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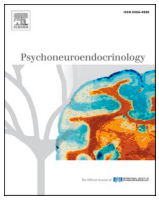

Effects of the mu-opioid receptor agonist morphine on facial mimicry and emotion recognition

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ABSTRACT

Facial mimicry and emotion recognition are two socio-cognitive abilities involved in adaptive socio-emotional behavior, promoting affiliation and the establishment of social bonds. The mu-opioid receptor (MOR) system plays a key role in affiliation and social bonding. However, it remains unclear whether MORs are involved in the categorization and spontaneous mimicry of emotional facial expressions. Using a randomized, placebo-controlled, double-blind, between-subjects design, we investigated in 82 healthy female volunteers the effects of the specific MOR agonist morphine on the recognition accuracy of emotional faces (happiness, anger, fear), and on their facial mimicry (measured with electromyography). Frequentist statistics did not reveal any significant effects of drug administration on facial mimicry or emotion recognition abilities. However, post hoc Bayesian analyses provided support for an effect of morphine on facial mimicry of fearful facial expressions. Specifically, compared to placebo, morphine reduced mimicry of fear, as shown by lower activity of the frontalis muscle. Bayesian analyses also provided support for the absence of a drug effect on mimicry of happy and angry facial expressions, which were assessed with the zygomaticus major and corrugator supercilii muscles, as well as on emotion recognition accuracy. These findings suggest that MOR activity is involved in automatic facial responses to fearful stimuli, but not in their identification. Overall, the current results, together with the previously reported small effects of opioid compounds, suggest a relatively marginal role of the MOR system in emotion simulation and perception.

1. Introduction

Human faces are fundamental means of social communication, providing a rich source of information regarding others' emotions, intentions, and dispositions, including one's interest for social affiliation (Keltner and Haidt, 1999). Correctly inferring emotional states from facial signals aids individuals to adaptively tailor their behavior towards others, increasing social understanding. Impairments in facial emotion recognition have indeed been observed in clinical conditions characterized by difficulties in social functioning, such as autism (Trevisan and Birmingham, 2016) and schizophrenia (Kohler et al., 2010).

Besides providing information through inference, emotional facial signals influence behavior through contagion processes, such as mimicry. Facial mimicry, that is the unconscious and automatic imitation of others' emotional facial expressions (Dimberg et al., 2002), can facilitate the recognition of others' emotions and fosters affiliation by generating feelings of similarity and connection (Hess and Fischer, 2013). Accordingly, experimental manipulations and clinical conditions interfering with the activity of facial muscles impair the ability to identify aspects of others' emotional expressions, and their recognition (Wood et al., 2016). Further, facial mimicry was shown to modulate authenticity judgments of different kind of smiles (Korb et al., 2014), and to affect interpersonal liking (van der Schalk et al., 2011; Yabar and Hess, 2007).

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Previous research findings suggest that the endogenous mu-opioid receptor (MOR) system is a key neurochemical mediator of affiliation and bonding. For instance, endogenous MORs modulate responses to social signals, such as laughter and crying (Sun et al., 2021). Further, MOR blockade decreases social motivation (e.g., effort exerted to watch an attractive face (Chelnokova et al., 2014) and to receive social touch (Korb et al., 2020)), feelings of connectedness (Inagaki, 2018), as well as hedonic reactions to social stimuli (e.g., Buchel et al., 2018; Chelnokova et al., 2014; Korb et al., 2020). Interestingly, impairments in social cognitive functions, including spontaneous mimicry, identification of emotional facial expressions, and empathy for pain, have been observed after long-term use of opioids (Kroll et al., 2021, 2018; Terrett et al., 2020). However, unlike pharmacological challenges in healthy participants, cross-sectional case-control studies cannot reveal cause-effect relationships.

At present, pharmacological studies in opioid-naïve volunteers providing causal evidence of MOR involvement in mimicry and emotion identification are scarce and have led to inconsistent findings (Kraaijenvanger et al., 2017; Nummenmaa and Tuominen, 2018). Administration of the non-specific opioid antagonist naltrexone resulted in negatively-valenced facial responses to happy faces in one study (Meier et al., 2016), but had no effects on facial responses to positive or negative emotional faces in another study (Wardle et al., 2016). Further, naltrexone was shown to increase attention to emotional stimuli (fear, anger, sadness and happiness), but also to selectively impair the identification of fear and sadness (Wardle et al., 2016), and to reduce the discrimination of pain expressions (Zhao et al., 2021). Similarly, the mu-opioid partial agonist buprenorphine reduced attention and recognition of fearful expressions (Bershad et al., 2018, 2016; Ipser et al., 2013).

While buprenorphine and naltrexone have opposite effects on the MOR system (agonism vs antagonism), they are also both antagonists at the kappa-opioid receptor (KOR) system, which could explain some of the inconsistencies in the literature. Indeed, as KOR antagonism has anxiolytic-like properties (Bruijnzeel, 2009), some of the observed effects of naltrexone and buprenorphine on facial emotional processing might be explained by the modulation of KORs, rather than of MORs. To date, only one study has investigated the effects of a highly selective mu-opioid agonist (i.e., morphine) on emotion perception, showing a reduction of perceived anger in neutral and implicit emotional expressions (Løseth et al., 2018). In summary, the current evidence of MOR regulation of facial mimicry and emotion recognition is scant and most of the previous pharmacological studies have employed non-specific opioid agonists and antagonists acting on both MOR and KOR systems, preventing a clear understanding of the specific contribution of each class of opioid receptors.

In the current study, we used a randomized, placebo-controlled, double-blind, between-subjects design to investigate the effects of morphine administration on the categorization and spontaneous mimicry of emotional facial expressions. We examined three basic facial emotional expressions signaling threat or affiliation: anger, fear, and happiness; and recorded electromyographic activity of the related facial muscles: corrugator supercilii, lateral frontalis, and zygomaticus major. Based on previous findings indicating a mu-opioid down-regulation of social threat cues and up-regulation of positive affiliative cues (for a recent review see Meier et al., 2021), we hypothesized that morphine reduces mimicry and recognition rates for anger and fear, and increases mimicry and improves recognition of happiness. We expected the drug effects on emotion recognition to be limited to or stronger for stimuli with low emotional intensity (Løseth et al., 2018). As mimicry can aid emotion identification (but see Holland et al., 2021), we hypothesized our measures of mimicry and recognition to be linked. Specifically, we expected that a morphine-induced decrease of facial mimicry of threatening facial expression predicts decreased recognition of those same emotions; and that a morphine-induced enhancement of facial mimicry for affiliative facial expressions predicts their improved recognition.

2. Materials and methods

2.1. Participants

A sample of 82 healthy female volunteers took part in the study (other aspects of this data set were reported in Massaccesi et al., 2022). Each participant was randomly assigned to one of two groups to receive either morphine (n = 42) or placebo (n = 40). The groups did not differ significantly (Table 1) in terms of age, Body-Mass-Index (BMI), autistic traits (short version of the German Autism Spectrum Quotient, AQ-k; Freitag et al., 2007) and alexithymic traits (20-item Toronto Alexithymia Scale, TAS-20; Bagby et al., 1994). The sample was restricted to female participants to increase data consistency, as gender differences in opioid pharmacokinetics (Zubieta et al., 1999), as well as in the amplitude of facial mimicry (Dimberg and Lundquist, 1990), are known, and could also extend to the underlying neural network (Korb et al., 2015). For similar reasons, only participants without intake of hormonal contraceptives were included, and they were tested only during the self-reported luteal phase of their menstrual cycle. All participants reported to be right-handed, to smoke less than 10 cigarettes per week, not to have a history of current or former drug abuse, to have a BMI between 17 and 35, and to be free of psychiatric or neurological disorders. Other exclusion criteria were: single or repeated use of any strong opioids in the last two years, regular intake of medications, current pregnancy or breastfeeding, suffering from impaired respiratory functions, respiratory weakness or lung disease.

To determine the required sample size, an a priori power analysis for F-tests was conducted using G*Power (Faul et al., 2007) with repeated measures, within-between interaction (*emotion type* × *drug*), assuming a small effect size of Cohen's f = 0.15, an α-error probability of 5%, and a power of 80%, which suggested a total minimum sample size of N = 74.

Table 1
Demographic and self-reported substance use characteristics of the participants.

	PLACEBO	MORPHINE	*p* value
N	40	42	–
Age (years)	23.9 ± 3.9	23.1 ± 3.1	0.28
BMI (kg/m^2)	22.3 ± 2.7	21.4 ± 3.4	0.22
Autism (AQ-k)	5.7 ± 3.6	6.4 ± 3.7	0.37
Alexithymia (TAS-20)	40.2 ± 7.8	41.0 ± 9.0	0.65
Alcohol use (%)[1]			
Never	7.5	7.1	–
Several times a year	30	23.8	–
Several times a month	35	45.2	–
1–2 times per week	27.5	21.4	–
3–4 times per week	0	2.4	–
Tobacco use (%)[2]			
Not smoking	90	88.1	–
Occasionally (< 10 cigarettes per week)	10	11.9	–
Drug use (% lifetime – last year)[3]			
Cannabis	60 – 32.5	45.2 – 26.2	–
Tranquilizers	5 – 2.5	9.5 – 4.8	–
Stimulants	17.5 – 7.5	26.2 – 9.5	–
Opiates	2.5 – 0	9.5 – 0	–
Hallucinogens	12.5 – 2.5	14.3 – 2.4	–
Other	2.5 – 0	7.1 – 2.4	–

[1] Self-report ("How often do you consume alcohol?"). Participants were excluded if they reported to consume alcohol more than 3–4 times per week and were screened for alcohol abuse/dependence using the Mini-International Neuropsychiatric Interview.

[2] Self-report ("How often do you smoke cigarettes?"). Participants were excluded if they reported to smoke more than 10 cigarettes per week.

[3] Self-report ("For each of the listed substances, please report if you have ever consumed the substance in your lifetime and/or if you have consumed it within the past year."). Participants were excluded if they reported consumption of opiates within the past year and were screened for illicit substances regular use/abuse/dependence using the Mini-International Neuropsychiatric Interview.

The effect size was determined based on previous research investigating the effects of opioid compounds on emotion recognition and facial mimicry. For example, the study from Meier et al. (2016) reported a drug effect of medium size on facial mimicry (Cohen's f = 0.35), however, studies on emotion recognition found effects of smaller size (estimated Cohen's f between 0.1 and 0.2; Ipser et al., 2013; Løseth et al., 2018; Wardle et al., 2016).

The study was approved by the Ethics Committee of the Medical University of Vienna (EK 1393/2017) and was performed in line with the Declaration of Helsinki (World Medical Association, 2013). All participants signed a consent form before taking part in the study.

2.2. Drug administration

In a between-subjects, randomized, double-blind, placebo-controlled design, participants were orally administered either 10 mg of morphine sulfate (Morapid®) or a placebo. The dose was selected to stimulate the activity of the MOR system with minimal subjective and unwanted effects. Morphine is a selective MOR agonist and, for oral administration, has an average bioavailability of 30–40%, a maximal effect (t-max) at 1–2 h after administration, and a half-life of 2–4 h (Lugo and Kern, 2002). Placebo consisted of capsules containing 650 mg of mannitol (sugar), which were otherwise visually identical to the ones containing morphine.

2.3. Facial mimicry task

The stimulus material included 18 videoclips, each depicting the face of one of six models (3 females, 3 males) from the NimStim set of facial expressions (Tottenham et al., 2009), gradually changing (increments of 2% intensity) their facial expression from neutral to anger, fear or happiness (Fig. 1). Each trial consisted of a fixation cross (2000 ms), followed by one of the videoclips (3500 ms). In each video, a gradual change in emotion occurred during the first 2500 ms, and the last frame, displaying the full emotional expression, was displayed for additional 1000 ms (see Supplementary Material for further details). During the task, facial EMG was recorded using a g.USBamp amplifier (g.tec Medical Engineering GmbH) and the software Matlab (MathWorks, Inc). Reusable Ag/AgCl electrodes were attached bipolarly over the left corrugator supercilii, lateral frontalis, and zygomaticus major muscles (Fridlund and Cacioppo, 1986). These muscles were targeted because they are predominantly involved in angry, fearful and happy facial expressions, respectively (Van Boxtel, 2010). A ground electrode was attached to the participants' forehead and a reference electrode on the left mastoid. The sampling rate was 1200 Hz and impedances were kept below 20 kΩ. EMG data were lost for five participants in the morphine group and two participants in the placebo group, due to technical issues.

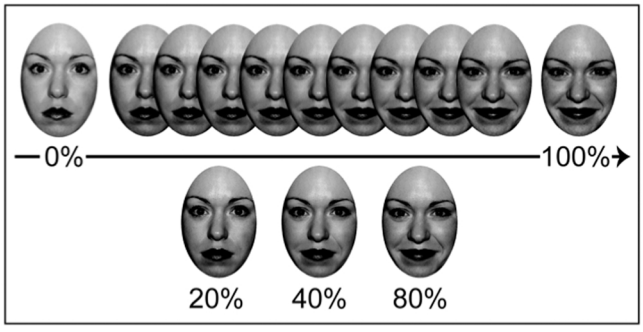

Fig. 1. Example stimuli. Top: In the facial mimicry task, participants viewed videos showing dynamic emotion changes, created by morphing a neutral face (0% emotion) with a 100% emotional face (happy, fearful, angry). Bottom: single frames with 20%, 40% and 80% emotional intensity were extracted from the videos and displayed in the emotion recognition task.

2.4. Emotion recognition task

Stimuli consisted of three individual frames from each of the 18 videos presented in the facial mimicry task (Fig. 1). In each trial, a fixation cross of 2000–3000 ms was followed by an image showing anger, fear, or happiness at 20, 40, or 80% intensity. Participants were asked to identify the emotion conveyed by the model's facial expression as fast and accurately as possible (see Supplementary Material for further details).

2.5. Control measures

Participants' mood was assessed immediately before drug administration (T1), 60 min after drug administration (T2), and immediately after completion of the emotion recognition task (T3), using an in-house set of self-report items and the German short version of the Profile of Mood States (POMS; Albani et al., 2005) (see Supplementary Material). At T1 and T2, 26 possible drug side-effects were also assessed (see Supplementary Material). Potential drug effects on cognitive functions were assessed 55 min after drug administration (just before T2), using the Trail Making Test (TMT; Reitan, 1958) and the Digit Symbol Substitution Test (DSST; Wechsler, 1939).

2.6. Procedure

In a first appointment, potential participants were screened for physical and mental health (blood examination, electrocardiogram, blood pressure measurement, and psychiatric interview). Eligible participants were then invited for a second appointment at which the experiment took place. At the beginning of the testing session participants underwent urine drug and pregnancy tests. Then, they received the assigned capsule and a standardized snack, and were prepared for facial EMG. The facial mimicry task was preceded by a socioeconomic game (data to be reported elsewhere) and was followed by the emotion recognition task. A fixed task order was used for all participants. To ensure relatively high and stable levels of morphine, the facial mimicry and emotion recognition tasks were completed between 75 and 100 min after drug administration. Following the emotion recognition task, other experimental tasks were implemented (see Massaccesi et al., 2022 and Fig. S2 in the Supplementary Material) and a blood sample was drawn to confirm drug uptake (~180 min after drug administration, data reported in Massaccesi et al., 2022).

2.7. Statistical analyses

Data pre-processing and transformation, and definition of outliers are described in the Supplementary Material. To test for the effect of morphine on facial mimicry we conducted a 2 × 3 × 7 mixed analysis of variance (ANOVA) with the between-subjects factor *drug* (morphine, placebo), and the within-subject factors *emotion type* (anger, fear, happiness) and *time* (bins 1–7). The effects of morphine on emotion recognition were assessed with two separate 2 × 3 × 3 mixed ANOVAs (one for reaction times (RTs) and one for accuracy) with the between-subjects factor *drug*, and the within-subject factors *emotion type* and *emotion intensity* (20%, 40%, 80%). To assess drug effects on the contribution of facial mimicry to recognition abilities, we calculated a *facial mimicry* score by averaging the EMG recorded in response to the videos presented in the facial mimicry task, at the time points corresponding to 20%, 40% and 80% emotional intensity: 500 ms (first bin), 1000 ms (second bin), and 2000 ms (fourth bin). For each emotion, only the activity of the main corresponding muscle was used. The *facial mimicry* score was log transformed (because of skewness), mean-centered, and entered in two linear models (one for RTs and one for accuracy), which also included *drug, emotion type, emotion intensity*.

A mood index was created by averaging mood scores at T2 and T3 and then subtracting the scores at T1. Similarly, for side-effects an index

was created computing the difference of the composite score at T1 and T2. Drug effects on mood and side-effects, as well as on cognitive functions (DSST, TMT) and baseline muscle activity, were assessed using independent sample t-tests.

Analyses were conducted in R (R Core Team, 2021). Where sphericity was violated, Greenhouse-Geisser correction was applied. Tukey correction for multiple comparisons was used. The data and analysis scripts supporting the manuscript are available online at https://osf.io/sz8e3/.

2.8. Post hoc statistical analyses

As frequentist statistics cannot provide evidence in favor of the null hypothesis (evidence of absence; Keysers et al., 2020), null findings were followed up with Bayesian analyses in JASP 0.15 (JASP team, 2021). First, the default multivariate Cauchy prior (r scale prior width for fixed effects =.5) was used for the repeated measure ANOVAs. Then, robustness checks were conducted using a narrower (r = .2, as well as a wider prior (r = 1), as recommended by Van Doorn et al. (2021). We computed Bayes factors (BF01) to estimate the evidence in favor of both the null and the alternative hypotheses. A BF01 between 3 and 10 is considered moderate, and a BF01 larger than 10 is considered strong evidence for the null hypothesis. In contrast, a BF01 between 0.3 and 0.1 is considered moderate, and a BF01 smaller than 0.1 is considered strong evidence for the alternative hypothesis (van Doorn et al., 2021).

3. Results

3.1. Drug blinding

After completing the session, 50% of participants who received morphine correctly guessed their group. Across both groups, 55% of participants believed to have been administered a placebo, 29% morphine, and 16% naltrexone.[1] Overall, these numbers indicate successful blinding.

3.2. Control measures

No significant effects of *drug* were found on positive and negative mood (all $t < -.02$, all $p > .83$, DSST and TMT (all $t < .29$, all $p > .77$, POMS subscales anger and depression (all $t < -1.98$, all $p > .05$) (Table 2), side-effects ($t(56.7) = -.86$, $p = 0.39$) (Fig. S1), and baseline activity of the corrugator, frontalis and zygomaticus muscles (all $t < -1.10$, all $p > .28$). Greater fatigue ($t(77.9) = -2.70$, $p < .01$) and lower vigor ($t(78) = 2.2$, $p = .03$) were expressed following morphine administration, compared to placebo (POMS subscales; Table 2). However, adding scores of vigor and fatigue, as well as BMI, as mean-centered covariates to the main analyses did not alter the pattern of results.

3.3. Effects of morphine administration on facial mimicry

For descriptive statistics (means and SDs), see Table S6 in the Supplementary Material.

3.3.1. Corrugator supercilii

A significant *emotion type* × *time* interaction effect was found ($F(4.13, 301.68) = 18.69$, $p < .001$, $\eta_p^2 = .20$). As expected, angry and happy faces resulted, respectively, in corrugator activation and relaxation (angry bin3–bin7 vs bin1: all $p < .02$; happy bin2–bin7 vs bin1: all $p < .001$), while fear did not result in significant changes in corrugator activity (bin2–bin7 vs bin1: all $p > .72$) (Fig. 2a). No significant main or interaction *drug* effects were observed (all $F < 2.29$, all $p > .14$). The Bayes factor analysis provided very strong support for the absence of *drug* × *emotion type* (BF01 = 59.3) and *drug* × *emotion type* × *time* interactions (BF01 = 6.232e+7, Table S1 in Supplementary Material). A similar result was shown using wider (r = 1, BF01 > 417.2) and narrower (r = .2, BF01 > 6.9) prior distributions.

Table 2
Scores on the Trial Making Test (TMT), Digit Symbol Substitution Test (DSST) and mood scales.

	PLACEBO	MORPHINE
TMT A (s)	26.4 ± 8.6	26.0 ± 8.0
TMT B (s)	58.9 ± 21.9	57.2 ± 32.4
DSST (N correct)	54.1 ± 9.3	54.3 ± 8.9
Positive mood		
T1	69.2 ± 16.4	73.7 ± 13.0
T2	69.7 ± 20.0	75.3 ± 15.2
T3	65.3 ± 20.5	68.8 ± 19.0
Negative mood		
T1	12.4 ± 10.1	12.3 ± 11.5
T2	9.5 ± 9.7	8.2 ± 10.9
T3	9.7 ± 9.6	11.5 ± 12.4
POMS Depression		
T1	18.0 ± 5.3	17.0 ± 4.6
T2	16.9 ± 4.6	16.7 ± 4.6
T3	16.8 ± 6.4	18.0 ± 6.9
POMS Anger		
T1	8.4 ± 2.2	7.9 ± 2.3
T2	8.0 ± 1.9	7.9 ± 2.0
T3	8.4 ± 3.0	8.5 ± 2.9
POMS Vigor		
T1	26.8 ± 6.9	27.7 ± 6.7
T2	24.4 ± 8.1	22.3 ± 7.2
T3	21.5 ± 8.5	19.6 ± 7.5
POMS Fatigue		
T1	12.7 ± 5.3	11.1 ± 4.3
T2	12.3 ± 6.9	14.4 ± 7.0
T3	15.2 ± 8.3	17.8 ± 9.2

Note: T1, immediately before drug administration; T2, 60 min after drug administration; T3, immediately after completion of the emotion recognition task; POMS, Profile of Mood States. Min-max ranges: 1–101 for positive and negative mood; 7–49 for POMS Anger, Fatigue, Vigor; 14–98 for POMS Depression.

3.3.2. Lateral frontalis

A significant *emotion type* × *time* interaction effect was found ($F(3.95, 284.13) = 15.55$, $p < .001$, $\eta_p^2 = .18$). As expected, fearful and happy faces resulted in frontalis activation and relaxation, respectively (fearful bin3–bin7 vs bin1: all $p < .001$; happy bin3–bin7 vs bin1: all $p < .001$), while anger did not result in significant changes in frontalis activity (bin2–bin7 vs bin1: all $p > .99$) (Fig. 2b). No significant main or interaction *drug* effects were observed (all $F < 2.11$, all $p > .15$). However, the Bayes factor analysis provided moderate support for a *drug* × *emotion type* interaction effect (BF01 =.2; Table S2 in Supplementary Material). As shown in Fig. 2b, participants administered with morphine showed reduced activation of the frontalis muscle while viewing fearful faces compared to the placebo group. A similar result was shown using a narrower prior distribution (r = .2, BF01 = .1, but anecdotal evidence was shown using a wider prior (r = 1, BF01 = 1.2).

3.3.3. Zygomaticus major

A significant *emotion type* × *time* interaction effect emerged ($F(2.26, 163.06) = 19.31$, $p < .001$, $\eta_p^2 = .21$). As expected, activity of the zygomaticus muscle increased while viewing happy faces (bin2–bin7 vs bin1: all $p < .04$) and did not significantly change for fear or anger (fearful bin2–bin7 vs bin1: all $p > .19$; angry bin2–bin7 vs bin1: all $p > .82$) (Fig. 2c). No significant main or interaction effects of *drug* were observed (all $F < .69$, all $p > .43$). The Bayes factor analysis provided

[1] To reduce drug-related expectancy, participants were told they might receive an opioid agonist (morphine), antagonist (naltrexone) or placebo (but in reality could receive only morphine or placebo). The guess from two participants is not available as they left the study before completion.

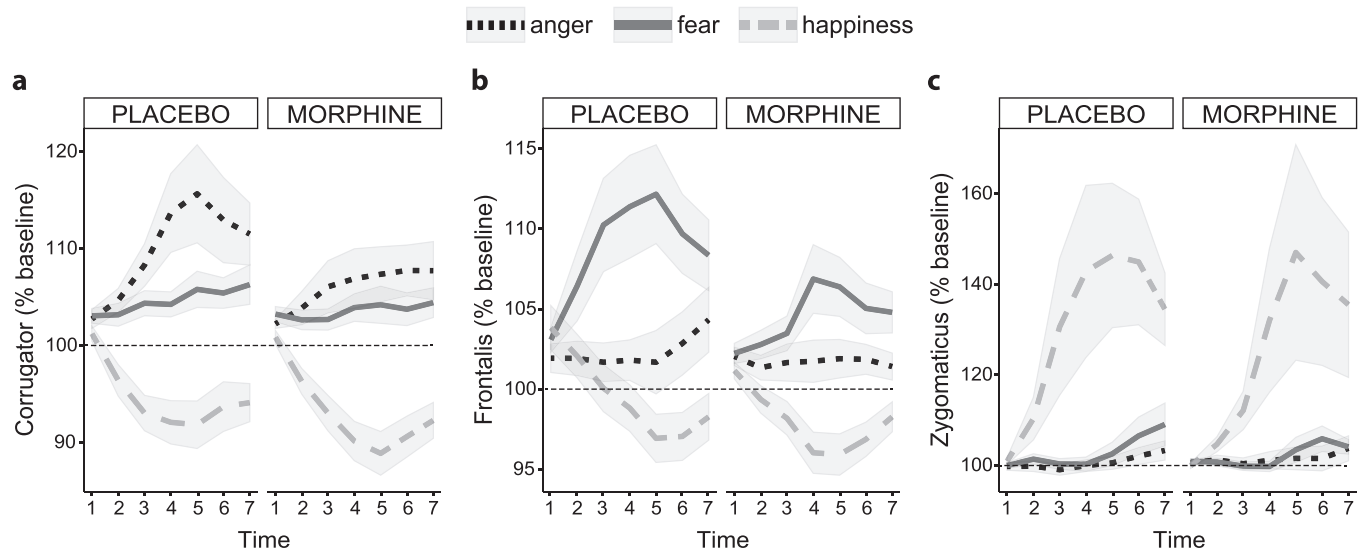

Fig. 2. Effects of morphine on facial mimicry. Mean activity (expressed as percentage of the baseline) of (a) corrugator supercilii, (b) lateral frontalis, and (c) zygomaticus major muscles during the videoclips in each type of emotion (anger, fear, happiness) following morphine and placebo administration. While facial mimicry occurred for all three emotions, only the activity of the frontalis muscle in response to fearful faces (b) was reduced by morphine, according to Bayesian (but not frequentist) statistics. The horizontal black dashed line marks the baseline level (100%), shaded ribbons represent standard error of the mean. Each of the seven time points displays the average amplitude over a 500 ms window.

moderate support for the absence of a *drug* × *emotion type* interaction effect (BF01 = 7.3) and very strong support for the absence of a *drug* × *emotion type* × *time* interaction effect (BF01 = 2.975e+7; Table S3 in Supplementary Material). A similar result was shown using a wider prior distribution (r = 1, BF01 > 47.9), but anecdotal evidence was shown for a *drug* × *emotion type* interaction using a narrower prior distribution (r = .2, BF01 = 1.1).

3.4. Effects of morphine administration on emotion recognition

For descriptive statistics (means and SDs), see Table S7 in the Supplementary Material.

3.4.1. Accuracy

The ANOVA revealed a significant *emotion type* × *emotion intensity* interaction effect ($F(3.05, 244.19) = 38.09$, $p < .001$, $\eta_p^2 = .32$). For stimuli with 20% intensity participants were significantly more accurate in recognizing fear as compared to happiness and anger (both $p < .001$), for stimuli with 40% intensity participants were significantly less accurate in recognizing anger as compared to fear and happiness (both $p < .01$), and for stimuli with 80% intensity participants were significantly less accurate in recognizing fear compared to happiness and anger, as well as in recognizing anger compared to happiness (all $p < .01$; Fig. 3a). No significant effects of *drug* were observed (all $F < 1.18$, all $p > .31$). The Bayes factor analysis provided very strong support for the absence of *drug* × *emotion type* (BF01 = 180.7) and *drug* × *emotion type* × *emotion intensity* (BF01 = 60,689.8) interactions. Similar results were obtained using different priors (Table S4 in Supplementary Material).

3.4.2. Reaction Times (RTs)

The ANOVA revealed a significant *emotion type* × *emotion intensity* interaction effect ($F(3.23, 258.09) = 37.43$, $p < .001$, $\eta_p^2 = .32$). For stimuli with 20% intensity participants were faster in recognizing fear compared to happiness ($p = .02$), for stimuli with 40% intensity participants were slower in recognizing fear compared to happiness and anger (both $p < .001$), and for stimuli with 80% intensity they were slower in recognizing fear compared to happiness and anger, as well as in recognizing anger compared to happiness (all $p < .01$; Fig. 3b). The

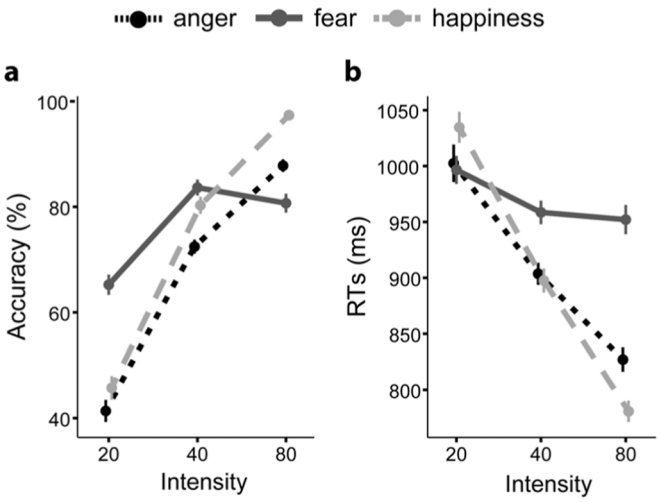

Fig. 3. Mean accuracy and reaction times in the emotion recognition task. Mean (a) accuracy (percentage of correct responses) and (b) reaction times (RTs) by emotion type (anger, fear, happiness) and intensity (20%, 40%, 80%). Error bars represent standard error of the mean.

Bayes factor analysis provided strong support for the absence of *drug* × *emotion type* (BF01 = 13.2) and *drug* × *emotion type* × *emotion intensity* (BF01 = 3535.1) interactions. Similar results were obtained using a wider prior, while only anecdotal evidence for the absence of a *drug* × *emotion type* interaction was observed with a narrower prior (but notice also the greater error in this case; Table S5 in Supplementary Material).

3.5. Effects of morphine on mimicry-recognition relationship

We had hypothesized that eventual effects of morphine on emotion recognition abilities would be predicted by morphine-induced changes in facial mimicry. However, as reported above, we did not observe any effect of the drug on accuracy and RTs in the emotion recognition task. Nevertheless, exploratory analyses were conducted to assess whether the relationship between facial mimicry and emotion recognition

abilities was altered following morphine administration, compared to placebo. These analyses did not reveal any significant effect of *facial mimicry* or *drug* (all $F < 1.88$, all $p > .15$).

4. Discussion

The current study aimed to investigate the effects of selective mu-opioid agonism on facial mimicry and emotion recognition of positive and negative emotional facial expressions (happiness, anger, and fear) in opioid-naïve, healthy subjects. All three emotions induced clear facial mimicry and were recognized with high accuracy – at least when emotional intensity reached 80%. Notably, morphine administration reduced fear mimicry, as shown by Bayesian analyses, but did not significantly affect the mimicry of angry or happy facial expressions. Further, response speed and accuracy in emotion recognition were not impacted by MOR stimulation. The null findings were confirmed by Bayesian statistics. No significant effects of facial mimicry nor of the interaction between facial mimicry and morphine were observed on emotion recognition.

The reduction of fear mimicry observed here is consistent with previous evidence showing that MOR activity down-regulates the processing of social threat cues. Previous studies indeed reported reduced attention to and recognition of fearful stimuli following administration of the MOR partial agonist buprenorphine (Bershad et al., 2018, 2016; Ipser et al., 2013). Further, MOR blockade via administration of naltrexone enhanced social threat learning (Haaker et al., 2017). At the same time, the lack of an effect of morphine on fear recognition in our data (confirmed by Bayesian statistics) is at odds with results from studies that had used other types of opioid manipulation, such as naltrexone or buprenorphine administration. These differences may be attributed to the specific action of those compounds on the different classes of opioid receptors. Indeed, while buprenorphine and naltrexone have agonistic and antagonistic effects on mu-receptors, respectively, they are also both antagonist of kappa-receptors. Endogenous KOR activity has been linked to inhibition of reward effects of social and non-social stimuli and dysphoric states, while KOR blockade produces anxiolytic-like effects (Bruijnzeel, 2009). Our lack of effects of morphine on fear recognition aligns with the interpretation that the previously observed effects of buprenorphine and naltrexone on fear identification may be attributable to KOR rather than MOR activity (Løseth et al., 2018; Wardle et al., 2016). According to this view, rather than having opposite effects, both buprenorphine and naltrexone have been shown to reduce recognition of fear (Ipser et al., 2013; Wardle et al., 2016). It should also be noted that the mimicry effect may be regarded as preliminary evidence awaiting replication, since it emerged with Bayesian but not with frequentist statistics and partially depended on prior selection.

Morphine administration did not modulate facial mimicry of anger, suggesting that the effect is not consistent with a generalized modulation of negative emotional stimuli. Indeed, while the activity of the corrugator during the observation of angry faces was lower under morphine compared to placebo, showing an activity pattern similar to the frontalis for fear (Fig. 2b), this effect did not reach significance in the frequentist ANOVA, and Bayesian statistics provided strong support for the null finding. The difference between the morphine effects on mimicry of anger and fear might be explained by fundamental differences in the nature of these two emotional displays. Indeed, while both are considered as threat signals, in the case of anger the expresser represents a direct threat to the observer, whereas a fearful expression signals the presence of a threat in the environment (Marsh et al., 2005). Further, angry expressions elicit mainly avoidance behavior, whereas fearful expressions may also trigger approach behavior and be perceived as affiliative (Marsh et al., 2005).

In contrast to the findings of Løseth and colleagues (2018), where an equal dose of morphine reduced perception of anger on implicit and neutral stimuli, we did not observe morphine effects on recognition of angry facial expressions of either high or low emotional intensity. These contrasting findings likely derive from experimental differences, particularly in the type of task used to assess emotional processing. Indeed, even though we have employed similar explicit and implicit stimuli, in the present study participants were forced to quickly categorize them within a specific label, while in Løseth et al. (2018) participants were allowed to express a more nuanced judgment (ratings of perceived anger and happiness). The study by Løseth et al. (2018) also employed a larger sample size than the current one, and in a within subject-design. However, as results from the Bayes factor analysis supported the absence of a drug effect on accuracy and RTs in the emotion recognition task, we believe it is unlikely that these null findings depend on low statistical power. Overall, these findings suggest that MOR stimulation may modulate core impressions of observed emotions (Løseth et al., 2018), rather than the more basic ability to identify them. Nevertheless, it will be necessary to further clarify the role of the MOR system in emotion perception/identification by combining different ways of assessing the processing of facial emotional expressions, in future studies.

Previous research showed an enhancement/reduction of motivational and hedonic processing of positive, rewarding social stimuli following MOR agonism/antagonism (Buchel et al., 2018; Chelnokova et al., 2014; Korb et al., 2020). Further, the MOR partial agonist buprenorphine was shown to improve short-term spatial memory for happy faces (Syal et al., 2015). While the absence of an effect of morphine on the processing of happy faces in the present study goes against these earlier findings, several other previous studies failed to show effects of various opioid compounds on the recognition of happy faces (Ipser et al., 2013; Løseth et al., 2018; Wardle et al., 2016). Although images depicting smiling faces of strangers have been shown to activate the reward brain circuitry (Spreckelmeyer et al., 2009), the social context (e.g., identity of the target, relationship with the observer) can largely affect mimicry and emotion perception (Forbes et al., 2021; Hess and Fischer, 2013; Korb et al., 2019). Future studies should include these features in their experimental design, by for example priming the participants with contextual information (such as creating affiliative vs competitive situations) or by modulating face familiarity.

Regarding facial mimicry, Meier and colleagues (2016) reported modulation of mimicry of happy facial expressions following MOR blockade. The effect was nevertheless limited to an increased activity of negatively-valenced facial responses (corrugator and depressor activity), as naltrexone did not affect the activity of the zygomaticus. Despite the use of a similar methodology, our study could not extend the evidence to opioid stimulation, as we failed to show drug effects on the activation patterns of the corrugator, frontalis, and zygomaticus muscles during observation of happiness. This might be due to the different magnitude of agonistic and antagonistic effects of the two drugs at the employed dosages. While 50 mg of naltrexone result in a full opioid-blockade (90% MOR occupancy; Lee et al., 1988), the agonistic effect of 10 mg of morphine sulfate is likely lower in magnitude (Cumming et al., 2019). However, administration of larger doses of morphine is problematic as they would produce sedation, which in turn would impair task performance.

As highlighted by Meier and colleagues (2021), to date the size of the effects observed following MOR manipulations in various processes, including emotion perception, in healthy individuals has been generally small. Regarding emotion processing specifically, this study is partially in line with previous findings, which reported overall a subtle reduced sensitivity to negative stimuli by MOR activity (Meier et al., 2021). Altogether, the evidence suggests that these processes are likely orchestrated by multiple neurochemical systems and that the role of the MOR system may be limited to a fine-tuning action rather than a full regulation (Meier et al., 2021).

Some limitations of the current study need to be considered. The inclusion of only female participants, and the investigation of solely three basic emotions limits the generalizability of the findings. Future

studies should extend the investigation to male participants, to assess possible gender differences, and other emotions. Independently of drug administration, recognition of fearful stimuli with 80% emotional intensity was slower and less accurate (Fig. 3) - despite having borrowed the original faces from a validated data set. Fearful expressions have already been shown to be more difficult to recognize compared to other emotions such as happiness (Palermo and Coltheart, 2004). This is also possibly due to the fact that an important feature of fearful expressions, the open mouth, was not present in the selected stimuli. Stimuli with closed mouth were preferred for all emotions to achieve a better morphing.

5. Conclusion

In conclusion, we observed that morphine administration reduced mimicry of fearful facial expressions, compared to placebo, without affecting mimicry of happiness and anger. These findings are in line with previous evidence that MOR stimulation reduces sensitivity to fearful stimuli but contrast with the hypothesis that MOR stimulation generally decreases social threat cues and increases perception of positive social stimuli. The absence of a drug effect on emotion recognition, confirmed by post hoc Bayesian statistics, suggests that mu-opioid signaling may not be involved in the ability to identify emotions from facial signals. Overall, the present findings, together with the previously reported small and inconsistent effects, suggest that the MOR system plays only a marginal role in the perception of emotional facial expressions. Given that the present and previous findings come from highly standardized, non-affiliative contexts (faces presented as isolated stimuli), future studies should investigate the influence of social contextual factors and assess measures tapping on motivational aspects or more implicit measures of categorization (e.g., the mousetracker task, http://www.mousetracker.org/).

CRediT authorship contribution statement

CM: Conceptualization, Data curation, Software, Formal analysis, Supervision, Investigation, Visualization, Methodology, Project administration, Funding acquisition, Writing - original draft, Writing - review and editing; **SK**: Conceptualization, Writing - review and editing; **MW**: Conceptualization, Project administration, Medical testing, Funding acquisition; **BBQ**: Conceptualization, Writing - review and editing; **GS**: Conceptualization, Supervision, Methodology, Funding acquisition, Project administration, Writing - review and editing. All authors revised the manuscript and approved its final version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105801.

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