own affective states. The present review builds on these theoretical origins by examining whether modulating personal pain processing and perception can alter this simulation-based understanding of others.

Social cognition encompasses distinct but interrelated processes, including emotion recognition (the perceptual identification of others' emotional states), empathy (the affective and cognitive sharing of those states, including empathy for pain and other emotions), and prosocial behavior (the decision to act in ways that benefit others).[12,25] These domains rely on partly different psychological and neural systems: While emotion recognition is often rapid and automatic, prosocial behavior involves deliberation and motivational control. Different outcome measures—ranging from recognition accuracy to empathy ratings or helping behavior—thus reflect complementary levels of a broader construct. Notably, many of these measures can be conceptualized within the framework of signal detection theory,[24] which distinguishes sensitivity to emotional cues from response tendencies or biases. This perspective helps interpret how pain

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manipulation alters perceptual and evaluative thresholds in social contexts.

The perception–action model (PAM) of empathy[76] provides a useful framework for understanding how pain ties into these processes. According to the PAM, perceiving another's emotional or sensory state automatically activates corresponding representations in the observer—an internal simulation that enables empathic understanding. These shared representations bridge self and other: When attention is directed to another's state, the observer's sensory, motor, and affective systems are partially reactivated, creating an embodied understanding of the other's experience. This reactivation is typically not consciously felt as one's own pain, but rather reflects a proximate mechanism linking self-related and social processes.

The PAM is often illustrated as a set of *Russian dolls*, insofar as complex forms of social cognition build upon simpler, evolutionarily conserved layers. At the core of the model are automatic perception–action couplings such as emotional contagion or mimicry, which can be extended and regulated into empathic concern, perspective-taking, and prosocial motivation. The strength of these shared self-other representations varies with attention, experience, motivation, and bodily state, allowing for both amplification or inhibition, depending on the context.

Pain provides an especially powerful context for examining these mechanisms. Self-experienced and observed pain engage overlapping affective and motivational components, suggesting that modulating one's own pain processing should influence how social information is perceived, evaluated, and acted upon. Experimental pain manipulations therefore offer a unique window into the coupling between bodily and social processes—revealing how changes in one's own affective state can shape one's perception and understanding of others.

Indeed, empirical evidence supports this link, with pain-modulating interventions such as placebo analgesia or acetaminophen having been shown to influence empathy for pain in others and related social outcomes.[28,55,65] These effects emerge across modalities, from behavior to event-related potentials,[63] functional magnetic resonance imaging (fMRI) responses,[65] and neurochemical markers.[63] Some findings even extend beyond pain-related contexts. For instance, placebo analgesia was found to affect the empathic experience of unpleasant touch,[66] and acetaminophen was reported to reduce positive empathic feelings.[54] While together, these studies suggest that the systems underlying pain and social cognition are closely intertwined, the evidence remains fragmented. Different studies emphasize distinct outcomes without consistently situating them within a unifying theoretical framework, rendering it difficult to assess the broader implications. Moreover, previous reviews have addressed related questions—such as emotional awareness in chronic pain[51] or the role of opioids in emotion[56]—but none have systematically examined how modulating one's own pain processing affects the multiple components of social cognition and behavior.

To address these gaps, the present review uses the PAM as an overarching framework to organize and interpret diverse social outcomes. Our identified outcome categories—emotion recognition, reactions to emotional stimuli, empathy for pain and other emotions, perspective-taking, social closeness, and prosocial behavior—capture successive expressions of social cognition, from perceptual resonance to higher-order reasoning and action. Within this framework, we consider social cognition not as a fixed capacity but as a dynamic process that can be modulated by changes in affective state. This view is consistent with neurobiological models such as the brain opioid theory of social attachment[58] and the state-dependent μ-opioid modulation of social motivation,[49] which propose that endogenous opioid signaling regulates social bonding and affiliative motivation. Accordingly, manipulations of pain—pharmacological, psychological, or incidental—may alter social cognition and behavior even when no social effect is intended.

Guided by this framework, we conducted a pre-registered systematic literature review in accordance with PRISMA guidelines.[47] Outcome measures were categorized into conceptually distinct but interconnected domains of social cognition, reflecting the continuum outlined above, from perceptual resonance to higher-order reasoning and action. We examined how direct pharmacological manipulations (eg, opioids, opioid antagonists, acetaminophen, capsaicin), indirect pharmacological manipulations (eg, cannabinoids, ketamine, alcohol), and psychological interventions (eg, placebo or hypnotic analgesia) affect these domains. Although some agents, such as alcohol, have complex pharmacological profiles, they were included due to their analgesic properties and their broader relevance to social and affective modulation.[72]

Our overarching hypothesis was that altering one's own pain processing would systematically influence social cognition and behavior across behavioral, neurophysiological, and neurochemical levels. By organizing the evidence according to theoretically defined dimensions, we were able to identify converging patterns across heterogeneous findings and to delineate where different manipulations exert similar or divergent effects.

This review aimed to provide a comprehensive synthesis of an emerging interdisciplinary field, bridging research on pain and social neuroscience. By clarifying how interventions that modulate pain—whether intentionally or as a side effect—may also influence social perception, empathy, and interpersonal behavior, we highlight both the mechanistic connections between pain and social cognition and the potential unintended social consequences of pain-modulating treatments.

2. Materials and methods

2.1. Open science

In accordance with the guidelines for systematic reviews, before conducting our review, we designed a search strategy, deciding on selection criteria, databases, search query, data extraction, analysis methods, and assessment of bias. The research protocol was pre-registered before data collection (https://osf.io/mfh73/). Initial preparatory searches were conducted before pre-registration to refine the keywords and search criteria.

2.2. Inclusion and exclusion criteria

We defined our selection criteria using the PICO framework[32]: (1) (Population) Studies were included if they examined healthy participants aged 18 years and older with no medical or psychiatric conditions. To reduce the risk of selection bias, studies could include participants of all sexes and from any sociocultural background; (2) (Intervention) studies had to include a direct or indirect manipulation of participants' own pain perception, either through pharmacological (eg, opioids or opioid antagonists) or psychological (eg, placebo induction) methods; (3) (Comparison) studies needed to include an adequate control condition (either between- or within-subjects); and (4) (Outcome) studies needed to assess social emotions or behaviors. Our aim regarding the outcome measures was to include a broad range of outcomes, enabling us to identify the existing work in the field and

determine where research may still be lacking. Therefore, we did not specify certain outcomes before the start of the search, as we wished to remain open regarding which outcomes (and ways to operationalize them) would be identified in the literature. We included outcomes that were reported in at least one published study. The identified outcomes were emotional face recognition, reaction to social and nonsocial emotional stimuli, empathy for pain (the ability to understand and share the pain of others),[62] empathy for other emotions (eg, sadness or happiness), social closeness (feeling connected to others),[33] and prosocial behavior (behavior that benefits another individual but may be costly to oneself).[60]

We included behavioral (subjective ratings, questionnaires, or interviews), physiological (heart rate variability [HRV], skin conductance responses, electromyography), or neuronal (electroencephalography [EEG], fMRI) outcome measures. All included studies had to be experimental, quasi-experimental, or randomized controlled trials. Other systematic reviews were not included, but were used to identify further empirical work. The publication language had to be either English or German.

2.3. Data collection

The database search took place on January 19, 2023, applying our pre-registered search queries (see Supplement, http://links.lww.com/PAIN/C450). We searched the following databases: PubMed (including MEDLINE), Scopus, and Web of Science. To minimize the risk of publication bias, we additionally searched PsyArXiv. Our search strategy was based on the PRISMA 2020 guideline for new systematic reviews,[57] and the study selection process was conducted in 2 separate rounds (**Fig. 1**), with further details provided in the Supplement, http://links.lww.com/PAIN/C450.

In sum, we included 50 studies in this systematic review. All screened, included, and excluded studies, including reasons for exclusion, are provided on the Open Science Framework (OSF) project here.

2.4. Data extraction and analysis

Data extraction details are provided in the Supplement, http://links.lww.com/PAIN/C450. The data analysis followed a qualitative method of narrative data synthesis (as opposed to a meta-analytical approach), due to the heterogeneity of interventions and outcomes. Therefore, we extracted information about key variables such as population, intervention, outcomes, and results from the articles. Below, we summarize the results, methods, strengths, and weaknesses of each study, grouping studies by type of pain manipulation and measured outcomes. The findings were judged as significant based on the respective criterion of statistical significance reported by the original authors.

2.5. Risk of bias

After data extraction, we conducted a risk of bias assessment based on an adapted version of the Cochrane risk of bias tool 2,[29] assessing risk of bias arising from (1) randomization, (2) sequence effects, (3) performance, (4) detection, (5) attrition, and (6) selective reporting. In addition, we computed an overall risk of bias score for each study, as the sum of the 6 aforementioned categories. The overall risk of bias was classified as low in 24 studies,[2,3,5,7–9,11,14,15,18,19,22,23,30,34,37,40,48,52,54,61,67,77,80] medium in 12 studies,[16,17,26–28,33,38,41,53,55,70,71] and high in 14 studies.[1,4,10,39,43,46,59,63–66,73,74,79] We further assessed whether the studies reported a successful pain manipulation check: Only 12 of the 50 studies (24%) found that the intervention was effective in reducing first-hand pain, while the manipulation check was unclear for the other 38 studies. Detailed results on risk of bias are provided in the Supplement, http://links.lww.com/PAIN/C450 and on the OSF.

3. Results

All identified studies applied a manipulation known to affect first-hand pain processing in a direct (eg, opioids) or indirect (eg, cannabinoids) way, and subsequently measured whether these treatments affected different levels of social emotions and/or behavior (emotional face recognition, reaction to emotional stimuli, empathy for different emotions, social closeness, and prosocial behavior). **Table 1** summarizes an overview of the chosen social cognition outcomes, their respective operationalizations, and an interpretation of the results for each outcome, while **Figures 2 and 3** present an overview of the findings. Figures S1-S6 (http://links.lww.com/PAIN/C450) depict the direction of effects for each manipulation type, separately for each outcome. Below, the interventions are sorted into pharmacological (either directly or indirectly targeting pain) and psychological manipulations. Within each manipulation, we systematically report on all identified outcomes. In cases where the effects of a manipulation on first-hand pain were assessed, we additionally note this, as such assessments are crucial for evaluating evidence for or against shared representations. Of note, this was only the case for a small number of studies, which explicitly tested this theory. Unless otherwise stated, all mentioned results and comparisons relate to a control group or condition (placebo administration in pharmacological studies, no-expectation conditions in psychological studies).

3.1. Opioids and opioid antagonists

All opioid agonist/antagonist studies used oral capsule administration, except one study,[23] which used an injection.

Studies using opioid agonists[7,52] or antagonists[43,53,77] reported mixed findings regarding facial mimicry. One antagonist study using naltrexone reported increases in negatively valenced facial muscle activity (significant difference in corrugator supercilii muscle, accompanied by a trend for a difference in depressor jaw muscle activity) in mimic responses to dynamic facial expressions of happiness.[53] However, the other studies, which used either static facial expression stimuli (eg, pictures of faces)[7,77] or comparably longer dynamic facial expression stimuli (eg, videos of [morphing] faces),[43,52] found no differences.

Similarly, the effects on emotion recognition performance were heterogeneous across the studies and seemed to be partly influenced by the nature of the used stimulus sets. While one study using dynamic stimuli found a dampening effect of the opioid agonist buprenorphine on recognition accuracy for fear,[34] a more recent study using static stimuli did not.[52] The latter study likewise reported no effect of the opioid agonist morphine on the recognition of other emotions. Løseth et al.,[48] in contrast, found reduced perceived intensity of anger in static neutral faces and stimuli with implicit anger, but not in explicit anger expressions, suggesting a very subtle effect of morphine in this context. No effects on emotion recognition performance were found for sadness[34] or happiness.[48,52] One study reported a lowered recognition threshold for fearful and sad faces at higher doses of naltrexone (50 mg vs 25 mg dose), but no effects on thresholds for happy and angry faces at either dose.[77]

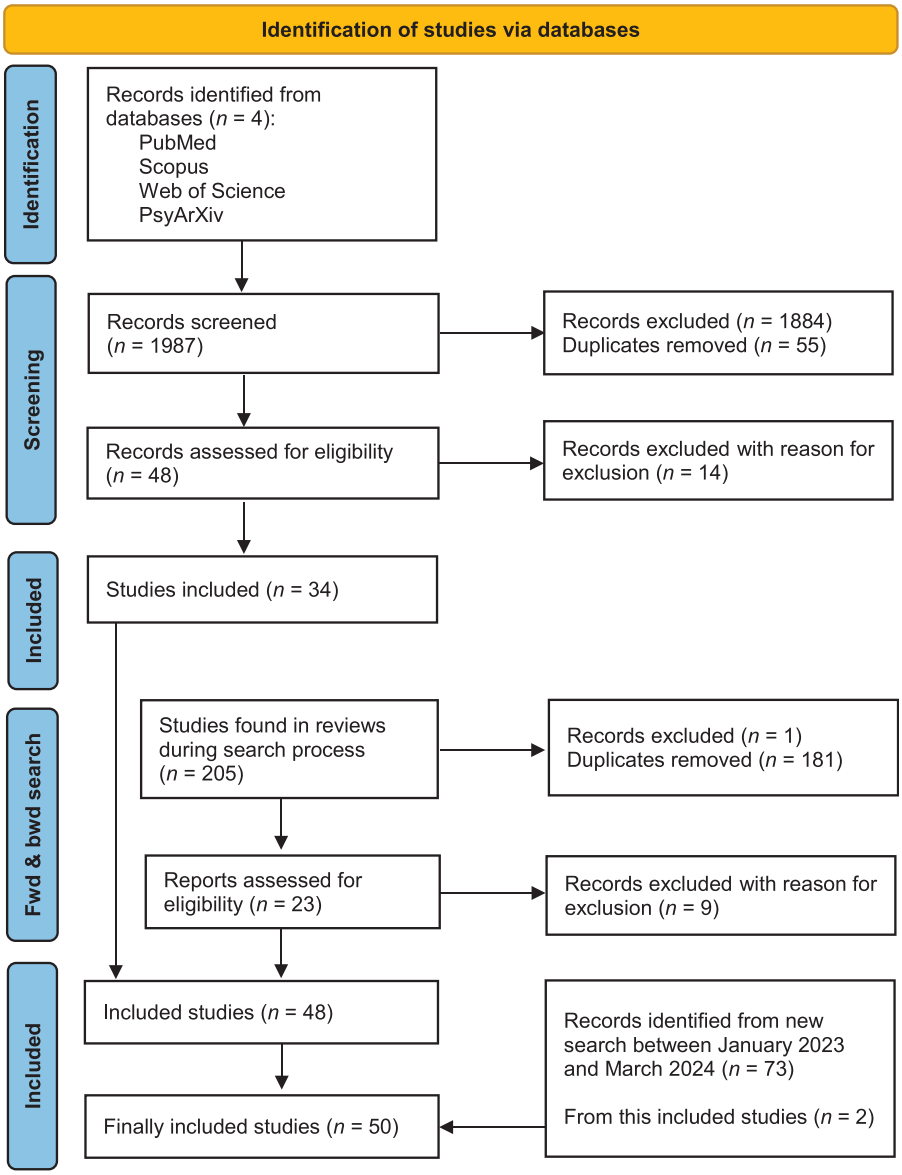

Figure 1. PRISMA flow chart depicting the data collection process. Bwd, backward; Fwd, forward.

Research examining the impact of opioids and opioid antagonists on empathy for pain, other emotions, and touch highlights the intricate modulation of empathic responses. Naltrexone was found to normalize empathic responses, characterized by heightened ratings of empathic pain and personal unpleasantness,[65] along with increased amplitudes of the pain-related event-related potential P2.[64] The administration of naltrexone also led to a diminished ability to discriminate between pain and disgust, which was associated with parametric modulation (different % of pain intensities vs baseline) of neural activity in the fusiform face area.[80] Opioid agonists, on the other hand, seem to influence empathy for emotions other than pain differently, with an observed enhancement in positivity to social emotional pictures (ie, involving people) but no discernible effects on nonsocial emotional pictures.[7,23] Interestingly,[23] also found higher pleasantness ratings for neutral pictures. Notably, the opioid antagonist naltrexone was linked to reduced ratings of arousal in response to emotional scenes, particularly at higher doses (50 mg vs 25 mg).[77] Regarding empathy for affective touch, naltrexone exerted no significant effect, irrespective of whether pleasant, neutral, or unpleasant touch was applied.[66]

Using a Cyberball task, in which players are excluded from participating in a ballgame to induce social pain, Bershad et al.[7] demonstrated a reduced perception of social exclusion and a trend toward decreased negative mood during social exclusion under the influence of the opioid agonist buprenorphine, although positive mood remained unaffected. Tchalova et al.[70] observed that the opioid antagonist naltrexone led to reduced sharing of personal information about the self during closeness-building social interactions, but did not significantly affect feelings of social closeness, desire for social closeness, or expectations of social recognition or threat. Inagaki et al.[33] found that naltrexone altered brain activity during the perception of social bonding, with reduced activity in the 2 selected regions of interest, the ventral striatum and middle insula, in response to reading warm messages from close others vs strangers, and compared with placebo administration.

Table 1

Overview of identified social cognition outcome concepts and measures, their respective operationalizations, and an interpretation of the results for each outcome.

Outcome concept	Outcome measure	Definition	Authors' result interpretation	Example reference
Emotional face recognition ($k = 29$)	Accuracy; hits	Number/percentage of correct emotion identifications in a face or targets (globally or for one emotion)	Higher values = better emotion recognition	Kamboj et al.,[40] 2013
	Arousal rating	Degree of arousal in response to emotional faces	Higher values = higher arousal toward certain emotional faces	Bloomfield et al.,[8] 2022
	Balance point	Estimate of the point at which a participant is equally likely to choose one of 2 emotions in a morphed face	Higher/lower values = higher bias toward one of the 2 emotions	Eastwood et al.,[15] 2020
	BOLD signal change during fMRI	(De)activation of brain regions during face viewing, contrasted against a control condition	Depending on the brain region, eg, higher activity = higher sensitivity to emotion	Abel et al.,[1] 2003
	Discrimination or recognition threshold; sensitivity	Point of recognizing the emotion in a face starting from a neutral expression (0%-100% emotion)	Higher values = lower sensitivity to detect a certain emotion	Eastwood et al.,[15] 2020
		Recognizing the emotion in a face changing from one emotion to the other (eg, pain to disgust; proportion of answering pain)	More pain choices = higher sensitivity to detect pain	Zhao et al.,[79] 2020
	Discrimination index	Probability that a face stimulus crosses a recognition threshold (hits—false alarms)	Higher values = higher discrimination ability	Kamboj et al.,[40] 2013
	Emotional/perceptual sensitivity	Judging morphed faces to be of a certain emotion; discriminability between different emotions	Higher matching between shown face and rated emotion = higher emotional sensitivity (eg, happiness ratings for happy faces)	Løseth et al.,[48] 2018
	Facial mimicry	Facial muscle activity (eg, corrugator supercilii for angry emotions) during face viewing	Higher activity = higher emotional mimicry	Massaccesi et al.,[52] 2022
	False alarms; error rate	Number/percentage of incorrect emotion identifications in a face	Higher values = lower emotion recognition	Eastwood et al.,[15] 2020
	Reaction time	Time taken to (correctly) identify an emotion in a face	Higher values = lower emotional sensitivity; higher recognition difficulty	Kamboj et al.,[40] 2013
	Response bias	Systematic tendency to indicate a particular emotion in a face when another is presented	Higher values = higher bias, ie, more liberal response criteria for selecting a certain emotion	Kamboj et al.,[40] 2013
	Sensitivity index	A measure of sensitivity to detect an emotion in a face independent of response bias	Higher values = higher sensitivity to detect an emotion; 0 = chance level	Schmidt et al.,[67] 2013
	(Total) attentional bias	Number/percentage of first gazes toward (and/or total time looking at) an emotional vs a neutral face measured with EOG or reaction time	EOG: Higher values = higher attention toward emotional faces RT: higher values = slower response to emotional faces	Bershad et al.,[7] 2016
	Valence rating	Degree of valence in response to faces of different emotions (positive to negative)	Depending on the emotion, eg, positive values = higher match with positive emotions, but lower match with negative emotions	Francis et al.,[17] 2019
Reaction to emotional stimuli ($k = 5$)	Accuracy	Number/percentage of correct emotion identifications when viewing an emotional stimulus (globally or for one emotion)	Higher values = better emotion recognition	Li et al.,[46] 2020
	Arousal rating	Degree of arousal in response to different emotional stimuli	Higher values = higher arousal toward certain scenes	Ballard et al.,[5] 2012
	Emotional reaction rating	Kind of emotional state after viewing an emotional stimulus (eg, from unhappy to happy)	Depending on the emotion, eg, positive values = higher match with happy stimuli, but lower match with unhappy stimuli	Li et al.,[46] 2020

(*continued on next page*)

Table 1 (*continued*)

Outcome concept	Outcome measure	Definition	Authors' result interpretation	Example reference
	Facial mimicry	Facial muscle activity (eg, corrugator supercilii for angry emotional stimuli)	Higher activity = higher emotional mimicry	Bershad et al.,[7] 2016
	Reaction time	Time taken to identify an emotion in a stimulus or recognize an image from a previous viewing phase	Higher values = lower emotional sensitivity; higher recognition difficulty	Li et al.,[46] 2020
	Recognition errors	Amount of incorrect image recognitions from a previous viewing phase	Higher values = higher recognition	Gospic et al.,[23] 2008
	Social disinhibition	Valence associations in response to emotional stimuli	Higher values = provision of more positive utterances; lower values = more negative responses	Johnson et al.,[39] 2018
	(Un)pleasantness ratings	Degree of (un)pleasantness toward the content of emotional stimuli	Higher values = higher unpleasantness	Gospic et al.,[23] 2008
	Valence rating	Degree of valence in response to different emotional stimuli (positive and negative)	Depending on the emotion, eg, positive values = higher match with positive emotions, but lower match with negative emotions	Bershad et al.,[7] 2016
Empathy for pain ($k = 16$)	BOLD signal change during fMRI	Activation of brain regions in pain vs no pain conditions	Depending on the brain region, but usually higher activity = higher empathy/ resonance in pain-related areas	Rütgen et al.,[64] 2015
	EEG band power, mu rhythm power, and ERP components	Activation of brain regions in pain vs no pain conditions	Depending on the brain region, but usually higher activity = higher empathy/ resonance in pain-related areas	De Pascalis and Vecchio, 2022[59]; Vecchio and De Pascalis, 2021[74]
	Pain intensity rating	Degree of perceived pain intensity in another person	Higher values = higher (cognitive-evaluative) empathy	Rütgen et al.,[64] 2015
	Personal distress/empathic concern/unpleasantness/negative emotion rating	Degree of felt distress/concern/ unpleasantness/negativity in oneself	Higher values = higher (affective-motivational) empathy	Rütgen et al.,[64] 2015
Empathy for other emotions ($k = 4$)	Arousal rating	Degree of arousal during watching a person in a scene	Higher values = higher (implicit) emotional empathy	Dolder et al.,[14] 2017
	Emotional empathy/concern rating	Degree of "feeling for" of a person in a scene	Higher values = higher (explicit) emotional empathy/concern	Dolder et al.,[14] 2017
	Empathic accuracy	Correlation between perceiver ratings with target ratings	Higher values = higher empathic accuracy	Thiel et al.,[71] 2018
	Empathic feelings rating	Degree of empathic feelings from reading positive scenario vignettes	Higher values = higher empathy	Mischkowski et al.,[55] 2016
	Inferring of mental state	Ability to infer the mental state of a person in a scene (correct vs total responses)	Higher values = higher cognitive empathy	Dolder et al.,[14] 2017
	Participant or experimenter rating of interpersonal skills	Degree of interpersonal skills during an interview situation with their partner	Higher values = higher empathy	Janowsky et al.,[37] 1979
	Perceived pleasure rating	Degree of pleasure perceived in another person from reading positive scenario vignettes	Higher values = higher empathy	Mischkowski et al.,[55] 2016
	Perceived positivity rating	Degree of positivity in positive scenario vignettes	Higher values = higher empathy	Mischkowski et al.,[55] 2016
	Personal pleasure rating	Degree of own pleasure from reading positive scenario vignettes	Higher values = higher empathy	Mischkowski et al.,[55] 2016
	Touch pleasantness rating	Degree of (un)pleasantness of observing another person being touched with different stimuli	More extreme values (positive or negative) = higher empathy	Rütgen et al.,[66] 2021
Social closeness/ connection ($k = 2$)	BOLD signal change during fMRI	(De)activation of brain regions, contrasted against a control condition	Depending on the brain region, but usually higher activity = stronger processing of closeness	Inagaki et al.,[33] 2019
	Closeness/connectedness rating	Degree of felt or desired closeness to one's partner during an interaction	Higher values = higher closeness to another person	Tchalova et al.,[70] 2020

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Table 1 (*continued*)

Outcome concept	Outcome measure	Definition	Authors' result interpretation	Example reference
	Self-disclosure rating	Degree of self-disclosure during an interaction (judged for oneself or for another person)	Higher values = higher self-disclosure/openness toward another person	Tchalova et al.,[70] 2020
Prosocial behavior ($k = 2$)	Exerted effort	Amount of physical effort a person puts in to help another person in need (measured as AUC)	Higher effort exertion/AUC = higher prosociality	Hartmann et al.,[26] 2022
	Moral decision-making	Amount of (non-)utilitarian responses to the footbridge dilemma	Higher preference for nonutilitarian moral judgments = increased emotional reactivity	Francis et al.,[17] 2019
	Prosocial choices	Number/percentage of prosocial choices that help another person in need	Higher values = higher prosociality	Hartmann et al.,[26] 2022
	Reaction time	Time taken to make a (prosocial) decision	Higher values = longer time to decide for prosociality	Hartmann et al.,[26] 2022

Outcome measures sorted alphabetically.
AUC, area under the curve; BOLD, blood oxygen level dependent; EOG, electrooculography; ERP, event-related potentials; fMRI, functional magnetic resonance imaging; *k*, number of studies; RT, reaction time.

We identified no studies examining the influence of opioids or opioid antagonists on prosocial behavior.

3.2. Acetaminophen

We did not identify any study examining the effects of acetaminophen on mimic reactivity, emotion recognition, or prosocial behavior. However, 3 studies examined the effects of acetaminophen on empathy for physical and social pain (one study[38] administered acetaminophen as a capsule, the other 2[54,55] as a liquid).

Mischkowski et al.[55] found that the administration of 1000 mg acetaminophen led to decreased empathic concern and personal unpleasantness in response to reading vignettes in which the protagonists experience physical pain. In addition, acetaminophen attenuated empathy for social pain, as indicated by reduced empathic concern and unpleasantness in response to reading socially distressing scenarios. The authors also tested the effect of acetaminophen on both the first-hand and the empathic experience of painful noise blasts. Both experiences were significantly reduced by acetaminophen, and a mediation analysis showed that empathy for painful noise blasts was mediated by the effect of acetaminophen on unpleasantness during self-experienced noise blasts. This study was the only acetaminophen study that also assessed first-hand pain reduction as a manipulation check. Moreover, Mischkowski et al.[54] observed a reduction in empathy for positive emotions, characterized by diminished empathy and personal pleasantness ratings in response to reading about positive emotional scenarios. However, acetaminophen did not significantly affect the perceived positivity or pleasure of these positive emotional scenarios. In a Cyberball task, participants in the acetaminophen group showed less empathy for social pain and reduced empathic concern for an ostracized player.[55] Surprisingly, one study[38] found that 1000 mg of acetaminophen was associated with greater mu suppression at the C3 location during EEG while viewing images of painful situations; moreover, the acetaminophen group took longer to rate their personal distress compared with the control group.

3.3. Capsaicin

Topical capsaicin administration resulted in longer reaction times to emotional faces, indicating a potential delay in emotional processing.[46] However, capsaicin did not significantly affect accuracy in recognizing emotional faces, suggesting that while reaction time may be affected, the ability to correctly identify emotional expressions remains relatively unchanged. Moreover, capsaicin exhibited no discernible effects on accuracy or reaction time for specific emotional expression categories such as happy, sad, or neutral faces. Interestingly, capsaicin did not have an effect on emotional reactions to emotional pictures and faces, indicating a lack of direct affective modulation. Nevertheless, it did impair accuracy and prolong reaction time in recognizing emotional scenes. No studies were found in the domains of empathy, social connection, or prosocial behavior.

3.4. Cannabinoids

There are several studies shedding light on the influence of cannabinoids, particularly Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), on emotion recognition processes. One study administered cannabinoids in the liquid form, 6 as capsules, and 3 as inhalation.

High doses (15 mg) of THC reduced the accuracy in identifying expressions of anger and fear, while moderate doses (7.5 mg) showed a significant reduction in identifying anger only.[5] There was no significant effect on recognizing sadness or happiness at any dose. Tetrahydrocannabinol (8 mg) decreased the accuracy in identifying overall emotions in ambiguous facial expressions (40% expression intensity), whereas CBD (16 mg) enhanced overall emotion recognition in expressions with 60% intensity.[18] A third experimental group in the latter study received both THC and CBD, and showed no differences to the placebo group. Across various studies, cannabinoids did not significantly affect accuracy, reaction time, or threshold for recognizing expressions of sadness, happiness, or fear. These studies used low doses of THC (6-7.5 mg)[9,22,61] or applied liquid CBD.[2]

Neuroimaging studies have elucidated the effects of THC and CBD on brain activity and connectivity during the processing of various emotions. Tetrahydrocannabinol administration led to reduced activity in the right inferior parietal lobule, the left precuneus, and the primary sensorimotor cortex in response to intensely fearful expressions (100% expression intensity) compared with baseline.[19] Another study found reduced activity in the vermis, left and right occipital cortex, left hippocampus, right prefrontal cortex, right superior parietal lobule, right

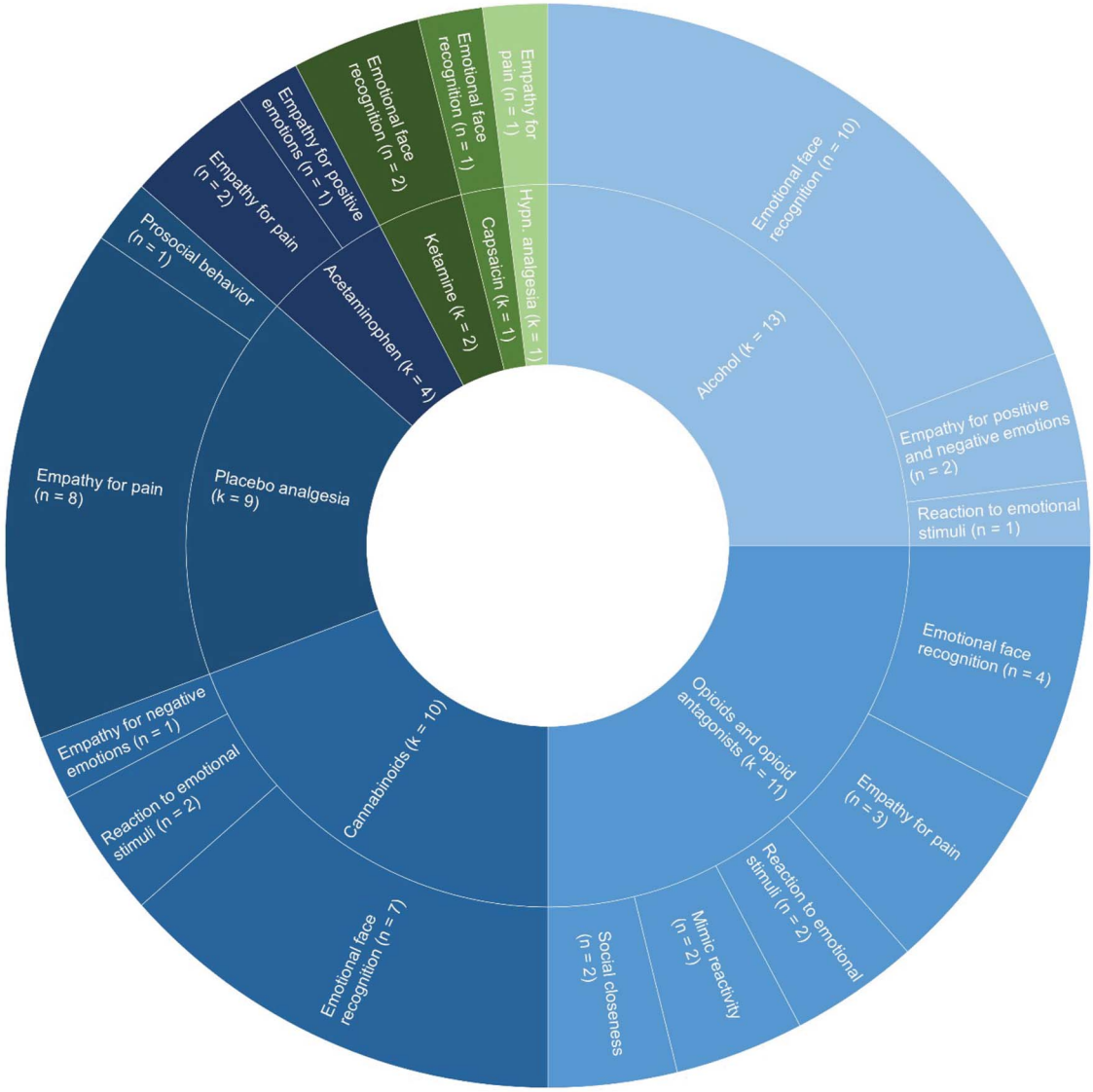

Figure 2. Overview of the identified studies for each pain manipulation and each outcome. *k* = number of identified studies per pain manipulation; *n* = number of identified studies per outcome. Two studies included both placebo analgesia and naltrexone as manipulations, leading to a total of 52 outcomes.

supplementary motor area, and right lateral amygdala in response to pooled happy and fearful emotions compared with a sensorimotor control condition.[9] However, THC did not affect the intrinsic connection between the anterior cingulate gyrus and amygdala.[18] Conversely, CBD administration led to reduced activity in the posterior cerebellum, left medial temporal region,

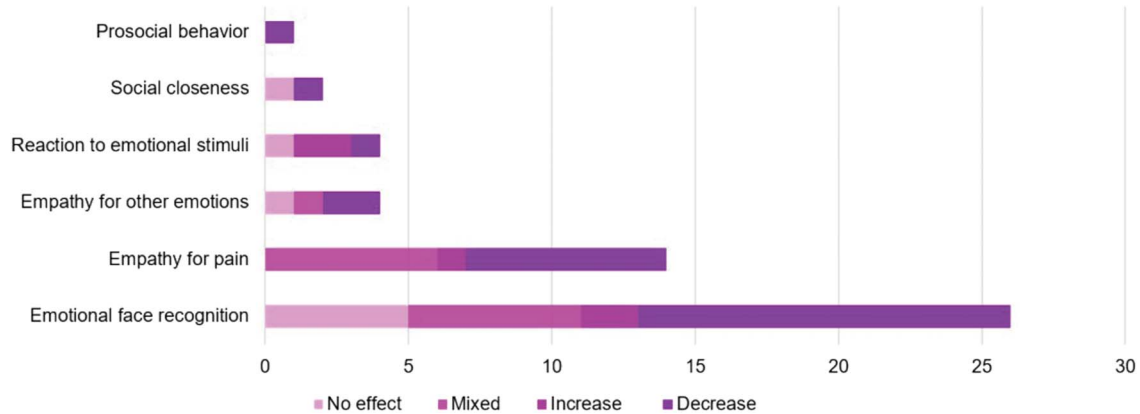

Figure 3. Direction of results (either no effect, mixed, increase, or decrease), collapsed over type of pain manipulation. The x-axis depicts the number of studies. One study included more than one measure[26] (empathy for pain and prosocial behavior), leading to a total of 51 effects.

anterior left parahippocampal gyrus, anterior and posterior cingulate gyrus, and left medial occipital lobe in response to moderately fearful expressions (50% expression intensity) compared with baseline.[19] Furthermore, CBD reduced intrinsic connectivity between the anterior cingulate gyrus and amygdala in response to intensely fearful faces compared with baseline.[18] When THC and CBD were administered together, no such effects on intrinsic connectivity were observed.[18] During the processing of neutral emotional faces (vs. baseline), THC increased activity in the medial posterior temporal gyrus and inferior parietal lobule, while CBD had no effect.[19] In another study,[61] the authors compared amygdala responses to threatening emotions (fear and pain) vs nonthreatening emotions (happy), and replicated previous findings of heightened responses during threat in the placebo condition. Tetrahydrocannabinol attenuated this difference, leading to comparable amygdala responses to threatening and nonthreatening faces, but did not modulate visual or motor responses. For the processing of happy (vs. control) faces, differences in the activity of the inferior orbital frontal gyrus and the right supplementary motor area were found after THC administration.[9] Using the same threat processing task,[61] another study[22] observed increased functional coupling of the basolateral and superficial amygdala with the rostral anterior cingulate gyrus and the medial prefrontal cortex during threatening face processing (fear and anger vs control shapes) after THC administration.

A further study[19] reported that THC administration significantly increased the number of skin conductance (SC) fluctuations during fear-inducing situations, whereas CBD administration led to a reduction of SC fluctuations under similar conditions. However, THC and CBD did not exert any significant effects on the amplitude or latency of SC responses during fear. Notably, in neutral scenarios, neither THC nor CBD showed any significant impact on the amplitude, number of fluctuations, or latency of SC responses.

An early study[37] examining the effect of THC (6 mg) on empathy reported reduced empathy in an interview situation (as rated by external judges and participants' partners). Similarly,[5] reported increased negativity and arousal ratings for neutral pictures and increased arousal ratings for negative pictures at a comparably low dose of THC (7.5 mg), but no effects at a higher dose (15 mg) or for ratings of positive pictures at any dose. Studies on CBD mostly reported no effects on empathic ratings of emotional pictures.[2,8] A neuroimaging study on effects of CBD (600 mg capsules) during a facial emotion processing task found no significant whole-brain effects and no effect in a predefined region of interest in the amygdala.[8]

No effect of CBD was found on social exclusion or self-esteem during social exclusion and inclusion.[2] To the best of our knowledge, there are no studies on the relation between cannabinoids and mimic reactivity or prosocial behavior.

3.5. Ketamine

Ketamine administration (always given as an infusion) led to reduced discrimination ability for facial expressions, particularly fearful and happy vs neutral faces,[67] accompanied by a decrease in N170 amplitude across all facial expressions, indicating disrupted early visual processing of emotional stimuli. However, ketamine did not affect the P100 amplitude. Another study reported increased activity in the right precuneus and bilateral nucleus caudate during the perception of neutral vs fearful faces under the influence of ketamine,[1] indicating altered neural responses in regions associated with attention and reward processing. Conversely, ketamine reduced activity in the right cerebellum during the processing of fearful vs neutral faces, suggesting a modulation of cerebellar involvement in emotional processing. We did not identify any studies investigating potential effects of ketamine on empathy, social connection, or prosocial behavior.

3.6. Alcohol

Many studies investigated the effects of alcohol (always administered as a liquid) on social emotions. Tucker et al. (1983)[73] observed reduced accuracy for emotion processing and recognition of emotions in general. Similarly impaired performance in general emotion recognition sensitivity was found in another study.[15] Regarding anger, one study (substudy 1 of Ref. 41) observed an increased false alarm rate in people under the influence of alcohol, ie, poorer performance. By contrast, other studies found no effects of alcohol on accuracy,[14,16,40] false alarms (Ref. 40, substudy 2 of Ref. 41), sensitivity or bias,[15,40] reaction time,[4,11,14,16,40] or total hits.[41] Regarding sadness, reduced sensitivity[15,40] and an increased threshold[11] were found. Other studies found no effects regarding accuracy,[14,16,40] false alarms,[41] sensitivity,[40] bias,[15,40] reaction time,[14,16,40] threshold,[11] or total hits.[41] Regarding happiness, 2 studies reported reduced false alarms (substudy 1 of Ref. 41) and a reduced bias.[15] No effects of alcohol were found on accuracy,[14,16,40] false alarms (Ref. 40, substudy 2 of Ref. 41), sensitivity,[15,40] bias or reaction time,[40] threshold,[3,11] and total hits.[41] Regarding fear, only one study found reduced sensitivity for fear after consuming alcohol.[15] The other studies found no effects on accuracy,[14,16,40] false alarms,[40,41] sensitivity,[40] bias,[15,40] reaction time,[14,16,40] or total hits.[41] Regarding disgust, one study reported increased accuracy[16] and one reported reduced sensitivity.[15] No effects were found on accuracy,[14,40] false alarms,[40,41] sensitivity,[40] bias,[15,40] reaction time,[14,16,40] or total hits.[41] Regarding surprise, no study observed effects on accuracy and reaction time[14,16] or false alarms and total hits.[41]

Some studies also investigated the ability to discriminate between emotions after alcohol consumption. No effects were found regarding discrimination between happiness and anger,[4,15,41] but a bias toward anger in the discrimination between anger and disgust was observed for male but not female faces.[4] In addition, a bias toward sadness when discriminating between sadness and happiness was reported.[15]

There were some findings regarding the dosage of alcohol. Moderate (0.40 g/kg) but not high doses (0.80 g/kg) led to an increased bias for neutral emotions.[40] High (0.6 g/kg for men and 0.52 g/kg for women) but not low doses (0.2 g/kg for men and 0.17 g/kg for women) were associated with increased accuracy for contempt.[16]

One study found no effect of alcohol on empathy for pain or neutral emotional states,[17] but did find reduced empathy for happy and sad emotions at higher doses (0.80 g/kg vs 0.40 g/kg). Thiel et al. (2018)[71] observed reduced empathic accuracy (a measure of cognitive empathy) when viewing people narrating positive biographical events but not negative events (0.56 g/kg alcohol). By contrast, one study,[14] using a comparably low dose (0.30 g/kg in men, 0.25 g/kg in women), reported increased empathy for positive emotions but no effects on empathy for negative emotions or on cognitive empathy.

Alcohol-intoxicated individuals showed inhibited negative responses to negative social information but difficulty inhibiting negative responses to social information requiring Theory of Mind (understanding others' beliefs, desires, and intentions).[39] The

authors concluded that alcohol-intoxicated individuals are able to adjust their responses when provided with specific guidelines on how to respond.

We did not identify any studies investigating potential effects of alcohol on social connection or prosocial behavior.

3.7. Placebo analgesia and hypnotic analgesia

Placebo analgesia was used in 10 studies (8 independent samples; the same sample was tested in Refs. 59,74 and in Refs. 27,28; one study used sham acupuncture, 2 used topical gels, and 7 used orally administered pills), and hypnotic analgesia through headphones was applied in one study.[10]

On the behavioral level, 5 studies/samples found that placebo analgesia causally reduced empathy for another's pain, either in real time using abstract cues depicting another person receiving physical pain, or when passively viewing pictures of other people in pain.[63–66,79] No such effect was reported in the other 3 samples.[26–28,59,74] These decreases in pain empathy were positively correlated with first-hand pain perception ($r = 0.56$)[65]; the magnitude of self- vs other-related pain decreases through placebo analgesia did not significantly differ.[64,65] Seven studies reported a reduction in personal unpleasantness when observing another in pain, again either in real time or through pictures.[59,63–65,74,80] Three studies[26–28] found no effects on unpleasantness.

On the neurophysiological level, placebo analgesia reduced pain-related vs non–pain-related brain activity measured with fMRI in the anterior midcingulate cortex (aMCC) and left anterior insular (AI),[65,66] and in the posterior insula, superior temporal gyrus, and posterior gyrus.[79] Two studies[27,28] did not find effects of localized placebo analgesia on brain activity in the aMCC, AI, or primary/secondary somatosensory cortex (S1/S2). The studies applying EEG observed a reduced N1 peak amplitude[74] and a reduced P2 amplitude.[63] Moreover, the reduction in empathy for pain under placebo analgesia correlated negatively with midline θ-band power changes, positively with midline β2-band power changes, and positively with a placebo-related reduction of HRV.[59] The study using hypnotic analgesia found reduced pain-related vs non–pain-related brain activity measured using fMRI in the right amygdala, bilateral insula, periaqueductal gray, posterior thalamus, and supplementary motor area.[10]

One study investigated the generalizing effects of placebo analgesia on empathy for pleasant and unpleasant touch,[66] and found no behavioral effects on empathy for pleasant touch, but did find reduced empathy for unpleasant touch in the placebo group. The authors further reported reduced activity in the right central occipital gyrus during empathizing with pleasant stimuli and reduced activity in the right AI, left fusiform gyrus, and right S2 during empathizing with unpleasant stimuli received by another person.

Only one study[26] found that placebo analgesia reduces prosocial behavior, measured through pressing a grip force device to alleviate electric shocks applied to another person. The authors also reported a positive correlation between participants' empathic unpleasantness in response to another's pain and the number of prosocial choices. Finally, the effect of placebo analgesia on prosociality was fully mediated by participants' amount of affect-sharing for another person in pain. None of the included studies using placebo and hypnotic analgesia investigated the effects of these manipulations on mimic reactivity, emotion recognition, or social connection. Importantly, 10 of the 11 studies assessed first-hand pain reduction as a manipulation check.

4. Discussion

Changes to the pain processing system through external or cognitive influences may influence how we perceive the world around us and interact with other people. The aim of this PRISMA-guided systematic literature review was to investigate the causal effects of different types of pain modulation on social emotions and behavior. We qualitatively summarized the results of 50 of 2060 screened empirical studies. Our identified outcomes were emotional face recognition, reactions to emotional stimuli, empathy for pain, empathy for other emotions, social closeness, and prosocial behavior. Corresponding to the Results section, below, we first discuss the findings for each manipulation separately, before providing a general discussion and outlook.

4.1. Opioids and opioid antagonists

The impact of opioids and opioid antagonists on the modulation of social cognition abilities seems particularly complex. While opioid antagonists such as naltrexone seem to heighten sensitivity to others' pain and to alter neural correlates associated with pain and emotion discrimination,[80] their effects on other affective states are less clear-cut. For instance, no significant effects of naltrexone on affective touch perception were observed, regardless of whether the touch was pleasant, neutral, or unpleasant.[66] Conversely, opioid agonists such as morphine enhanced positive affect in response to social emotional scenes but did not significantly influence reactions to nonsocial emotional stimuli.[7] These findings suggest that opioid modulation may be domain-specific, with more pronounced effects in social than in nonsocial contexts.

Regarding affiliative processes, morphine was shown to alleviate negative mood associated with social exclusion, highlighting its potential as a buffer against social stressors.[7] On the other hand, naltrexone reduced intimate self-disclosure when sharing personal information about the self,[70] suggesting a possible dampening of the drive for deeper social connections. This finding contrasts with the lack of changes in feelings of social closeness or desire for social connection, indicating that naltrexone might affect specific aspects of social interactions rather than broadly influencing social affinity.

It is also crucial to highlight the role of different stimulus sets in shaping outcomes. The mixed results observed for mimic reactivity and emotion recognition partly stem from the nature of the stimuli used. Studies using static facial expressions (eg, pictures) revealed different patterns of mimicry and recognition compared with those using dynamic stimuli (eg, videos). Static stimuli offer less contextual and temporal information, potentially leading to weaker effects on emotional processing than dynamic, context-rich stimuli, which might elicit more nuanced responses. Naturalism also seems to be relevant: In one study, the dynamic change from a neutral facial expression to the display of full emotional expression lasted for 2500 ms,[52] compared with only 1300 ms in another study,[53] which found an effect of naltrexone on happiness recognition. The latter time period is more in line with recommendations regarding the unfolding of emotional expressions in dynamic stimuli.[31] This underscores the importance of using naturalistic dynamic stimuli for investigating subtle differences in mimic reactivity.[44] In addition, the subtlety or explicitness of the emotional cues could further influence the outcomes. For example, Løseth et al.[48] found subtle effects of morphine on the perception of implicit anger, suggesting that the sensitivity of the measure and the complexity of the emotion being

assessed play a significant role in detecting opioid-induced changes.

Finally, our understanding of the impact of opioids on prosocial behavior is still lacking. Despite extensive research into emotional processing and social connection, no studies have directly examined how opioids or opioid antagonists influence prosocial actions. Surprisingly, despite an abundance of opioidergic medication prescriptions and the ongoing opioid crisis,[21,75] it remains unclear how these substances affect elements of social and societal interactions, in turn influencing policy-making.

4.2. Acetaminophen

Acetaminophen, a common analgesic, has been shown to reduce empathic responses across a range of contexts involving both physical and social pain. Studies consistently indicate that acetaminophen diminishes empathic concern and unpleasantness in response to painful stimuli, in line with the shared representations account. This dampening effect extends to both social pain and positive empathy, suggesting that acetaminophen specifically reduces emotional resonance with others' experiences. In turn, this may exert effects on prosocial behavior, with indiscriminate analgesic consumption having been found to reduce trait empathic concern and prosocial behavior.[6] Nevertheless, in view of the finding of increased mu suppression after acetaminophen,[38] further investigation is needed to clarify the neural mechanisms involved, as the interpretation of mu suppression in this context is not entirely clear. It is possible that mu suppression, while indicative of neural engagement with painful stimuli, does not straightforwardly translate to increased empathic concern or emotional resonance.

4.3. Capsaicin

Only one study investigated the effects of capsaicin on social processing.[46] The results are in line with the hypothesis that capsaicin-induced ongoing pain slows down the processing of other stimuli, although it did not affect overall accuracy and its effects were not specific to any emotion. Accuracy and reaction time were, however, impaired under capsaicin when viewing emotional scenes, suggesting context specificity.

4.4. Cannabinoids

When evaluating the effects of cannabinoids, it is important to consider the active compound, THC or CBD. Interestingly, THC showed the most pronounced negative effects on the recognition of anger and fear, with higher doses leading to stronger effects. By contrast, other emotions were unaffected, regardless of the dosage. These effects seem to be largely independent of administration route. The neurophysiological findings underscore the differential effects of THC and CBD on brain activity and connectivity during fear processing, with THC generally leading to widespread reductions in activity across various brain regions, and CBD exhibiting more specific effects on certain regions and connectivity patterns. The findings regarding skin conductance responses suggest a differential modulation by THC and CBD in fear-inducing situations, with THC increasing and CBD reducing the number of signal fluctuations (which are associated with increased anxiety), but no significant effects in neutral contexts. Studies measuring empathy observed a reduction of empathic skills in an interview situation under THC. Moreover, increased perceived negativity of neutral emotional scenes was observed for lower doses of THC, while no such effects were observed for CBD. Given that combining THC and CBD led to null findings in all studies, these 2 compounds may act in very different ways and need to be studied separately. Moreover, it is evident that cannabinoids exert their effects mainly on negative, especially threatening emotions such as anger or fear. Effects of cannabinoids on mimic reactivity, social exclusion, empathy for pain, and prosocial behavior remain to be investigated in future studies.

4.5. Ketamine

The few studies that investigated the effects of ketamine on social processing focused on reduced abilities to discriminate faces, particularly happy and fearful ones. The behavioral effects were accompanied by neural effects, indicating a disruption of early visual processing as well as attention and reward processing. As one study found a reduction of cerebellar activity when watching fearful faces, the cerebellum might be an interesting target for future studies. However, more work on ketamine's effects regarding empathy, social connection, and prosocial behavior is needed.

4.6. Alcohol

Alcohol's effects on emotion processing and empathy are complex and inconsistent. While a few studies observed impairments in recognizing and processing emotions in general, most studies reported no significant effects. Negative emotion-specific findings were occasionally reported, with impairments noted for anger, sadness, and fear, while happiness and disgust showed mixed or negligible effects. Alcohol's influence also seemed to be dose-dependent, with higher doses exerting stronger impairments, although one study with a comparably low dose reported increased affective empathy for positive emotions but not for negative emotions. Empathy for pain was unaffected, irrespective of the applied dosage. The lack of studies on alcohol's effects on social connection and prosocial behavior highlights a research gap. Overall, the inconsistency of findings may be due to the use of non-optimal tasks in the existing literature (mainly forced-choice emotion recognition tasks with static images), suggesting the need for more naturalistic, video-based tasks, which would possibly allow for the detection of small effects.

4.7. Placebo analgesia and hypnotic analgesia

Regarding the effects of placebo analgesia, 5 studies/samples found reduced empathic abilities in the domain of pain, 5 studies (encompassing 3 independent samples) found no effects, and no study reported increased abilities. These behavioral effects were accompanied by widespread reductions of brain activity, especially in areas associated with the affective-motivational component of pain. The findings seemed to be largely independent of the placebo administration route. Thus, the evidence speaks more in favor of a reduction of first-hand pain leading to a reduction of empathy for pain, which corresponds to the shared representations account. However, these transfer effects might be moderate in size and disappear in specific scenarios or contexts (eg, when focusing on the somatosensory pain component[27,28] or prosocial behavior).[26] In addition, placebo analgesic effects extend as far as reducing our actual motivation to help others in need.[26]

The pattern of findings might be explained by the specific study designs: Although 7 between-subjects studies reported a reduction of personal unpleasantness when observing another in pain, the 3 within-subjects studies found no such effect. Some

studies also included only psychology students, which may have restricted the credibility of the placebo manipulation and may have led to null findings. Finally, empathy decreases were mainly found when the control condition was described as an "inactive treatment," and not in the studies where it was introduced as a drug with a "minor analgesic effect." These methodological differences highlight the need for large, representative samples and robust study designs that allow for a clear distinction between placebo and control conditions.

Beyond pain, placebo analgesia was found to affect empathy for unpleasant but not pleasant or neutral touch, suggesting domain-general effects. The finding that an opioid antagonist only blocked the effects on pain, and not on touch, indicates a pain-specific involvement of the opioidergic system in pain empathy, although this warrants replication. Future studies could further explore the effects of hypnotic analgesia. Although one single study observed reduced empathy and associated brain activity, more studies are needed to substantiate this finding.

4.8. General discussion

Based on the reviewed literature, it is clear that various substances and interventions, which are regularly used in pain management (and beyond), can significantly affect social and emotional processing to varying degrees.

A prominent finding is that pain relief itself, whether achieved through pharmacological or psychological means, seems to influence how individuals experience and respond to the pain and emotions of others. Acetaminophen, a widely used analgesic, seems to broadly reduce empathy, affecting responses to physical pain, social pain, and even positive emotional experiences of others. Similarly, placebo analgesia reduces empathy for pain, a finding consistent with the idea that reducing one's own pain diminishes the ability to empathize with others' pain (shared representations account). Importantly, this reduction in empathy has been shown to lead to decreased prosocial behavior in specific contexts. Opioids show domain-specific effects, which are often more pronounced in social situations. Agonists such as morphine tend to blunt negative emotional responses such as distress during social exclusion, while opioid antagonists such as naltrexone can augment empathy for pain. Cannabinoids, particularly THC, seem to primarily impair the recognition of negative emotions such as anger and fear, and can reduce empathic skills. Alcohol's effects on emotion processing are complex and often inconsistent, although higher doses are associated with reduced affective empathy and empathic accuracy (a measure of cognitive empathy). Such variability likely reflects moderating influences of contextual and individual factors—eg, motivational state, social context, or sex—which may shape how pharmacological and psychological pain manipulations act on social affect and cognition. Ketamine affects face discrimination abilities, while capsaicin influences reaction times when judging emotional stimuli. While intervention effects on emotions and empathy are notable, their translation into real-world helping behaviors remains largely unexplored.

Some general considerations and implications of this review are worthy of discussion. First, our search strategy was restricted to studies including healthy, neurotypical participants without prior medical conditions. As such, the findings of this review might not readily generalize to clinical populations, who typically experience greater pain and often have varied treatment histories. Instead, the findings in healthy participants may serve as a starting point for planning similar research in patient populations, eg, individuals suffering from postoperative or chronic pain.

This consideration is crucial when distinguishing statistical significance from clinical relevance.[42] The present review assessed effects based on statistical significance reported in original studies. To adequately assess clinical significance, the authors need to estimate and report effect sizes (eg, difference in means, difference in frequencies, or risk/odds ratio) alongside confidence intervals, which indicate precision. Kieser et al. (2013)[42] discuss approaches to the assessment of clinical relevance based on responder analyses and the so-called relative effect or probabilistic index. The latter promises to make the *P*-value not only a measure of evidence against the null hypothesis but, together with the sample size, also a measure of the relevance of the observed treatment effect. Therefore, given the heterogeneity of findings, a consistent use of statistical markers of effect size will be needed in the future to mark the average direction, relevance, and size of different effects.

Notably, the overall risk of bias analysis showed that 52% of all studies were prone to bias, with 28% highly prone, underscoring the need to reduce bias in future research. Particular attention should be given to participant blinding and the implementation of appropriate control conditions.

In general, the pain-relieving effects of many of the reviewed manipulations are beyond question and can be inferred from the overall literature. Thus, the reported findings are relevant for pain practitioners and researchers. From a social neuroscience perspective, when focusing on the mechanisms underlying the reported effects on social emotions and behavior, 2 further aspects should be considered: first, the degree to which the manipulation altered self-pain (to draw comparisons with the degree to which the manipulation altered, eg, empathic pain), and second, uncovering shared underlying mechanisms by comparing (neuro-)physiological measures during self-experienced pain and social emotions. In line with this "shared representations" viewpoint, only 24% of the studies specifically evaluated the effectiveness of the respective intervention in reducing first-hand pain. This manipulation check is crucial to evaluate the findings in the light of the shared representations account. Such causal evidence of a joint reduction of first-hand and empathic experiences was only reported for the 12 studies investigating empathy for pain and prosocial behavior, and only for studies using acetaminophen, placebo analgesia, hypnotic analgesia, or opioids/opioid antagonists as interventions. When assessing only the findings of the studies measuring empathy for pain (Fig. S2, http://links.lww.com/PAIN/C450) and prosocial behavior (Fig. S6, http://links.lww.com/PAIN/C450) within these interventions, we observed a stronger picture of first-hand pain reduction leading to a reduction of social emotions and behavior. The other studies likely did not focus on testing this theory explicitly, which limits our ability to draw connections to simulation accounts of empathy. Relatedly, although some studies connected the self- and other-related effects of placebo analgesia to each other, these between-subject studies render a direct comparison of effects difficult.

In a similar vein, research has shown that while alcohol or ketamine may have downstream analgesic effects, which might in turn influence social emotions and behaviors, the picture is less clear-cut for cannabinoids, which also show effects on negative affect. For example, a review highlighted that cannabinoid-based drugs produce heterogeneous effects.[50] They primarily affect the affective dimension of pain rather than its sensory perception, exhibit only moderate analgesic efficacy, and may occasionally lead to hyperalgesic effects. This notion is relevant when considering the 2 studies which reported evidence that placebo analgesia only affects empathy generally on an affective level, and not in a somatosensory-specific way.[27,28] It is thus possible that

these substances do not directly affect nociceptive processing, but instead exert effects on the general processing of affective stimuli.[50] A review[69] reported that in only one of 7 studies (joint n = 611) was analgesia provided by cannabinoids superior to placebo. In summary, for many of the reviewed manipulations, other mechanisms and systems besides the pain processing system are likely involved in the observed effects on social emotions and behavior. While this complicates the determination of potential underlying mechanisms for social neuroscience researchers, it does not diminish the obvious relevance of such effects in the social domain for the treatment of pain. At the same time, some manipulations—such as opioidergic interventions and placebo analgesia—likely converge on endogenous opioid pathways, whereas others (eg, cannabinoids, acetaminophen, ketamine, alcohol) act through distinct or partially overlapping neurochemical mechanisms, potentially explaining the divergent effects.

Viewed through the lens of the PAM, the reviewed findings suggest that altering one's own affective and nociceptive states can modulate shared self-other representations. However, the heterogeneity across manipulations also indicates that engagement of these shared networks depends on neurochemical, contextual, and motivational boundary conditions—refining the PAM's predictions about when self-other coupling supports or dampens social responsiveness. This interpretation aligns with recent theoretical extensions,[62] which propose that alterations in shared pain representations can shape prosocial behavior and social functioning—such that aberrant or pharmacologically modified pain processing may disrupt interpersonal connection and carry clinical significance.

It is important to mention that single studies in this review often had very specific research designs and answered their own research questions. While a comprehensive evaluation of all the different study designs is beyond the scope of this review, we critically evaluated the validity of each methodology to measure the specific outcomes and highlighted different methods to measure, for example, empathy, in **Table 1**. This also makes direct statistical comparisons between studies difficult and led us to refrain from conducting an additional meta-analysis on the data. To facilitate such endeavors and use existing research findings in a sustainable way, ongoing and future work should focus on sharing data openly (https://osf.io/mfh73/).

As we included all outcomes that were assessed in at least one study, we identified only one or a few studies for some outcomes, such as social connection or prosocial behavior. This illustrates on the one hand that more research is needed in these areas, and on the other hand that the results of these single studies need to be interpreted with caution, as replication is needed before more definite conclusions can be drawn. Relatedly, research on the effects of nonsteroidal anti-inflammatory drugs on social emotions or behavior is urgently needed.

In conclusion, our review strongly highlights that many fields are still under-researched and crucially in need of systematic studies with adequate sample sizes. Aiming to be as broad as possible, we included a wide range of social and affiliative emotions and behaviors. To clarify the role of the pain processing system for social emotions and behaviors, proper manipulation checks and causal evidence are crucial. Only then may we begin to understand how the self-experience of emotions is related to the experience of our emotional environment.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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