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 via external or cognitive influences may influence how we perceive the world around us and interact with other people. To investigate the causal effects of different types of (psycho)pharmacological pain modulation on social emotions and behaviour, we conducted a pre-registered PRISMA-guided, systematic literature review. Our main aim was to investigate how interfering with the perception of pain in oneself 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 out of 2060 screened studies. Included studies investigated the effects of opioids and 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 the 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, i.e., 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 effect and mode 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, systematic replications and meta-analyses.

Keywords

pain modulation, placebo analgesia, nocebo hyperalgesia, opioid, prosocial behaviour, empathy, emotion recognition

1 Introduction

Pain perception is an ubiquitous emotion in our daily life and is uniquely connected to the way we perceive, process, and react to our surroundings, for example, others in pain (Jackson et al., 2006 for a review; Lamm et al., 2011 for a meta-analysis; Singer et al., 2004; Zaki et al., 2016 for a review). Processing, sharing, and understanding others' emotions, including pain, involves multiple steps that each describe different hierarchical and interacting reactions (Cuff et al., 2016; Hall & Schwartz, 2018 for reviews). These reactions can range from an automatic contagion of another's emotional state over a more cognitive processing and evaluation of that state, up to a (pro)social reaction towards the target.

A multitude of studies have shown the importance of our own first-hand emotions, specifically pain, for processing the emotions of others (Keysers et al., 2010 for a review). For example, some groups have investigated causal effects of pain-modulating substances such as placebo painkillers or acetaminophen on empathy for pain (see e.g., Hartmann et al., 2021a; 2021b; Mischkowski et al., 2016; Rütgen et al., 2015a; 2015b). These studies involved either pharmacological or psychopharmacological methods, and suggested a positive causal relationship between one's own pain on the one hand, and others' emotion processing, and resulting reactions towards other people's pain on the other hand, on the levels of behaviour, event-related potentials (Rütgen, Seidel, Riečanský, et al., 2015), fMRI (Rütgen, Seidel, Silani, et al., 2015), and underlying neurochemistry (Rütgen et al., 2018, 2021). These findings are in line with simulation or shared representation accounts, which posit that we come to empathically understand and share the emotions of conspecifics by reactivating and simulating the other's emotional state in ourselves, as if we were experiencing it first-hand (Decety & Grèzes, 2006; Lamm & Majdandžić, 2015 for reviews). Interestingly, some studies also find generalisation and transfer of pain manipulations to emotions beyond pain, such as unpleasant touch stimuli (Rütgen et al., 2021) or even positive emotions (Mischkowski et al., 2019).

In sum, modulations of our own pain processing system may have causal effects on our social emotions and behaviour, and potentially also generalise beyond pain to other

emotions and associated behaviours. Depending on the level and degree of modulated affective and cognitive functions, these effects can range from subtle to strong influences, and may substantially impact our actions, and, consequently, our social relationships (see Rütgen & Lamm, 2024, for a recent opinion paper illustrating this view). However, empirical evidence regarding these effects so far seems mixed and inconclusive. A few specialised earlier reviews exist (e.g., Lumley et al., 2011 on persistent pain and effects on emotional awareness; Nummenmaa & Tuominen, 2018 on the opioid system and emotions in general), but these do not specifically address social emotion processing or behaviour. No study to date has qualitatively summarised the status quo of empirical research on this topic in a broad, systematic and comprehensive way. However, such a summary is crucial to inform and help shape future work in this research area.

To close this gap, we conducted a preregistered, systematic literature review in line with PRISMA guidelines (Page et al., 2021). This review intends to provide an overview over existing work, identify general directions of findings, and give an outlook on worthwhile future work. Our main aim was to investigate how directly interfering with the perception of pain in oneself affects our abilities to perceive, process and react to positive and negative emotions (including pain) in other individuals. We hypothesised that, overall, manipulating one's own pain processing affects social emotions and behaviour, on the behavioural, neurophysiological and neurochemical level. To this end, we included a broad selection of manipulations that have consistently shown effects on pain processing in past research – ranging from direct pharmacological manipulations such as opioids, opioid antagonists, acetaminophen, and capsaicin, over indirect pharmacological manipulations such as cannabinoids, ketamine, and alcohol to psychological manipulations such as placebo analgesia and hypnotic analgesia. While the pharmacological effects of alcohol are quite complex, research does point to a crucial role in analgesia and is relevant in regard to substance abuse in chronic pain conditions (Thompson et al., 2017).

2 Materials and Methods

2.1 Open science practices

Adhering to the requirements for systematic reviews, we designed a search strategy prior to conduction of our review. We decided on selection criteria, databases, search query, search strategy, data extraction, analysis methods and bias assessment. The whole research protocol was preregistered prior to the start of data collection (see preregistration). Initial preparatory searches were conducted prior to preregistration to refine the keywords and search criteria. The detailed risk of bias analysis and lists of screened, excluded, and included studies are freely available in the corresponding OSF project.

2.2 Inclusion and exclusion criteria

We defined our selection criteria using the PICO Schema (Howard et al., 2022): 1) Studies were included if they studied healthy adult participants to ensure our findings could be applied to neurotypical individuals. Study participants had to be over 18 years of age and free from any medical or psychiatric conditions. To reduce risk of selection bias, studies with participants from all genders and sociocultural backgrounds were included; 2) studies must have include a manipulation of one's own pain perception, either through pharmacological (e.g., opioids, or opioid antagonists) or psychopharmacological (e.g., placebo or nocebo inductions) methods; 3) studies must include an adequate control condition, which could be either between- or within-subjects; and 4) Studies must assess social emotions or social behaviours (e.g., empathy for pain or prosocial behaviour). We included behavioural (e.g., subjective ratings, questionnaires, or interviews), physiological (heart rate variability (HRV), skin conductance responses (SCR), electromyography (EMG)) or neuronal (electroencephalography (EEG), functional magnetic resonance imaging (fMRI)) outcome measures. Moreover, all included studies had to be experimental, quasi-experimental or randomised controlled trials. Other systematic reviews were not included, but were used to identify further empirical work (see below). The publication language had to be either English or German.

2.3 Search queries

Aiming to maximise sensitivity and specificity, we designed search queries based on our selection criteria. Despite differing database specific operators all search queries contained the exact same keywords. We considered different spelling, synonyms and used the * operator following word stems (e. g. analges* or modulat*) as wildcards to include multiple word endings. Following this procedure, we ran preparatory searches, adapted keywords and added excluding keywords according to the test search results, increasing the specificity of our search queries. The exact search queries can be found in the supplement.

2.4 Data collection

For published work, we searched the following databases: Pubmed incl. Medline, Scopus, Web of Science: Core Collection. Additionally, we searched PsyArXiv for preprints to minimise risk for publication bias. Our search strategy was based on the Prisma 2020 Guideline for new systematic reviews (Page et al., 2021) and complemented by forward and backward searches of all finally included studies, especially for the identified systematic reviews. The above databases were searched using our preregistered search queries (see Supplement) on January 19th 2023. The study selection process was conducted in two separate rounds (see Figure 1 for the PRISMA flowchart).

In the first round, selection criteria were checked based on title and abstract alone. Duplicates were removed and article PDFs extracted following the first round of study selection. The same searches were re-run on February 24th 2024 to include recently published work. This new search resulted in 28, 18, 27, and zero additional studies (in PubMed, Web of Science, Scopus, and PsyArXiv, respectively), two of which we included in this systematic review (Jelsone-Swain et al., 2023; Korb et al., 2023).

In the second round, selection criteria were checked based on the full text. Additionally, we ran forward and backward searches for all finally included studies, i.e., we searched the included studies' reference lists and citations for additional studies. Lastly, we ran backward searches for all identified systematic reviews identified during the search process. For studies found during forward and backward searches, the selection process was conducted

in the same manner as detailed above. All steps were independently run by two researchers (HH and PD) and later compared. In case of conflicts, a third researcher (MR) additionally checked the given study and the group discussed until consent was found. In sum, we included 50 studies in this systematic review. All screened, included, and excluded studies including reasons for exclusions can be found on the OSF project here.

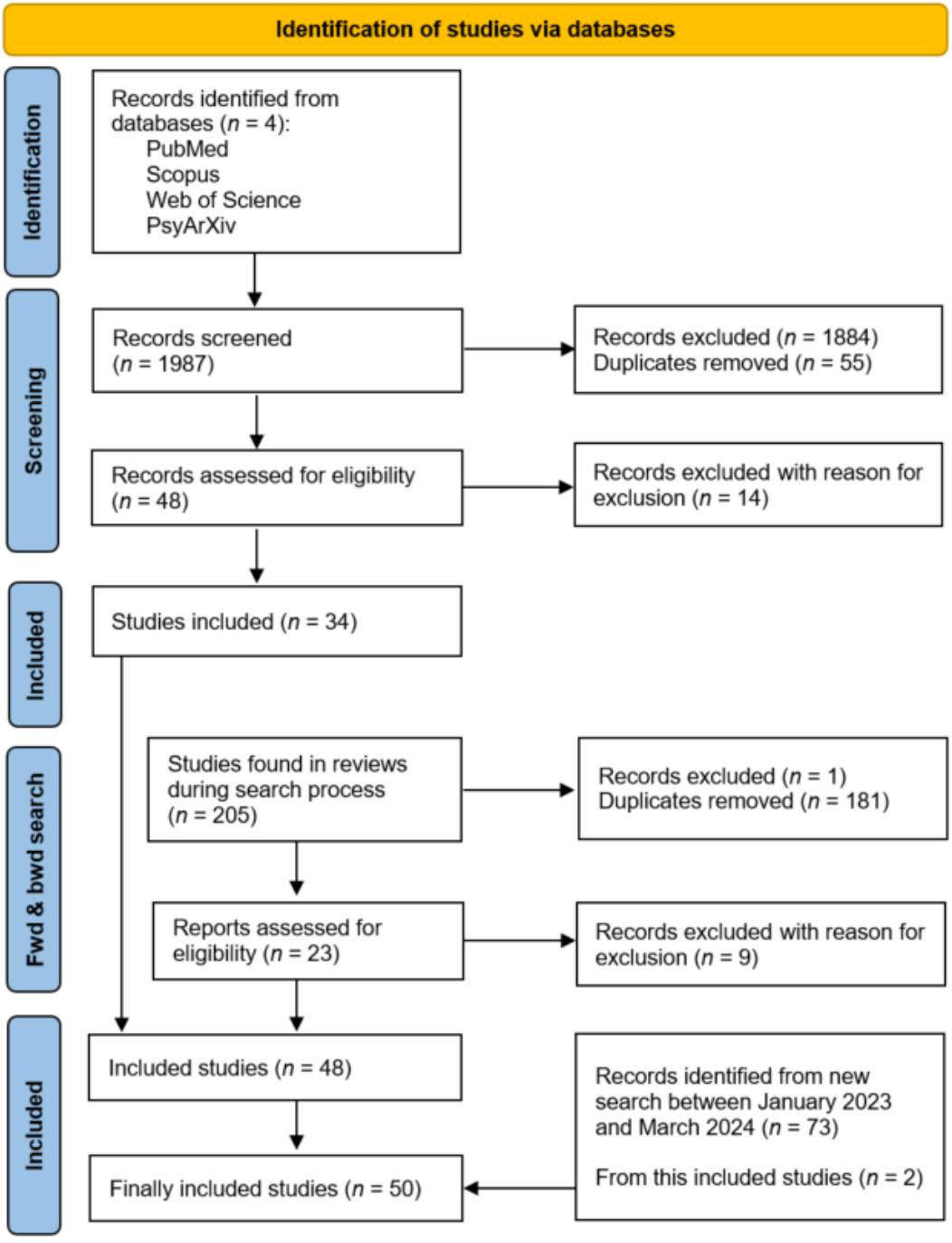

Figure 1. The PRISMA flowchart depicting the data collection process. Fwd = forward; bwd = backward.

2.5 Data extraction and preparation

Data extraction lasted from January 19th to March 27th 2023. Data management was based on Siddaway et al. (2019) and adapted for this review. For data extraction, we created a data extraction form including a legend, based on the Cochrane data extraction form (The Cochrane Developmental, Psychosocial and Learning Problems Review Group, 2014, see OSF page, https://training.cochrane.org/data-collection-form-rcts). To assess whether the data extraction form provided sufficient objectivity, two researchers (HH and PD) independently extracted data from the same five studies using the form and we assessed if the extracted data was identical. Uncertainties were discussed and necessary adaptations were made, before the full data extraction began. A list of the extracted data columns can be found in the Supplement and on the OSF.

Following this selection process, the agreement of the researchers regarding the study selection was quantified using Cohen's Kappa. This agreement was determined using the data from the first step of the selection process. The researchers agreed in their assessment for 1863 of 1987 studies (73 additional studies were added during a later search in February 2024 and are not part of this calculation). This corresponds to an agreement of 93.8%. A Cohen's Kappa of 0.526 was calculated from this agreement. According to Landis and Koch, a Cohen's Kappa of 0.4-0.6 corresponds to moderate agreement (Landis and Koch, 1977).

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. This means we extracted information about key variables, such as population, intervention, outcomes, and results, from the full-texts of the manuscripts (see the Supplement for the complete list of all extracted variables). Below, we therefore summarize and report results, methods, strengths, and weaknesses of each study, grouping studies by type of pain manipulation and measured outcomes. A finding was judged as significant based on the criterion of statistical significance reported by the original authors.

2.6 Risk of bias

Following data extraction, we conducted a detailed risk of bias assessment based on an adapted version of the Cochrane risk of bias tool 2 (Higgins et al., 2019). We assessed the risk of bias arising from 1) randomisation, 2) sequence effects, 3) performance, 4) detection, 5) attrition and 6) selective reporting. Additionally, we assessed the overall risk of bias for each study by means of total bias scores. This total bias score was based on rating the risk of bias from the different bias categories mentioned above. Importantly we assessed and reported whether the included studies checked if their pain manipulation was successful. A total of 23 studies showed a low overall risk of bias. In 12 studies, the overall risk of bias was classified as medium (Felisberti et al., 2015, Francis et al., 2019, Hartmann et al., 2021a, Hartmann et al., 2021b, Hartmann et al., 2022, Inagaki et al., 2019, Jelsone-Swain et al., 2023, Khouja et al., 2019, Meier et al., 2017, Mischkowski et al., 2016, Tchalova et al., 2020, Thiel et al., 2018). In 14 of the included studies, the overall risk of bias was assessed as high (Abel et al., 2004, Attwood et al., 2009a, Braboszcz et al., 2017, DePascalis et al, 2022, Johnson et al., 2018, Korb et al., 2023, Li et al., 2020, Rütgen et al., 2015a, Rütgen et al., 2015b, Rütgen et al., 2018, Rütgen et al., 2021, Tucker et al., 1983, Vecchio et al., 2021, Zhao et al., 2020). Besides these biases, we checked for possible conflicts of interest through funding sources (39 studies declared no conflicts, for 9 studies, conflicts are improbable, and for two studies, no information was given). Detailed bias results for these biases are provided in the Supplement and on the OSF. Moreover, 12 out of 50 studies (24%) evaluated the effectiveness of the intervention in reducing first-hand pain. While all of these studies found such a reduction, this manipulation check is unclear for the other 38 studies.

3 Results

An overview of the findings can be found in Figures 2 and 3. Additional figures similar to Figure 3 displaying the direction of effects for each manipulation type and separately for each outcome can be found in Figures S1-S6 in the Supplement. Below, the interventions are sorted into pharmacological (either directly or indirectly targeting pain) and non-

pharmacological, psychological manipulations. Our identified outcomes were empathy for pain, empathy for other emotions, reaction to emotional stimuli, emotional face recognition, social closeness, and prosocial behavior.

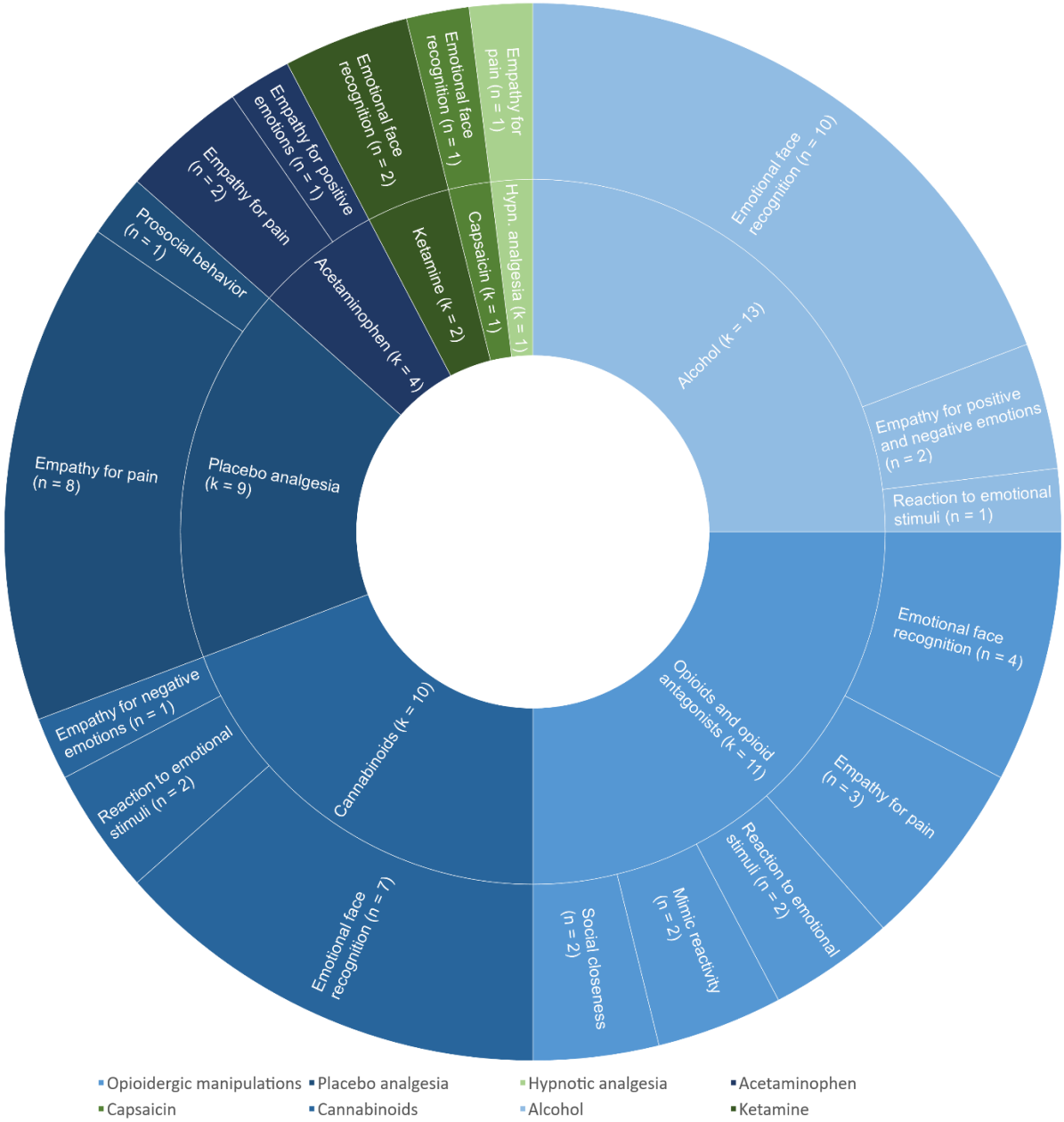

Figure 2. Overview of the identified studies for each pain manipulation and each outcome. *k* = number of identified studies per pain manipulation; *n* = number of identified studies per outcome. Two studies included both placebo analgesia and naltrexone as manipulations, leading to a total of 52 outcomes.

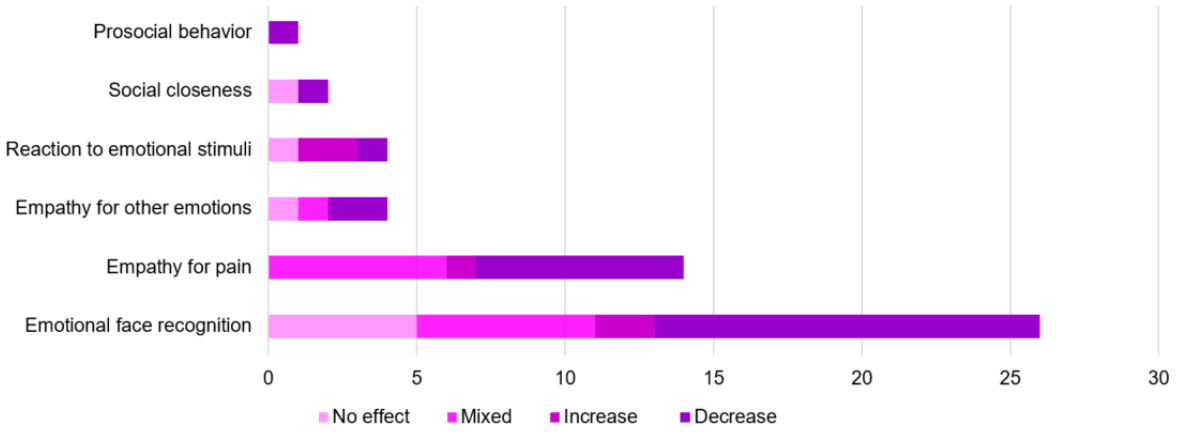

Figure 3. Direction of results (either no effect, mixed, increase or decrease), collapsed over type of pain manipulation. The x-axis depicts the number of studies. One study included more than one measure (Hartmann et al., 2022 measured empathy for pain and prosocial behaviour), leading to a total of 51 effects.

3.1 Opioids and opioid antagonists

None of the included studies using either opioid agonists (Massaccesi et al., 2022; Bershad et al., 2016) or antagonists (Korb et al., 2023; Meier et al., 2017; Wardle et al., 2016) found effects on facial mimicry of happiness and anger (Korb et al., 2023), mimic reactivity to emotions in the negative domain (fear, anger, sadness), or to both social and non-social scenes (Wardle et al., 2016). For the emotion of happiness, findings were mixed, with one antagonist study reporting increases in negatively-valenced facial muscle activity (significant difference in corrugator supercilii muscle, accompanied by a trend for depressor jaw muscle activity) in mimic responses to dynamic facial expressions of happiness (Meier et al., 2017), but no differences in any of the other included studies, which used either static facial expression stimuli (Bershad et al., 2016, Wardle et al., 2016) or comparably much longer dynamic facial expression stimuli (Massaccesi et al., 2022).

Similarly, the effects on emotion recognition performance were heterogeneous across studies, and again seem to be partly influenced by the nature of the employed stimulus sets. While one study using dynamic stimuli found a dampening effect of the opioid agonist buprenorphine on recognition accuracy for fear (Ipser et al., 2013), a more recent study using static stimuli (for the emotion recognition part of their experiment) did not (Massaccesi et al., 2022). The latter study also did not report any effect of the opioid agonist morphine on the

recognition of other emotions. Løseth et al. (2018), in contrast, found reduced perceived intensity of anger in static neutral faces and stimuli with implicit anger, but not in explicit anger expressions, speaking for a very subtle effect of morphine in that case. No effects on emotion recognition performance were found for sadness (Ipser et al., 2013) or happiness (Løseth et al., 2018; Massaccesi et al., 2022). Employing the opioid antagonist naltrexone, one study reported a lowered recognition threshold for fearful and sad faces at higher doses of the antagonist (50 mg vs. 25 mg), but no effects on thresholds for happy and angry faces at either dose (Wardle et al., 2016).

Research examining the impact of opioids and opioid antagonists on empathy for pain, other emotions, and touch highlights the intricate modulation of empathic responses. Opioid antagonists (namely naltrexone) have demonstrated an augmentation of empathy for pain, characterised by heightened ratings of empathic pain and personal unpleasantness (Rütgen et al., 2015), along with increased amplitudes of the pain-related event-related potential P2 (Rütgen et al., 2018). The administration of naltrexone also led to a diminished ability to discriminate between pain and disgust, which was associated with modulation of neural activity in the fusiform face area (Zhao et al., 2021). Opioid agonists, on the other hand, appear to influence empathy for other emotions than pain differently, with an observed enhancement in positivity towards social emotional pictures but no discernible effects on non-social emotional pictures (Bershad et al., 2016; Gospic et al., 2008). Interestingly, Gospic et al. also found higher pleasantness ratings for neutral pictures. Notably, the opioid antagonist naltrexone, particularly at higher doses (50 mg vs. 25 mg), has been linked to reduced ratings of arousal in response to emotional scenes (Wardle et al., 2016). Regarding empathy for touch, opioid antagonists (naltrexone) exhibit no significant effect, irrespective of whether pleasant, neutral or unpleasant touch is applied (Rütgen et al., 2021). These findings collectively underscore the complex interplay between pharmacological modulation and social-emotional processing, highlighting the need for further research to elucidate the underlying mechanisms and implications of opioid modulation on empathic responses.

The influence of opioids on measures of social connection has garnered some attention in recent research. Bershad et al. (2016) demonstrated a reduced perception of social exclusion and a trend towards decreased negative mood during social exclusion under the influence of the opioid agonist buprenorphine. However, positive mood remained unaffected. Tchalova et al. (2020) observed that the opioid antagonist naltrexone led to reduced intimate self-disclosure during closeness-building social interactions, but did not significantly impact feelings of social closeness, desire for social closeness, or expectations of social recognition or threat. Inagaki et al. (2019) found that naltrexone altered brain activity during the perception of social bonding, with reduced activity in the ventral striatum and mid insula. Additionally, the association between feelings of social bonding and brain activity differed significantly between the opioid antagonist group and the control group, suggesting a nuanced role of opioids in social processing. These findings underscore the complex interplay between opioids and social behaviour, shedding light on both the potential benefits and drawbacks of opioid modulation on social connection.

We identified no studies on the influence of opioids or opioid antagonists on prosocial behaviour, which constitutes a research gap in this field. None of the studies assessed first-hand pain reduction as a manipulation check.

3.2 Acetaminophen

While there are no reports about effects of acetaminophen on mimic reactivity, emotion recognition or prosocial behaviour, three studies have looked into effects of this popular pain manipulation on empathy for physical and social pain.

Mischkowski et al. (2016) found that the administration of 1000 mg acetaminophen led to reduced empathy for pain, as evidenced by decreased empathic concern and personal unpleasantness in response to painful stimuli (reading vignettes of painful situations). Additionally, acetaminophen attenuated empathy for social pain, as indicated by reduced empathic concern and unpleasantness towards 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. These findings suggest a broad suppression of empathic responses under acetaminophen influence, extending beyond physical pain to include social distress. This study was the only acetaminophen study that also assessed first-hand pain reduction as a manipulation check. Moreover, Mischkowski et al. (2019) observed a reduction in empathy for positive emotions, characterised by diminished empathy and personal pleasantness ratings in response to positive emotional scenarios. However, acetaminophen did not significantly affect the perceived positivity or pleasure of positive emotional scenarios. In a cyberball task, Mischkowski et al. (2016) observed reduced empathy for social pain and reduced empathic concern for an ostracised player in the acetaminophen group. Lastly, Jelsone-Swain et al. (2023) surprisingly found that 1000 mg of acetaminophen was associated with greater mu suppression at the C3 location while viewing images of painful situations. These authors also found a small effect of the acetaminophen group taking longer to rate their personal distress than the control group.

3.3 Capsaicin

Li et al. (2020) observed that topical capsaicin administration resulted in generally increased reaction time to emotional faces, indicating a potential delay in emotional processing. However, capsaicin did not significantly affect accuracy for the recognition of emotional faces, suggesting that while reaction time may be impacted, 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 towards emotional pictures and faces, indicating a lack of direct affective modulation. However, it did impair accuracy and prolong reaction time in recognizing emotional scenes, suggesting a more pronounced effect on cognitive processes involved in scene-based emotion recognition. Beyond these findings, our literature search did

not yield any relevant studies in the domains of empathy, social connection, or prosocial behaviour. None of the studies assessed first-hand pain reduction as a manipulation check.

3.4 Cannabinoids

Research on cannabinoids has so far not investigated its effects on mimic reactivity, but there are several studies shedding light on the influence of cannabinoids, particularly Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), on emotion recognition processes. Notably, Ballard et al. (2012) found that high doses (15 mg) of THC reduced accuracy in identifying expressions of anger and fear, while moderate doses (7.5 mg) showed a significant reduction on identifying anger only. No significant effect on recognizing sadness or happiness were found for any of the doses. Hindocha et al. (2015) reported that THC (8 mg) decreased 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. A third experimental group was administered both THC and CBD, and showed no differences to the placebo group in that study. Moreover, across various studies, cannabinoids did not significantly affect accuracy, reaction time, or threshold for recognizing expressions of sadness, happiness, or fear. These studies either used low doses of THC (6 to 7.5 mg; Bossong et al., 2016; Gorka et al., 2015; Phan et al., 2008) or applied liquid CBD (Arndt et al., 2017).

Neuroimaging studies have elucidated the effects of THC and CBD on brain activity and connectivity during processing of various emotions. For the emotion of fear, THC led to reduced activity in the right inferior parietal lobule, the left precuneus and the primary sensorimotor cortex (Fusar-Poli et al., 2009). Additionally, Bossong et al. (2016) observed decreased activity in the vermis, left and right occipital cortex, left hippocampus, right prefrontal cortex, right superior parietal lobule, right supplementary motor area, and right lateral amygdala following THC administration. However, THC did not affect the intrinsic connection between the anterior cingulate gyrus and amygdala (Fusar-Poli et al., 2010). Conversely, CBD administration led to reduced activity in the posterior cerebellum, left medial temporal region, anterior left parahippocampal gyrus, anterior and posterior cingulate

gyrus, and left medial occipital lobe (Fusar-Poli et al., 2009). Furthermore, Fusar-Poli et al. (2010) demonstrated that CBD reduced intrinsic connectivity between the anterior cingulate gyrus and amygdala. When THC and CBD were administered together, no such effects on intrinsic connectivity were observed (Fusar-Poli et al., 2010). During the processing of neutral emotional faces, THC increased activity in the medial posterior temporal gyrus and the inferior parietal lobule, while CBD had no effect (Fusar-Poli et al., 2009).

In a study by Phan et al. (2008), the authors compared amygdala responses to threatening emotions (fear and pain) vs. non-threatening emotions (happy expressions), and replicated previous findings of heightened responses during threat in their placebo control condition. THC attenuated this difference, leading to comparable amygdala responses during threatening and non-threatening faces, while not modulating visual or motor responses. For processing of happy faces, Bossong et al. (2016) found activation differences due to THC in the inferior orbital frontal gyrus and the right supplementary motor area.

Using the same threat processing task as Phan et al, Gorka and colleagues (2015) 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) after THC administration.

In a study by Fusar-Poli et al. (2009), the effects of cannabinoids on skin conductance response were investigated, particularly in the context of fear and neutral stimuli. It was found that THC administration significantly increased the number of fluctuations during fear-inducing situations, whereas CBD administration led to a reduction in the number of fluctuations under similar conditions. However, THC and CBD did not exert any significant effects on the amplitude or latency of skin conductance responses during fear. Notably, in neutral scenarios, neither THC nor CBD showed any significant impact on the amplitude, number of fluctuations, or latency of skin conductance responses. These findings suggest a differential modulation of skin conductance responses by THC and CBD in fear-inducing situations, with THC increasing and CBD reducing the number of fluctuations, while both cannabinoids exhibit no significant effects in neutral contexts.

An early study (Janowsky et al., 1979) on the effect of THC (6 mg) on empathy reported reduced empathy in an interview situation (as rated by external judges and partners of the experimental subjects). Similarly, Ballard et al. (2012) reported increased negativity and arousal ratings towards neutral pictures as well as increased arousal ratings towards negative pictures for a comparably low dose of THC (7.5 mg), but no effects for a higher dose (15 mg) or for any ratings of positive pictures for any dose. Studies on CBD mostly reported no effects of it on empathic ratings of emotional pictures (Arndt et al., 2017; Bloomfield et al., 2022). A neuroimaging study on effects of CBD (600 mg capsules) during a facial emotion processing task did neither report significant whole-brain effects, nor any effect in a pre-defined region of interest in the amygdala (Bloomfield et al., 2022).

Arndt and colleagues (2017) also reported no effects of CBD on social exclusion, as well as self-esteem during social exclusion and inclusion. To our knowledge, there are also no studies on the relation between cannabinoids and prosocial behaviour. None of the studies assessed first-hand pain reduction as a manipulation check.

3.5 Ketamine

Research investigating the effects of Ketamine on emotion recognition suggests significant alterations in perceptual and neural processing. Schmidt et al. (2013) found that Ketamine administration led to reduced discrimination ability for facial expressions, particularly for fearful and happy faces. This reduction in discrimination ability was 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. Furthermore, Abel et al. (2004) reported increased activity in the right precuneus and bilateral nucleus caudate during the perception of neutral faces under Ketamine influence, 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 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 behaviour. None of the studies assessed first-hand pain reduction as a manipulation check.

3.6 Alcohol

Many studies investigated the effects of alcohol on social emotions. Tucker et al. (1983) observed reduced accuracy for emotion processing and recognition of emotions in general. Similarly impaired performance in general emotion recognition sensitivity was found by Eastwood et al. (2020).

Regarding anger, one study by Khouja et al. (2019, study 1) observed an increased false alarm rate in people under alcohol. In contrast, other studies found no effects of alcohol on accuracy (Dolder et al., 2017; Felisberti et al., 2015; Kamboj et al., 2019), false alarms (Kamboj et al., 2019; Khouja et al., 2019, study 2), sensitivity or bias (Eastwood et al., 2020; Kamboj et al., 2013), reaction time (Attwood et al., 2009b; Craig et al., 2009; Dolder et al., 2017; Felisberti et al., 2015, Kamboj et al., 2013) or total hits (Khouja et al., 2019, studies 1 and 2).

Regarding sadness, while Eastwood et al (2020) found reduced sensitivity, Craig et al. (2009) observed an increased threshold. No effects were found regarding accuracy (Dolder et al., 2017; Felisberti et al., 2015; Kamboj et al., 2013), false alarms (Khouja et al., 2019, studies 1 and 2), sensitivity (Kamboj et al., 2013), bias (Eastwood et al., 2020; Kamboj et al., 2013), reaction time (Dolder et al., 2017; Felisberti et al., 2015; Kamboj et al., 2013), threshold (Attwood et al., 2009a) and total hits (Khouja et al., 2019, studies 1 and 2).

Regarding happiness, Khouja et al. (2019, study 1) observed reduced false alarms, Eastwood et al. (2020) a reduced bias, and Felisberti et al. (2015) reduced reaction time. No effects of alcohol were found on accuracy (Dolder et al., 2017; Felisberti et al., 2015; Kamboj et al., 2013), false alarms (Kamboj et al., 2013; Khouja et al., 2019, study 2), sensitivity (Eastwood et al., 2020; Kamboj et al., 2013), bias (Kamboj et al., 2013), reaction time (Kamboj et al., 2013), threshold (Attwood et al., 2009a; Craig et al., 2009), and total hits (Khouja et al., 2019, studies 1 and 2).

Regarding fear, the only study finding reduced sensitivity for fear under alcohol was by Eastwood et al. (2020). The other studies found no effects on accuracy (Dolder et al., 2017; Felisberti et al., 2015; Kamboj et al., 2013), false alarms (Kamboj et al., 2013; Khouja et al., 2019, studies 1 and 2), sensitivity (Kamboj et al., 2013), bias (Eastwood et al., 2020; Kamboj et al., 2013), reaction time (Dolder et al., 2017; Felisberti et al., 2015; Kamboj et al., 2013), and total hits (Khouja et al., 2019, studies 1 and 2).

Regarding disgust, one study each found increased accuracy (Felisberti et al., 2015) and reduced sensitivity (Eastwood et al., 2020). No effects were found on accuracy (Dolder et al., 2017; Kamboj et al., 2013), false alarms (Kamboj et al., 2013; Khouja et al., 2019, studies 1 and 2) sensitivity (Kamboj et al., 2013), bias (Eastwood et al., 2020; Kamboj et al., 2013), reaction time (Dolder et al., 2017; Felisberti et al., 2015; Kamboj et al., 2013), and total hits (Khouja et al., 2019, studies 1 and 2).

Regarding surprise, no study observed effects on accuracy and reaction time (Dolder et al., 2017), as well as false alarms and total hits (Khouja et al., 2019, studies 1 and 2). One study also found no effect of alcohol on reaction time when judging contempt (Felisberti et al., 2015).

There were some findings regarding the dosage of alcohol. Kamboj et al. (2013) found an increased bias for neutral emotions at moderate (0.40 g/kg) but not high doses (0.80 g/kg). High (0.6 g/kg for men and 0.52 g/kg for women) but not low dosage (0.2 g/kg for men and 0.17 g/kg for women) was associated with increased accuracy for contempt (Felisberti et al., 2015).

Some studies also investigated discrimination abilities between emotions under alcohol. No effects were found for discrimination between happiness and anger (Attwood et al., 2009b; Eastwood et al., 2020; Khouja et al., 2019), but a bias towards anger in the discrimination between anger and disgust was observed for male but not female faces (Attwood et al., 2009b). Eastwood et al. (2020) also reported a bias towards sadness in the discrimination between sadness and happiness.

One study found no effect of alcohol on empathy for pain or neutral emotional states (Francis et al., 2019), but reduced empathy for happy and sad emotions. Thiel et al. (2018) observed reduced empathy for positive emotions, but no effect on negative emotions. In contrast, Dolder et al. (2017) reported increased explicit empathy for positive emotions, and again no effect on empathy for negative emotions as well as indirect or cognitive empathy.

Johnson et al. (2018) observed that alcohol-intoxicated individuals may inhibit negative responses to negative social information, but display difficulty inhibiting negative responses to social information that requires Theory of Mind. They also suggest that people under the influence of alcohol can adjust their responses when provided with specific guidelines on how to respond.

Lastly, we did not identify any studies investigating potential effects of alcohol on social connection or prosocial behaviour. None of the studies assessed first-hand pain reduction as a manipulation check.

3.7 Placebo analgesia and hypnotic analgesia

Next, we report the behavioural and neurophysiological effects of placebo and hypnotic analgesia on social emotions and behaviour. None of the included studies investigated the effects of these manipulations on mimic reactivity, emotion recognition or social connection. Placebo analgesia was used in 10 studies (8 independent samples; the same sample was tested in DePascalis & Vecchio, 2022 and Vecchio & DePascalis, 2021, and in Hartmann et al. 2021a and 2021b), and hypnotic analgesia in one study (Braboszcz et al., 2017).

On the behavioural level, five studies found that placebo analgesia causally reduced empathy for another's pain, either in real time using abstract cues depicting who was receiving pain or in pictures (Rütgen et al., 2015a; Rütgen et al., 2015b; Rütgen et al., 2018; Rütgen et al., 2021; Zhao et al., 2020), while no such effect was reported in the other five studies (Hartmann et al., 2021a; Hartmann et al., 2021b; Hartmann et al., 2022; DePascalis & Vecchio, 2022; Vecchio & DePascalis et al., 2021). These decreases in pain empathy were positively correlated with first-hand pain perception (r = .56; Rütgen et al., 2015a), and the magnitude of self- and other-related pain decreases through placebo analgesia did not differ

significantly in Rütgen et al. (2015a; 2015b). Moreover, seven studies reported a reduction in personal unpleasantness when observing another in pain, either in real time or in pictures (DePascalis & Vecchio, 2022; Rütgen et al., 2015a; Rütgen et al., 2015b; Rütgen et al., 2018; Vecchio & DePascalis, 2021; Zhao et al., 2020). Only Hartmann et al. (2021a; 2021b; 2022) found no effects on unpleasantness. Interestingly, the studies by Hartmann and colleagues used a within-subject design and a different task that focused on somatosensory aspects of the empathic experience, which might explain the different findings.

On the neurophysiological level, placebo analgesia reduced brain activity measured with functional magnetic resonance imaging (fMRI) in anterior midcingulate cortex (aMCC) and left anterior insular (AI) in Rütgen et al. (2015a, 2021), and in posterior insula, superior temporal gyrus, and posterior gyrus in Zhao et al. (2020). Hartmann et al. (2021a; 2021b) did not find effects of localised placebo analgesia on brain activity in aMCC, AI, and primary/secondary somatosensory cortex (S1/S2). In the studies measuring electroencephalography (EEG), a reduced N1 peak amplitude (Vecchio & DePascalis, 2021) or a reduced P2 amplitude (Rütgen et al., 2015b; Rütgen et al., 2018). 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 heart rate variability (HRV; DePascalis & Vecchio, 2022). The study employing hypnotic analgesia found reduced brain activity measured using fMRI in right amygdala, bilateral insula, periaqueductal grey, posterior thalamus, and supplementary motor area (Braboszcz et al., 2017).

One study investigated the generalising effects of placebo analgesia on empathy for pleasant and unpleasant touch (Rütgen et al., 2021). This study found no behavioural effects on empathy for pleasant, but reduced empathy for unpleasant touch in the placebo vs. the control group. On the neural level, the authors also reported reduced activity in right central occipital gyrus during empathising with pleasant stimuli, and reduced activity in right anterior insula, left fusiform gyrus, and right secondary somatosensory cortex during empathising with unpleasant stimuli another person received.

The only study that measured prosocial behaviour was from Hartmann et al. (2022). They found that placebo analgesia reduced prosocial behaviour, but only situations where people could only help little (as opposed to more). They also reported a positive correlation between the unpleasantness people felt for another in pain and their amount of prosocial choices. Finally, the effect that placebo analgesia had on prosociality was fully mediated by the amount of affect sharing people had for another in pain. Importantly, 10 out of 11 studies assessed first-hand pain reduction as a manipulation check.

4 Discussion

Changes to one's pain processing system via external or cognitive influences may influence how we perceive the world around us and interact with other people. The aim of the present preregistered, PRISMA-guided, systematic literature review was to investigate the causal effects of different types of pain modulations on social emotions and behaviour. We included and qualitatively summarised 50 out of 2060 screened empirical studies. Below, we discuss the effects that opioids and opioid antagonists, acetaminophen, capsaicin, cannabinoids, ketamine, alcohol, placebo analgesia, and hypnotic analgesia had on social emotions and behaviour in 50 included studies. Our investigated outcomes were empathy for pain, empathy for other emotions, reaction to emotional stimuli, emotional face recognition, social closeness, and prosocial behavior. Due to the findings' heterogeneity, we first discuss the findings for each (psycho)pharmacological pain manipulation separately, after which we turn to a general discussion of implications this systematic review has.

4.1 Opioids and opioid antagonists

In discussing the varied findings on the impact of opioids and opioid antagonists on social-emotional processing, it is crucial to highlight the role of different stimulus sets in shaping outcomes. The mixed results observed for mimic reactivity and emotion recognition can be partly attributed to the nature of the stimuli used in the studies. For instance, studies utilising static facial expressions reveal different patterns of mimicry and recognition compared to those employing dynamic stimuli. Static stimuli tend to offer less contextual and temporal information, potentially leading to less pronounced effects on emotional processing than

dynamic, context-rich stimuli that might elicit more nuanced emotional responses. Naturalism also appears to be a relevant factor: The dynamic change from a neutral facial expression to the display of the full emotional expression lasted 2500 ms in Massaccesi et al. (2022), while the corresponding time period in the study of Meier and colleagues (2017) (who found an effect of naltrexone on happiness recognition) lasted only 1300 ms, which is much more in line with recommendations regarding the unfolding of emotional expressions in dynamic stimuli (see e.g., Hoffmann et al., 2010). This points to the importance of using naturalistic dynamic stimuli for investigating subtle differences in mimic reactivity (Krumhuber et al., 2023, for review). Additionally, the subtlety or explicitness of the emotional cues presented could further influence the outcomes. For example, Løseth et al. (2018) 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 significant roles in detecting opioid-induced changes.

When considering the differential modulation effects of opioid antagonists and opioid agonists, these substances expectedly influence emotional and empathic responses in opposing ways. Naltrexone, for example, has been shown to augment empathy for pain, as demonstrated by heightened empathic pain ratings and increased neural activity related to pain processing (Rütgen et al., 2015; Zhao et al., 2021). In contrast, morphine appears to blunt certain negative emotional responses, such as reducing negative mood during experiences of social exclusion (Bershad et al., 2016). This dichotomy underscores the opposing roles these substances play in modulating different facets of emotional and social processing.

The modulation of empathy for pain, in particular, is notably complex. While opioid antagonists like naltrexone seem to heighten sensitivity to others' pain and alter neural correlates associated with pain and emotion discrimination (Zhao et al., 2021), their effects on other affective states are less clear-cut. For instance, no significant effects of naltrexone on the perception of touch were observed, regardless of whether the touch was pleasant, neutral, or unpleasant (Rütgen et al., 2021). Conversely, opioid agonists like morphine

enhance positive affect towards social emotional scenes but do not significantly influence reactions to non-social emotional stimuli (Bershad et al., 2016). These findings suggest that opioid modulation may have a domain-specific impact, with more pronounced effects in contexts involving social or interpersonal interactions than in non-social scenarios.

In terms of affiliative processes, morphine has been found to alleviate the negative mood associated with social exclusion, highlighting its potential to buffer against social stressors (Bershad et al., 2016). On the other hand, naltrexone appears to reduce intimate self-disclosure during closeness-building interactions (Tchalova et al., 2020), suggesting a possible dampening of the drive to form deeper social connections. This finding contrasts with the unchanged 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. These divergent effects emphasise the complex interplay between opioidergic system and social behaviour, which warrants further exploration to fully understand their implications.

Lastly, the current literature reveals a significant gap in our understanding of the impact of opioids on prosocial behaviour. Despite extensive research into emotional processing and social connection, no studies have directly examined how opioids or opioid antagonists influences prosocial actions. Especially surprising is the fact that despite an abundance of opioidergic medication prescriptions and the ongoing opioid crisis (Gardner et al., 2022; Volkow and Blanco, 2020), it is still unclear how these substances affect elements of social and societal interactions, in turn influencing policymaking. This absence represents a critical area for future research, as understanding the potential of opioids to modulate prosocial behaviour could provide valuable insights into their broader social effects and therapeutic applications.

4.2 Acetaminophen

It is evident that the common analgesic acetaminophen broadly suppresses empathic responses across different contexts of pain and emotional experiences. The studies reviewed consistently demonstrate that acetaminophen reduces empathic concern and

personal unpleasantness towards both physical and social pain. For example, Mischkowski et al. (2016) found that a 1000 mg dose of acetaminophen led to diminished empathic responses to painful vignettes and socially distressing scenarios. This suppression extends to the experience of painful noise blasts, where both first-hand and empathic unpleasantness were attenuated, suggesting a generalised dampening of empathy for negative stimuli, including physical and social pain. These findings are coherent across multiple studies, reinforcing the notion that acetaminophen exerts a broad-spectrum effect on reducing empathy for distressing experiences.

Furthermore, acetaminophen's impact is not limited to negative emotional contexts. Mischkowski et al. (2019) observed that the drug also reduces empathy and personal pleasantness ratings for positive emotional scenarios, indicating that the blunting effects of acetaminophen encompass both positive and negative affective states. Despite this reduction in empathic response, the perceived positivity or pleasure of the scenarios themselves remained unaffected, suggesting a specific dampening of the emotional resonance one might feel towards others' positive experiences rather than a general decrease in the perceived quality of those experiences. This finding underscores the idea that acetaminophen broadly diminishes emotional empathy, affecting the intensity of emotional reactions to both positive and negative stimuli.

One interesting facet of acetaminophen's effects on empathy is its influence on responses to social exclusion. In a study involving a cyberball task, Mischkowski et al. (2016) found that participants who took acetaminophen showed reduced empathic concern for an ostracised player, further highlighting the drug's capacity to attenuate emotional responses to social pain. This reduction in empathy for social exclusion is consistent with the broader pattern of findings, reinforcing the conclusion that acetaminophen dampens empathic concern across various forms of emotional distress.

The mediation of empathy for painful noise blasts through reduced unpleasantness during self-experienced noise blasts, as identified by Mischkowski et al. (2016), provides insight into the mechanisms underlying these effects. This mediation analysis suggests that

acetaminophen may reduce empathic concern for others' pain by diminishing the emotional salience of similar self-experienced pain. Such findings highlight the interconnectedness of personal and empathic pain experiences and suggest that interventions targeting personal pain experiences could have downstream effects on empathy for others' pain.

However, an intriguing and somewhat contradictory finding was recently reported by Jelsone-Swain et al. (2023), who observed greater mu suppression at the C3 location while participants viewed images of painful situations after taking acetaminophen. Mu suppression, often associated with sensorimotor processing and empathy, typically reflects reduced activity in the brain regions involved in motor inhibition and could be interpreted as an increase in empathic engagement with others' pain. This result is puzzling, as it contrasts with the general trend of reduced empathic concern and unpleasantness observed in other acetaminophen studies. The interpretation of mu suppression in this context is not entirely clear and warrants further investigation. 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.

Overall, the findings largely converge on the conclusion that acetaminophen reduces empathic responses to both physical and social pain, as well as to positive emotional experiences. This is in line with recent reports linking indiscriminate analgesic consumption to reduced trait empathic concern and prosocial behaviour (Banwinkler et al., 2023). These consistent effects across studies highlight the drug's broad impact on emotional and empathic processing, suggesting a potential mechanism by which acetaminophen modulates affective states. However, the observed increase in mu suppression presents an interesting anomaly that calls for more nuanced exploration of the neural correlates of empathy under the influence of acetaminophen. Additionally, future research should aim to elucidate the specific pathways through which acetaminophen affects empathy and whether these effects translate into real-world social behaviour.

4.3 Capsaicin

Only one single study investigated the effects of capsaicin on social processing. This study found slower reaction times, but no effects on emotional face recognition performance. These results are in line with the hypothesis that capsaicin-induced ongoing pain slows down the processing of other stimuli, although it does not impact overall accuracy nor were its effects specific to any emotion. Accuracy and reaction time were, however, impaired under capsaicin when viewing emotional scenes, indicating context specificity.

4.4 Cannabinoids

When evaluating the effects of cannabinoids on social emotions and behavior, one has to take into account the exact active compound, THC or CBD. Interestingly, THC showed the most pronounced effects on recognition of negative emotions such as anger or fear and ambiguous emotions, with higher doses leading to more reduced accuracy. In contrast, happiness and sadness were not affected no matter the dosage, and CBD was found to enhance recognition of ambiguous facial expressions. 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, while CBD exhibits more specific effects on certain regions and connectivity patterns. Interestingly, skin conductance fluctuations, which are associated with increased anxiety, were increased under THC and decreased under CBD. Studies measuring empathy observed a reduction under THC, albeit only for lower doses, while no such effects were observed for CBD. These findings point to the conclusion that these two compounds may act in different ways and need to be studied separately. Effects of cannabinoids on mimic reactivity, social exclusion, and prosocial behavior will still have to be investigated in future studies. Moreover, they highlight that cannabinoids exert their effects mainly on negative, especially threatening, emotions like anger or fear.

4.5 Ketamine

The few studies that investigated the effects of ketamine on social processing center 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. However, more work is needed on ketamine's effects regarding empathy, social connection, and prosocial behaviour. Since one study found a reduction of cerebellar activity when watching fearful faces, the cerebellum could be an interesting target for future studies.

4.6 Alcohol

Our systematic review revealed that alcohol's effects on emotion processing and empathy are complex and inconsistent. While few studies observed impairments in recognizing and processing emotions in general, such as reduced accuracy (e.g., Tucker et al., 1983) or sensitivity (e.g., Eastwood et al., 2020), the majority of studies reported no significant effects on general emotion recognition performance or on various emotion-specific metrics, including reaction time and false alarm rates. Occasional findings were emotion-specific, with impairments noted for anger, sadness, and fear, while happiness and disgust showed mixed or negligible effects. Alcohol's influence also appeared dose-dependent, with moderate and high doses showing differing impacts on emotion recognition (e.g., Kamboj et al., 2013; Felisberti et al., 2015). Regarding empathy, alcohol was associated with reduced empathy for positive emotions in some studies (e.g., Thiel et al., 2018) but not for negative emotions, and cognitive empathy remained unaffected. The lack of studies on alcohol's effects on social connection and prosocial behavior highlights a significant gap in the literature. Overall, the inconsistency of findings may be due to non-optimal tasks being used in the existing literature (mainly forced choice emotion recognition tasks with static images), which suggests a 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, half of all studies found reduced empathic abilities in the domain of pain on the behavioral level. The other half found no effects, although those included the same samples in two studies, and no study reported increased abilities. Summarizing these findings, evidence thus speaks more in favor of a reduction of first-hand pain leading to a reduction of empathy for pain. This is in line with the shared representations hypothesis, which posits that we come to understand another individual's pain by reactivating our own, first-hand pain network (Rütgen & Lamm, 2024 for a review). If this latter network is not working properly, as is the case under placebo analgesia, empathic and prosocial abilities are also negatively affected. These transfer effects may, however, be moderate in size, and disappear in specific scenarios or contexts (e.g., when focusing on the somatosensory component of pain as in Hartmann et al., 2021a, 2021b; or when focusing on prosocial behavior as in Hartmann et al., 2022). On the neurophysiological level, the behavioral effects were accompanied by widespread reductions of brain activity, especially in areas associated with the affective-motivational component of pain. Unsurprisingly, no such effects were found in the studies focusing on the somatosensory component of pain empathy.

Hartmann et al. (2022) additionally reported that placebo analgesia reduced prosocial behavior, and that this effect was fully mediated by the level of empathy people felt towards the other person in pain. This shows that the effects of a manipulated pain processing system reach as far as changing our actual motivation towards helping others in need, although the finding was restricted to situations where the degree of helping was lowest.

Some crucial design specifics differ between studies. While seven between-subjects studies reported a reduction of personal unpleasantness when observing another in pain, the three within-subjects studies found no such effect. Some studies also included only psychology students, which may have hampered the believability of the placebo manipulation and decreased its effects, which could have led to the null findings regarding pain empathy. Lastly, empathy decreases were mainly found when the control condition was described as

729 an “inactive treatment”, but not in the studies where it was introduced as a drug with a “minor
730 analgesic effect”. These differences in methodology highlight the need for large,
731 representative samples as well as robust study designs that allow for clear distinction
732 between placebo and control conditions and causal conclusions.
733 Beyond pain, placebo analgesia was found to affect empathy for unpleasant but not
734 pleasant or neutral touch, implicating domain-general effects of blunted first-hand pain. The
735 finding that an opioid antagonist only blocked these effects on pain but not touch indicates a
736 pain-specific involvement of the opioidergic system in pain empathy, although this warrants
737 replication. Placebo analgesic effects on mimic reactivity, emotion recognition, or social
738 connection have not been researched so far, and could thus be a focus of future studies. The
739 same goes for work investigating the effects of hypnotic analgesia. Although the one study
740 we found observed reduced empathy and associated brain activity, more studies are needed
741 to substantiate this promising finding.

742 **4.8 General considerations**

743 There are some general considerations and implications of this review that are worth
744 discussing. First of all, our search strategy was restricted to finding studies including healthy,
745 neurotypical participants without prior medical conditions. The findings of this review might
746 therefore not readily generalize to clinical populations who are usually under a great deal
747 more pain and often have a long history of different treatment approaches, experiences, and
748 expectations. The findings in healthy participants may thus merely be used as an
749 approximation to systematically plan similar research in different patient populations, e.g.,
750 people suffering from post-operative or chronic pain.
751 This consideration also is important to underline when we consider the difference in
752 interpretation between statistically significant and clinically meaningful effects (van Rijn et al.,
753 2017). This review assessed effects based on their statistical significance, as reported by the
754 original authors. To adequately assess clinical significance, authors need to estimate and
755 report effect sizes (e.g. a difference in means, a difference in frequencies, or risk/odds ratio)
756 in conjunction with their respective confidence intervals that provide a range of plausible

values, and thus the precision, for said effect. Kieser et al. (2023) 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 for the relevance of the observed treatment effect. Therefore, especially because of the heterogeneity of findings, statistical markers of effect size will be needed in the future, not only to mark the average direction and size of different effects, but also distinguish statistically significant from clinically relevant effects.

Of note, the overall risk of bias was medium in 12 and high in 14 studies, while it was low in 23. This shows that 52% of all studies are prone to bias, with 28% highly prone. These numbers are substantial and underscore the need to prioritize addressing and minimizing bias in future research. Particular attention should be given to participant blinding and the implementation of appropriate control conditions.

An critical consideration when interpreting the findings of this systematic review is that only 12 out of 50 studies (24%) specifically evaluated the effectiveness of the intervention in reducing first-hand pain. Notably, all 12 studies reported a significant reduction in first-hand pain as a result of the intervention. This manipulation check is, however, crucial to evaluate the findings in light of the shared representations account. Such causal evidence for a joint reduction of first-hand and empathic experiences was only reported for studies investigating empathy for pain and prosocial behavior, and only for studies using acetaminophen, placebo analgesia, hypnotic analgesia, or opioids/opioid antagonists as interventions. Assessing only the findings of the studies measuring empathy for pain (Figure S2 in the Supplement) and prosocial behavior (Figure S6 in the Supplement) under these interventions, we observe 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, but this limits the connections we can make to simulation accounts overall. Relatedly, although some studies related the self- and other-related effects of placebo analgesia to each other, these between-subject studies make a direct comparison of effects difficult.

Relatedly, research has shown that while for example alcohol (e.g., Thompson et al., 2017) or ketamine (e.g., Subramaniam et al., 2004) may have downstream analgesic effects, which could then, in turn, influence social emotions and behaviours, the picture is less clear cut for cannabinoids, which for example also show effects on negative affect. For example, Lötsch et al. (2018) highlighted in their review that cannabinoid-based drugs produce heterogeneous effects. They primarily impact 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 we consider the two studies of Hartmann et al. (2021ab), who only reported evidence for placebo analgesia affecting empathy generally on an affective level, but not in a somatosensory-specific way. It is thus possible that these substances do not directly affect nociceptive processing, but instead exert effects on the general processing of affective stimuli (Lötsch et al., 2018). Stevens and Higgins (2017) reported in their review, that in only one out of 7 studies (joint n = 611), analgesia provided by cannabinoids was superior to placebo. The specificity of substances that do not directly target the pain processing system, as well as their potential varying effects on social processes, will need to be explored in greater detail in future research.

In this context, it should also be mentioned that single studies in this review often had very specific research designs and answered their own research questions. This makes direct statistical comparisons between studies difficult and led us to refrain from conducting an additional meta-analysis on the data (although we did provide effect sizes reported in the individual papers in the final data sheet on the OSF). To make such endeavours possible and use existing research findings in a sustainable way, ongoing and future work should focus on sharing their data openly.

In conclusion, the review strongly highlights that many fields are still under-researched and crucially in need of systematic, well-powered studies with adequate sample sizes. Aiming to be as broad as possible, we included a wide range of social and affiliative emotions and behaviors. If we aim to shed more light on the role of our own pain processing system for social emotions and behaviours, we need proper manipulation checks and causal

evidence. Only then may we begin to understand how the self-experience is related to the experience of our environment.

5 CRediT author statement

HH: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration. **PD**: Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization. **UB:** Resources, Writing - Review & Editing, Funding acquisition. **MR:** Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration (Brand et al., 2015).

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7 Declarations of Interest

The authors declare that they have no financial interests or potential conflicts of interest.

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