Enhanced negative response to stress following morphine administration increases wanting of social reward

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Abstract

Animal research suggests a central role of the μ-opioid receptor (MOR) system in mediating contact seeking and the stress-buffering function of social touch. However, the human neurochemistry of social motivation in aversive situations is still poorly understood.

In a randomized, double-blind, between-subject design, healthy female volunteers (N = 80) received either 10 mg of the μ-opioid agonist morphine sulfate or a placebo. Following psychosocial stress induction, participants engaged in a social reward task, in which the motivation (subjective ratings of wanting and physical effort) to obtain skin-to-skin social touch and the hedonic reactions (subjective ratings of liking and facial electromyography) elicited by it were assessed.

Morphine administration prevented the increase of salivary cortisol, usually observed in response to acute stress exposure. The dampened physiological reaction to the psychosocial stress was associated with increased negative mood and subsequent higher subjective wanting of the most pleasurable touch. Furthermore, participants administered with morphine displayed greater activity of the corrugator muscle during reward anticipation, possibly tracking enhanced attention toward the social stimuli.

Overall, the results provide novel evidence on the effect of exogenous opioids administration on the reactions to psychosocial stress and point to a state-dependent regulation of social motivation.

Introduction

Social behaviors such as bonding and affiliation are crucial for the survival and wellbeing of many species. By providing fundamental benefits (e.g., promoting safety and enhancing stress resilience) and by generating comfort and pleasure, social stimuli (e.g., social contact) gain rewarding value, inducing approach motivation. Inability to form and maintain social bonds contributes to a range of psychiatric and physical pathologies (e.g., Cacioppo & Cacioppo, 2014; Uchino, 2006), therefore highlighting the importance to better understand the neurobiological basis of social motivation.

The Brain Opioid Theory of Social Attachment (BOTSA), originally inspired by the analogies between opioid addiction and social dependence, pinpoint the μ-opioid receptor (MOR) system as a key mediator of bonding and affiliation (Panksepp, 1998; Panksepp et al., 1980). Specifically, BOTSA predicts that social isolation results in reduced levels of basal opioid levels, which in turn motivate social contact seeking, and that rewarding social interactions elicit release of endogenous opioids, associated with euphoria and contentment. The two-fold role of the endogenous opioid system in reward and pain (Leknes & Tracey, 2008) therefore seems to apply also to experiences of social nature. In contexts of comfort, the activity of the MOR system during social contact mediates the rewarding properties, and associated pleasure, of social stimuli, positively reinforcing exploration and affiliation. In contexts of distress, the release of endogenous opioids via social contact reduces pain and negative affect, negatively reinforcing social behaviors (Loseth et al., 2014).

In line with this model, animal studies have shown that μ-opioids are released following physical social contact, such as grooming and playing (Keverne et al., 1989; Panksepp & Bishop, 1981; Vanderschuren et al., 1995). Pharmacological studies on separation-distress in animals further

confirmed BOTSA predictions, showing that administration of MOR agonists reduces, and of MOR antagonists increases distress responses and motivation for social contact, such as grooming (Keverne et al., 1989; Martel et al., 1995; Panksepp et al., 1980; Fabre-Nys et al., 1982; Meller et al., 1980; for a review see Machin & Dunbar, 2011; see Loseth et al., 2014 for a model accounting for divergent findings in different species).

In the last decade, preliminary confirmatory evidence on the μ-opioid mediation of the rewarding properties of social stimuli in humans have been provided. These studies mainly focused on two fundamental components: wanting, namely the motivational drive to obtain the social stimulus, and liking, namely the pleasure elicited once it is received. Results showed that pharmacological challenge of the MOR system affects wanting and/or liking of different kind of social stimuli, such as erotic pictures (Buchel et al., 2018), attractive faces (Chelnokova et al., 2014), and social touch (Korb, Götzendorfer, et al., 2020; but see also Løseth et al., 2019). MOR activation has been also associated with social laughter (Manninen et al., 2017), and MOR blockade was shown to reduce feelings of social connection (Inagaki et al., 2015, 2016, 2020), as well as of interpersonal closeness and social reward expectation (Tchalova & MacDonald, 2020). Using PET, Hsu et al. (2013) observed MOR activation in response to both social rejection and social acceptance. In the first case, MOR activity was correlated with reduced negative affect, while in the latter it was associated with increased desire for social interaction. These findings are consistent with a "protective" and an "affiliative" role of the MOR system during social distress and social comfort, respectively. Regarding the role of the MOR system in stress regulation, a recent study showed that MOR agonist administration reduces individuals' physiological stress response (as measured by cortisol), as well as the perceived difficulty of the stress task (Bershad et al., 2018). However,

89 direct evidence of an involvement of the MOR system in downregulating stress and how this
90 affects social contact seeking, as shown in non-human animal species, is still lacking.

91 Here, we aimed at filling this knowledge gap by investigating the effect of MOR agonist
92 administration (morphine) on social motivation and social pleasure following stress exposure.
93 Using a double-blind, placebo-controlled, randomized, between-subjects design, female
94 participants (N = 80) were orally administered with either 10 mg morphine sulfate (a highly
95 selective μ-opioid agonist) or placebo. Following a psychosocial stress induction procedure, the
96 motivation to obtain social touch (wanting) and the pleasure elicited by receiving it (liking) were
97 assessed (see Figure 1 for a detailed description). In order to enhance the translational value of the
98 study, the following steps were taken: i) as in previous animal research, which entailed social
99 separation, a stressor of social nature (via the Trier Social Stress Test, Kirschbaum et al., 1993)
100 was employed; ii) in addition to self-reports of wanting and liking, we assessed real physical effort
101 (via a hand-dynamometer) and hedonic facial reactions (via facial electromyography of corrugator
102 and zygomaticus muscles), approximating the motivational and hedonic (i.e., wanting and liking)
103 measures used in animal studies; iii) to parallel grooming in animals, skin-to-skin touch
104 administered at different speeds (6, 21, 27 cm/s, corresponding to high, low, and very low reward
105 levels) was employed as a social reward.

106 Based on the existing human and animal literature, we hypothesized that participants administered
107 with morphine, compared to placebo, would show reduced physiological and subjective responses
108 to stress, and that this would result in decreased social motivation. As previous studies had shown
109 an effect of stress on wanting rather than on liking of touch (Massaccesi et al., 2021) or food (e.g.
110 Pool et al., 2015) reward, we did not expect changes in the hedonic reactions to social contact.
111 Given that MOR manipulations have been shown to induce the strongest effects on the best reward

option available (Chelnokova et al., 2014; Eikemo et al., 2016), and considering the stress buffering function of C tactile (CT)-optimal touch (i.e., touch with stroking speed of 1 to 10 cm/s; Morrison, 2016), we expected the predicted effects to be stronger for the most valuable social reward (touch at 6 cm/s).

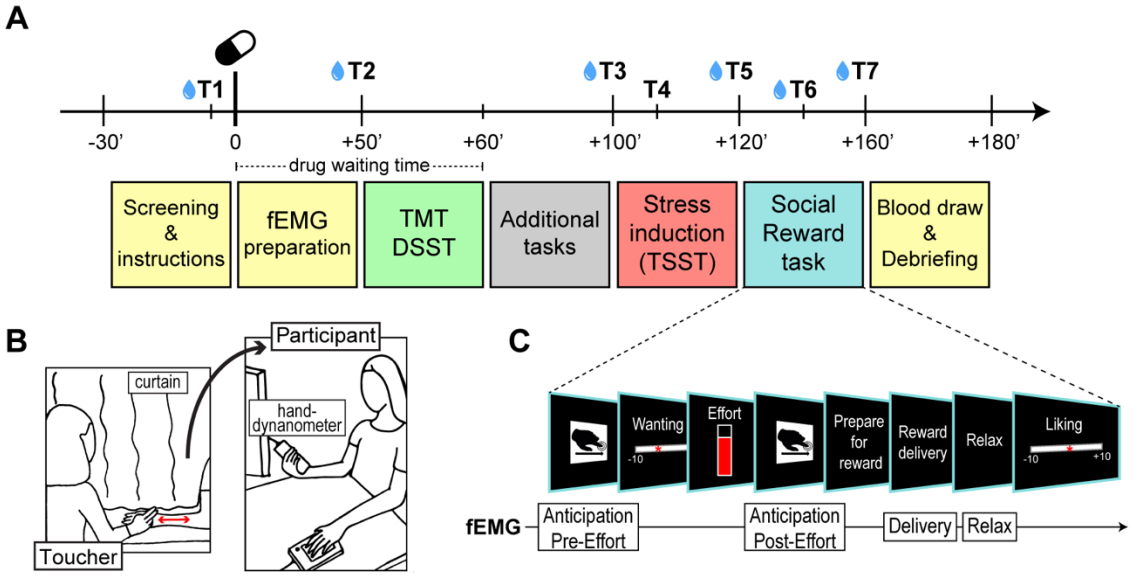

Figure 1. **Overview of the experimental session, set-up, and trial structure of the Social Reward task.** (A) Overview of the experimental session. T1 – T7 represent the time points at which subjective and/or physiological measures were obtained. Blue drops indicate saliva sample collection. (B) Set-up of the Social Reward task (based on Korb, Götzendorfer, et al., 2020; Massaccesi et al., 2021). Participants were seated in front of the monitor, holding the hand-dynamometer in the right hand. The left arm was rested on a cushion, next to a keyboard used to express judgements during the task. The toucher was seated on the other side of a curtain used to limit the participants' field of view to the monitor. Touch was administered on the participants' left forearm using the index and middle finger, at 3 stroking speeds corresponding to 3 levels of reward (high = 6 cm/s, low = 21 cm/s, very low = 27 cm/s). (C) Trial structure of the Social Reward task: i) announcement of the best attainable social reward (high or low); ii) rating of subjective wanting; iii) effort task requiring to squeeze a hand-dynamometer to obtain the announced reward. Participants' force exerted was indicated in real-time by a vertical bar filling in red. The top of the displayed vertical bar corresponded to their previously measured maximum voluntary contraction (MVC); iv) announcement of the reward attained (high, low, or – if insufficient effort had been exerted – very low); v) skin-to-skin touch administration; vi) relax phase; vii) rating of subjective liking. Facial electromyography (fEMG) was recorded during the whole task and analyzed in reward anticipation (Anticipation Pre-Effort and Post-Effort) and consumption (Delivery and Relax). TMT, Trail Making Test; DSST, Digit Symbol Substitution Test; TSST, Trier Social Stress Test.

137 # Results

138 ## Drug blinding

139 After completing the session, 50% of the participants correctly guessed they received morphine,
140 indicating successful blinding. Overall, 55% of the total sample believed to have been administered
141 with placebo, 29% with morphine, and 16% with naltrexone[1].

142 ## Effects of morphine on cognitive functions and drug side-effects

143 There were no significant differences in the Digit Symbol Substitution Test (DSST) and Trail
144 Making Test (TMT) scores across groups, indicating that drug administration did not have negative
145 effects on attention, psychomotor and processing speed, and visuo-perceptual functions (See Table
146 S1 in *Supplementary Material*). Morphine administration significantly increased self-reported
147 weakness (MORPH vs. PLB at T2: $t(69.9) = 2.64$, $p = 0.01$, and at T7: $t(55.96) = 2.19$, $p = 0.03$)
148 and dry mouth (MORPH vs. PLB at T7: $t(57.70) = 2.56$, $p = 0.01$). For all side-effect measures,
149 group average scores were generally low, and no side-effect was on average rated as moderate or
150 strong (see Figure S2 in *Supplementary Material*).

151 ## Effects of morphine on stress response

152 ***Subjective measures***

153 Morphine administration resulted in significantly higher scores of the Profile of Mood States
154 (POMS) subscale "Displeasure" after stress induction (Drug*Time: $F(4,312) = 2.97$, FDR $p =$
155 0.03; MORPH vs. PLB at T5: FDR $p < 0.01$) (Figure 2A). A similar pattern, though not reaching
156 statistical significance, was observed for negative mood (Drug*Time: $F(6,468) = 2.16$, FDR $p =$
157 0.068) (Figure 2A). No significant group differences were observed for positive mood or for the

[1] To reduce drug-related expectancy, participants were told they might receive an opioid agonist (morphine), antagonist (naltrexone) or placebo (but they could receive only morphine or placebo).

158 POMS subscales “Depression”, “Vigor”, and “Fatigue” (all FDR $p > .15$). Furthermore, no drug
159 effects were observed in anticipatory stress (PASA primary and secondary appraisal at T4; both t
160 < 0.60, $p > 0.55$), nor in the participants’ satisfaction towards their performance expressed after
161 TSST completion (T5; $t(75.2) = -0.63$, $p = 0.53$).

162 ***Physiological measures***

163 As physiological stress biomarkers, salivary cortisol (hypothalamic–pituitary–adrenal [HPA] axis
164 activity), salivary alpha-amylase and heart rate (autonomic nervous system [ANS] activity) had
165 been assessed at different time-points during the session (see Figure 1).

166 Morphine administration suppressed cortisol response to the TSST (Drug*Time: $F(5,375) = 7.68$,
167 FDR $p < 0.001$, Figure 2B). Specifically, the morphine group showed reduced salivary cortisol
168 compared to the placebo group at T2 (FDR $p = 0.079$), T3 (FDR $p < 0.01$), T5 (FDR $p < 0.001$),
169 T6 (FDR $p < 0.001$) and T7 (FDR $p < 0.001$) (Figure 2A). No drug effects were observed in
170 salivary alpha-amylase (all $F < 0.38$, all FDR $p > 0.62$) or in heart rate (all $F < 2.83$, all FDR $p >$
171 0.09) (Figure 2B).

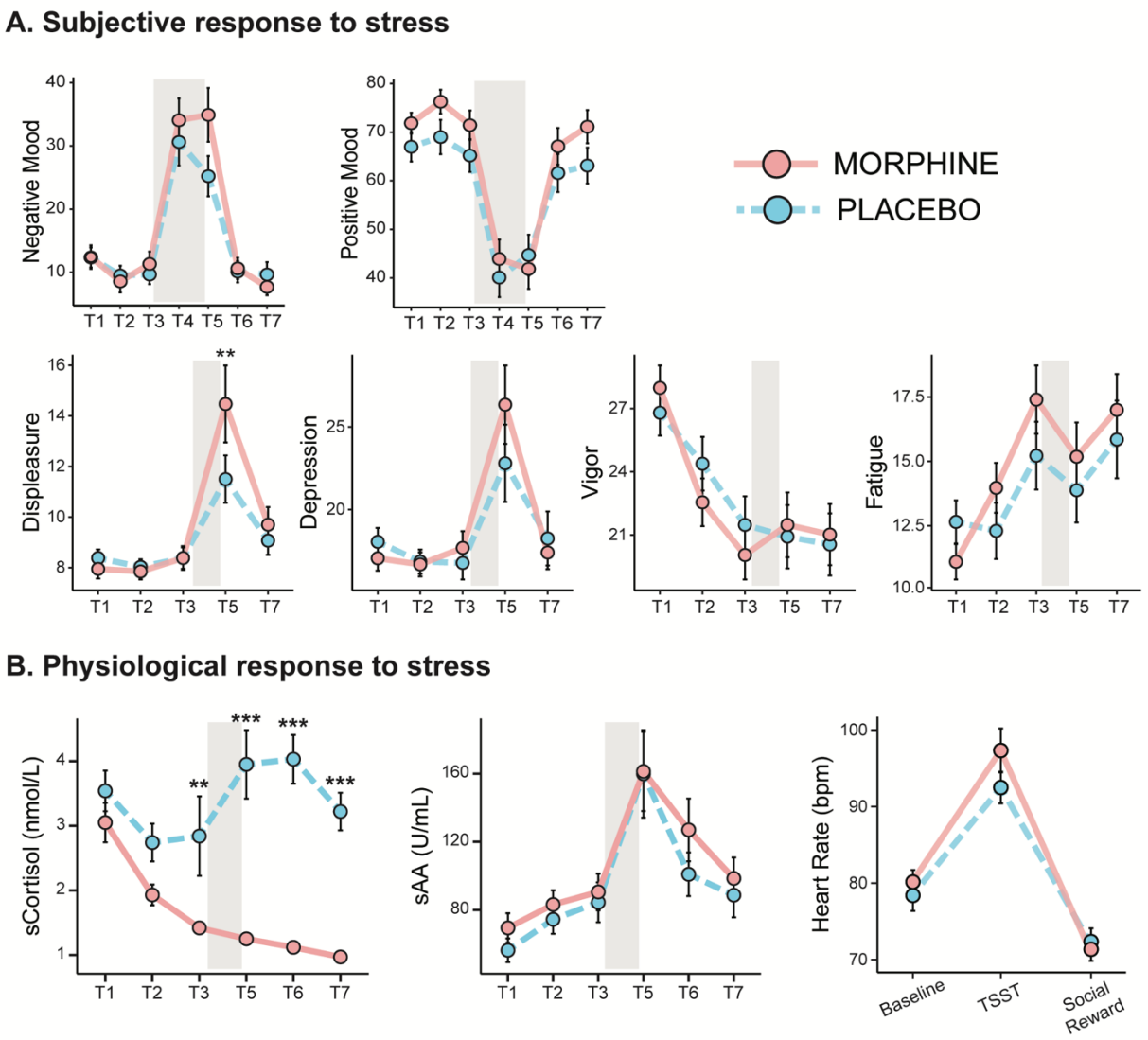

Figure 2. **Effects of morphine administration on subjective and physiological stress responses.** (A) Morphine administration increased the subjective negative response to stress, as shown by elevated negative mood (measured via visual analog scales) and higher scores at the "Displeasure" subscale (POMS) immediately after the Trier Social Stress Test (TSST). No significant drug effects were observed in positive mood or in any other POMS subscales (depression, vigor, fatigue). (B) Morphine administration suppressed the hypothalamic–pituitary–adrenal (HPA) axis activity, as shown by blunted salivary cortisol before and after stress induction. No significant drug effects were observed in the autonomic nervous system (ANS) response to stress, assessed via salivary alpha-amylase (sAA) and heart rate. Grey bars represent the TSST time window (anticipation, speech, and arithmetic task); error bars represent standard error of the mean; asterisks indicate significant differences between drug groups (* p <.05, *** p < .001).

184 ***Correlations between physiological and subjective measures of stress***

185 Given the observed opposite effect of the drug on cortisol and mood, we conducted a correlation
186 analysis to investigate the association between physiological and subjective measures of stress. To
187 this aim, we first computed the area under the curve in respect to increase (AUCi, from T3 to T7;
188 Pruessner et al., 2003) of the cortisol levels and of the negative mood ratings (VAS and POMS).
189 Results showed a negative correlation between salivary cortisol and negative mood (VAS; r_s = -
190 .36, *p bonferroni* = .048) as well as between cortisol and the Displeasure subscale of POMS (r_s =
191 -.37, *p bonferroni* = .044), suggesting an inverse relationship between HPA axis and mood
192 responses to stress.

193 **Effects of morphine on social reward processing**

194 Using a recently developed Social Reward task (Korb, Götzendorfer, et al., 2020; Massaccesi et
195 al., 2021), we assessed subjective wanting and liking of social reward in different levels.
196 Participants were announced with either high (6 cm/s, CT-optimal touch[2]) or low (21 cm/s, non-
197 CT-optimal touch) social reward and rated their wanting of the stimulus. Based on an effort task,
198 they could then receive the announced or the very low (27 cm/s, non-CT-optimal touch) social
199 reward and had to rate their liking of the received stimulus.

200 We first examined whether the number of high, low and very low rewards obtained during the task
201 was similar for the two groups. A linear model on number of trials was fitted, including Drug
202 (MORPH, PLB) and Reward Level (high, low, and very low). We observed only a main effect of
203 Reward Level ($F(2,369.5) = 11.28$, $p < 0.001$), indicating that participants obtained more often
204 high rewards as compared to low and very low rewards. We also tested for group differences in

[2] Touch administered at a velocity falling into the range of 1 to 10 cm/s activates CT afferents, a special class of nerve fibers found in human hairy skin involved in signaling the affective aspects of social touch (Morrison et al., 2010), and was shown to elicit greater pleasure, compared to touch administered at faster velocities.

205 the average maximum voluntary contraction (MVC), assessed before and after the Social Reward
206 task and used to calibrate the effort task. No significant differences emerged (all $t < -0.84$, all
207 $p > 0.40$), indicating no drug effects on participants' grip force at rest. Last, we tested for group
208 differences in the baseline activity of the corrugator and zygomaticus muscles. No significant
209 differences emerged (all $t < 1.27$, all $p > 0.21$).

210 ***Effects of morphine on subjective ratings of wanting and liking***

211 To investigate the effects of morphine administration on subjective wanting and liking of social
212 touch under stress, we fitted two linear mixed-effects models (LMM) on the ratings of wanting
213 and liking, including Drug (MORPH, PLB) and Reward Level (high, low for wanting ratings, and
214 high, low, very low for liking ratings) as fixed effects, and by-subject random intercepts and slopes
215 for Reward Level.

216 *Ratings of Wanting.* Participants administered morphine expressed significantly greater wanting
217 of the high social reward (CT-optimal touch) compared to the placebo group (Drug*Reward Level:
218 $F(1,78) = 10.56$, FDR $p = 0.003$; high social reward MORPH vs. PLB: FDR $p = 0.035$) (Figure
219 3A). No drug effects emerged for the low social reward (FDR $p = 0.72$).

220 *Ratings of Liking.* Participants in both groups expressed greater liking for high compared to low
221 social rewards, which in turn were more liked than the very low social rewards (Reward Level:
222 $F(2,72.9) = 20.93$, FDR $p < 0.001$; high vs. low vs. very low: all FDR $p < 0.001$). Further,
223 participants administered morphine generally liked the interpersonal touch (across all reward
224 levels) more compared to the placebo group, but the effect did not reach significance (Drug:
225 $F(1,78) = 4.23$, FDR $p = 0.065$) (Figure 3B).

226 ***Effects of morphine on force exerted and hedonic facial reactions***

227 We further assessed wanting of social rewards in terms of force exerted to obtain the tactile stimuli,
228 as well as hedonic facial reactions during reward anticipation (Anticipation Pre- and Post-Effort
229 phases). Hedonic facial reactions during and after consumption (Delivery and Relax phases) of the
230 social reward were employed as a measure of liking. Hedonic facial reactions were assessed via
231 facial electromyography (fEMG) of the corrugator (frowning) and zygomaticus (smiling) muscles.

232 *Force exerted.* Participants overall exerted greater force to obtain the high compared to the low
233 social reward (Reward Level: $F(1,78) = 14.23$, FDR $p < 0.001$). We also observed greater
234 difference in terms of force exerted for the high compared to the low reward in the morphine than
235 in the placebo group, but the effect did not reach significance (Drug*Reward Level interaction:
236 $F(1,78) = 4.13$, FDR $p = 0.068$) (Figure 3C).

237 *Corrugator (frowning).* During the announcement of the highest attainable social reward
238 (Anticipation Pre-Effort), we observed greater corrugator activity following morphine
239 administration, compared to placebo (Drug: $F(1,791.3) = 6.15$, FDR $p = 0.036$) (Figure 3D).
240 Opposite to previous evidence (e.g., Korb, Götzendorfer, et al., 2020; Korb, Massaccesi, et al.,
241 2020; Ree et al., 2020), in this phase greater frowning was associated with greater subjective
242 wanting in both groups (Wanting: $F(1,1203) = 7.94$, FDR $p = 0.036$) (Figure 3D). No significant
243 effects were observed in other phases of the task.

244 *Zygomaticus (smiling).* During the announcement of the obtained social reward (Anticipation Post-
245 Effort), activity of the zygomaticus was positively associated with subjective wanting of the social
246 reward (Wanting: $F(1,73.2) = 10.31$, FDR $p < 0.01$) (Figure 3E). No significant effects of drug
247 were observed in the activity of this muscle.

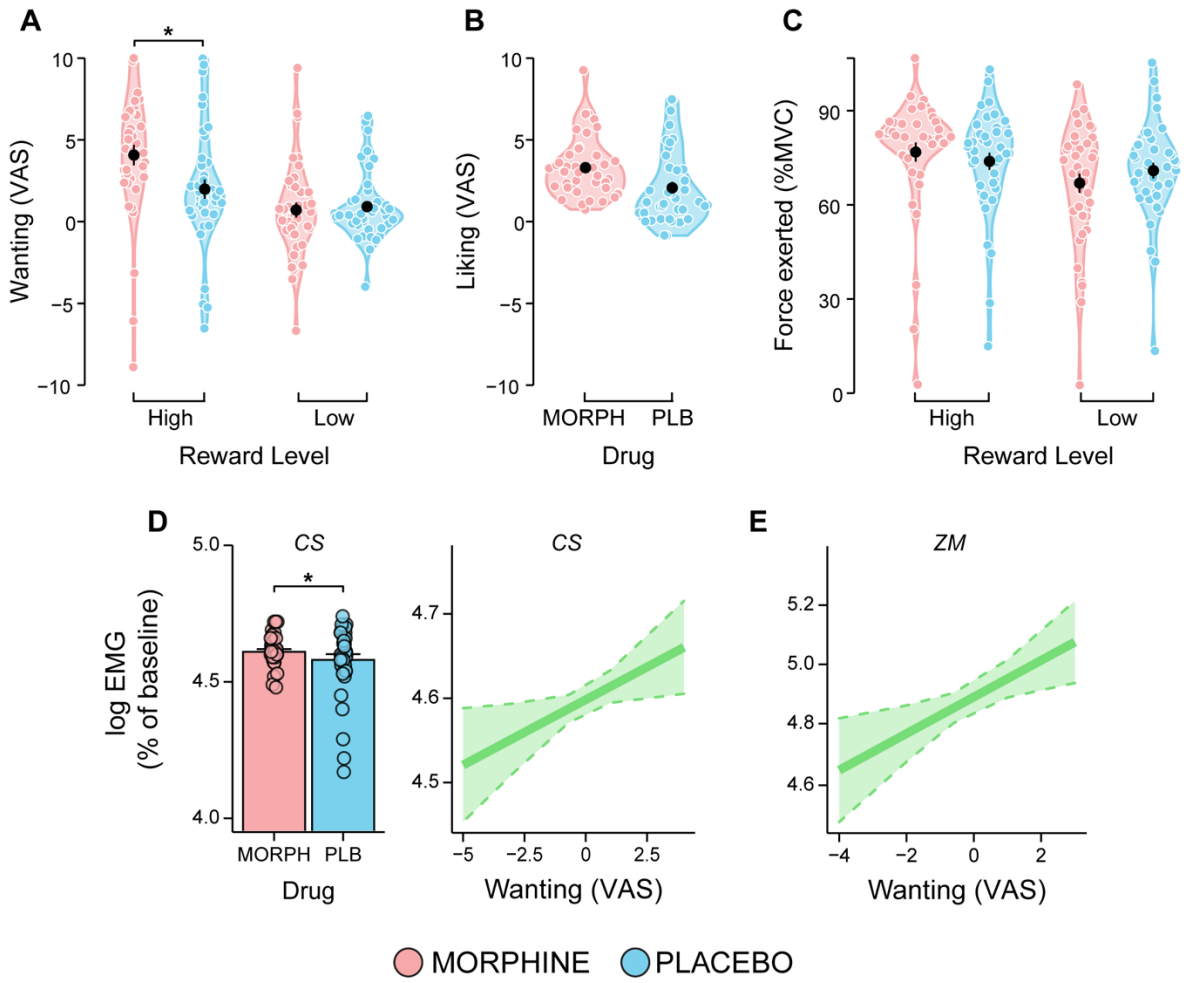

Figure 3. **Effects of morphine administration on social reward processing after stress exposure.** Morphine administration resulted in (A) significantly greater wanting for the high social reward (6 cm/s, CT-optimal touch), (B) greater liking of the social stimuli regardless of reward level (marginally significant drug main effect), and (C) greater differentiation of the high and low reward levels in terms of effort exerted (marginally significant drug by reward level interaction effect), compared to placebo. Regarding facial hedonic reactions, (D) during the announcement of the highest attainable reward (Anticipation Pre-Effort), the morphine group showed greater corrugator (CS) activity, which was generally positively associated with subjective wanting. (E) During the announcement of the gained reward (Anticipation Post-Effort), greater zygomaticus (ZM) activity was associated with greater subjective wanting, but no significant drug effects were observed for this muscle. Error bars represent standard error of the mean; black dots represent group means; colored dots represent individual means; asterisks indicate significant differences between conditions (* $p < .05$). VAS, Visual Analogue Scale; MORPH, morphine group; PLB, placebo group.

263 **Discussion**

264 Social motivation is a powerful force guiding behavior, as social rewards (e.g., social contact,
265 bonding, affiliation) are fundamental to the individual's physical and psychological well-being.
266 Despite the important role of social contact in stress resilience, the neurochemical mechanisms
267 underlying social contact seeking following stress exposure in humans are still poorly understood.
268 In this study, we pharmacologically challenged the μ-opioid receptor (MOR) system to investigate
269 its role in the regulation of the motivational and hedonic components of social reward processing
270 following stress induction. To parallel previous animal research, participants were exposed to a
271 stressor of social nature and interpersonal touch was used as a social reward. Further, force exerted
272 to obtain the reward as well as hedonic facial reactions during its anticipation and consumption
273 were assessed, together with subjective ratings of wanting and liking. Following the enhancement
274 of the MOR system activity via administration of its agonist morphine, we observed suppression
275 of the HPA axis activity (as indicated by a reduced cortisol response) and increased negative affect
276 in response to psychosocial stress. Notably, this increased negative response to stress following
277 morphine administration was associated with enhanced motivation for the most pleasurable social
278 reward.

279 *μ-opioid agonist morphine dampens cortisol and increases negative affect in response to stress*

280 In this study, single administration of the μ-opioid agonist morphine prior to TSST exposure
281 resulted in blunted salivary cortisol response, indicating suppression of the HPA axis reactivity to
282 stress. This is in line with previous animal and human evidence indicating an inhibitory role of μ-
283 opioids on cortisol release following stress exposure (Pechnick, 1993). Recently, two studies
284 investigated the effects of partial (buprenorphine) and full (hydromorphone) MOR agonists on
285 psychosocial stress, induced via TSST (Bershad et al., 2016, 2018). Akin to the present findings,

286 reduced cortisol responses to stress were observed. Buprenorphine and hydromorphone also
287 reduced the perceived threat and the appraisal of how challenging the participants found the stress
288 task, respectively. While the authors interpret the findings on cortisol and stress appraisal as
289 indicators of a reduced stress response, no mood-buffering effects of the drug were observed. This
290 is in contrast with the current study, where we find that the dampened cortisol response is
291 accompanied by an enhanced aversive reaction to stress, as shown by higher negative affect
292 following morphine compared to placebo administration. Human cortisol permeates the blood-
293 brain barrier to feedback the central nervous system, reducing HPA axis activity and promoting
294 emotion regulation (Het et al., 2012; McEwen, 1998). The observed inverse relationship between
295 the HPA axis activity and negative affect possibly indicates a disruption of this feedback loop by
296 morphine administration and is in line with a mood-buffering effect of cortisol (Het et al., 2012;
297 Het & Wolf, 2007). Accordingly, it was recently shown that pharmacological HPA axis
298 suppression, by means of dexamethasone administration, blunts the cortisol response to stress and
299 increases negative mood, especially in women (Ali et al., 2017, 2020).

300 Our results are opposite to our *a priori* hypothesis based on previous evidence from animal studies
301 on separation distress indicating a reduction of stress indices, such as distress vocalizations,
302 following MOR agonist administration (Panksepp et al., 1980). The paradoxical morphine effect
303 of enhanced aversive stress reaction observed in the current study vs. the previous animal literature
304 may be explained by experimental differences, such as route and timing of administration of the
305 opioid compounds. For instance, in animal research morphine is typically delivered intravenously
306 after stress induction, possibly allowing the system to prepare to face the stressor via an initial
307 mounting of the physiological stress response. In this study, morphine was administered orally to
308 minimize the invasiveness of the administration procedure. Unlike intravenous administration,

309 per-oral morphine has a slow pharmacokinetic profile and requires an average time of 60 min to
310 reach the peak blood concentration. As the subjective response to acute stress, especially its effect
311 on mood, typically lasts only for short periods of time after laboratory stress induction, orally
312 administering the drug and waiting for it to reach peak concentration after the TSST would not
313 have been feasible. For these reasons here the compound was administered prior to stress exposure.
314 However, the resulting suppression of the HPA axis activity before the beginning of the stress
315 induction may have led to the observed difference in the mood response. Accordingly, the raising
316 of cortisol levels, via cortisol administration, prior to stress induction has been shown to have a
317 protective role in women, lowering the negative subjective reaction to stress (Het & Wolf, 2007).

318 *Morphine-induced increased negative reaction to stress is associated with enhanced social*
319 *motivation*

320 BOTSA posits that when facing stressors, individuals seek physical social contact with others in
321 order to down-regulate the negative state and re-store comfort, via endogenous release of beta-
322 endorphins, unless opioids are externally provided. Contrary to our initial hypotheses, morphine
323 increased, rather than reduced, participants' negative reactions to the TSST, and such increased
324 stress responses were accompanied by enhanced social motivation. Specifically, we observed
325 greater subjective wanting of the most pleasurable social reward (CT-optimal touch) following
326 morphine administration, compared to placebo. This enhanced subjective wanting was also
327 accompanied by greater differentiation of the high and low social rewards (CT-optimal and non-
328 CT-optimal touch) in terms of effort exerted to obtain them in the morphine group compared to
329 placebo, but the effect did not reach statistical significance.

330 This pattern of results is consistent with previous findings from our group indicating that, as
331 already shown for other kinds of reward like food and money (e.g. Kumar et al., 2014; Lewis et
332 al., 2014; Pool et al., 2015), stress increases wanting of rewards of social nature, such as

interpersonal touch (Massaccesi et al., 2021). Differently from the present findings, in Massaccesi et al. (2021) the effect of enhanced wanting for the social reward was independent from reward magnitude. In other words, participants under stress expressed higher wanting ratings for all types of social touch compared to non-stressed individuals, regardless of reward magnitude. Here we observed an effect of morphine and stress on the most pleasurable touch only (high reward level), characterized by slow stroking velocity (CT-optimal touch).

This potentiation of wanting for the most pleasurable touch may be due to a specific influence of the enhanced MOR system activity. Indeed, previous research has shown that pharmacological challenges of the MOR system have strongest effects on rewards of greatest magnitude (e.g., Chelnokova et al., 2014; Eikemo et al., 2016). Therefore, it can be hypothesized that while stress alone may result in increased motivation for all available rewarding stimuli, an additional potentiation of motivation for the most valuable stimulus is seen for the best reward due to MOR stimulation. This would align well with the observation that participants administered with morphine also exerted more effort in order to obtain the high reward, as compared to the low reward, and that this difference in force exerted was greater than in the placebo group (but with FDR $p = 0.068$ did not reach the statistical significance). Alternatively, a reason for the partially different result pattern might be that, differently from the current study, in Massaccesi et al. (2021) participants were allowed to individually rank the three types of touch as high, low and very low. The high reward was therefore not necessarily the CT-optimal touch. This could have masked a possible impact of the type of touch. While Massaccesi et al. 2021 included different state manipulations, this study focused on the effects of stress. Since slow CT-optimal touch is more likely to convey affiliative intentions such as social support compared to faster touch (Kirsch et

355 al., 2017), here the slow CT-optimal touch was kept as fixed high reward to avoid possible
356 confounding effects related to the speed of stroking.

357 During reward anticipation (announcement of the best attainable reward), the increased subjective
358 wanting of social touch in the morphine group was accompanied by greater activity of the
359 corrugator muscle. Previous research indicates that individuals relax the corrugator during
360 anticipation and consumption of rewarding stimuli, showing an inverse relationship between
361 corrugator activity and reward wanting/liking (Korb, Götzendorfer, et al., 2020; Korb, Massaccesi,
362 et al., 2020; Massaccesi et al., 2021; Mayo et al., 2018; Ree et al., 2020; Sato et al., 2020). Here,
363 in contrast, we observed greater frowning for most wanted stimuli. Activity of the corrugator is
364 commonly associated with emotional processing, but it has been shown to be related also to
365 processes without emotional content, such as mental and physical effort, alertness, perceptual
366 attention, task engagement and difficulty (Cacioppo et al., 1985; Cohen et al., 1992; de Morree &
367 Marcora, 2010; Van Boxtel & Jessurun, 1993; Waterink & van Boxtel, 1994). As individuals are
368 more attentive to highly rewarding stimuli (e.g. Hickey et al., 2010; Hickey & van Zoest, 2012;
369 Theeuwes & Belopolsky, 2012) and, since morphine - at a similar dose - has already been shown
370 to enhance attentional processes such as set-shifting (Quednow et al., 2008), it is possible that the
371 observed pattern in the corrugator activity reflects enhanced attention/preparation towards the most
372 wanted stimuli. Together with the higher subjective of wanting, the greater saliency of the
373 anticipated social rewards, reflected in greater frowning, suggests an enhancement of social
374 motivation following stress exposure in the morphine group, compared to placebo.

375 Based on previous evidence, we predicted that the effects of morphine administration on social
376 touch processing under stress would be specific for the motivational component, without affecting
377 the hedonic aspect. Accordingly, we did not observe a significant effect of drug on the ratings of

liking or in the facial hedonic reactions during the reward consumption phase. However, we nevertheless observed that the ratings of liking were generally higher in the morphine group compared to the placebo group (FDR $p = 0.065$), and we therefore refrain to exclude an effect of the manipulation on social pleasure.

Study limitations

Some limitations of the study should be considered. First, while the use of a within-subject design is usually preferable in pharmacology, in this study we employed a between-subjects design. The choice was mainly motivated by the fact that repeated exposure to the TSST, especially with a short time interval, can lead to habituation of the stress response, resulting in low test re-test reliability (e.g., Gerra et al., 2001; Petrowski et al., 2012) and thus outweighing by far the possibly higher statistical power a within-subject design might have had in principle. Second, despite our efforts in enhancing the social properties of the administered touch (e.g., skin-to-skin administration), the absence of a social relationship between the toucher and the participant, as well as other methodological aspects (e.g., use of a curtain separating participant and toucher), might have affected our results. Nevertheless, in humans an involvement of the MOR system in bond formation, rather than just maintenance, has also been observed (Tchalova & MacDonald, 2020). Third, the current study tested a sample of healthy female participants, therefore a generalization to male individuals is not possible, especially given the known sex differences in stress reactivity and MOR system functioning. Finally, it is unlikely that a complex behavior such as social motivation can be fully explained by the activity of a single neurochemical system only. For instance, the neuropeptides oxytocin and vasopressin are well-known for their crucial role in bonding and reproductive functions (Donaldson & Young, 2008). Stress exposure induces a potent activation of the dopaminergic system (Bloomfield et al., 2019; Holly & Miczek, 2016), and it has

401 been shown that MOR stimulation disinhibits dopaminergic neurons in the ventral tegmental area
402 and increases dopamine release in the nucleus accumbens (Pan, 1998). To investigate how these
403 systems interact in driving social contact seeking during aversive states seems therefore necessary
404 to understand the neurobiology of social motivation.

405 *Conclusions*

406 To conclude, our findings show that enhancing μ-opioid signaling before psychosocial stress
407 exposure increases, rather than reduces, the aversive reaction to stress, leading to an increased
408 subjective motivation for the attainment of highly rewarding social contact. Specifically, we
409 showed that morphine administration blunted cortisol reactivity to stress and increased the
410 negativity of the adverse experience, in line with a mood-buffering effect of cortisol. Further, the
411 results indicate that this enhanced morphine-induced stress response was followed by increased
412 motivation to attain social rewards, both in terms of subjective wanting as well as of facial
413 reactions during reward anticipation.

414 Overall, the results provide novel evidence on the modulation of the physiological and subjective
415 responses to social stress by the MOR system and indicate a state-dependent regulation of social
416 motivation. To better understand the role of μ-opioids in the potentiation of social motivation
417 during aversive states, further investigation of the effects of MOR agonists and antagonists
418 administered after stress induction, as well as of the interaction with other neurochemical systems,
419 is needed.

420

421 # Materials & Methods

422 ## Study design

423 The between-subject, double-blind, placebo-controlled study consisted of one experimental
424 session in which participants received either 10 mg morphine sulfate or a placebo (60 mg
425 mannitol).

426 ## Participants

427 Based on previous work that had investigated the effects of stress on social reward processing
428 (Massaccesi et al., 2021) and the effects of similar compounds on stress responses (Bershad et al.,
429 2018), we aimed at collecting data from 40 participants per group. The study sample included 82
430 participants, of which 42 received morphine (MORPH) and 40 received a placebo (PLB). Two
431 participants (MORPH) did not complete the session and were therefore not included in data
432 analysis, yielding to a final sample size of 80 participants (40/group)[3]. Only female participants
433 were included due to i) gender differences in opioid pharmacokinetics (Fillingim & Gear, 2004;
434 Zubieta et al., 1999) and stress response (Kelly et al., 2008), ii) expected higher preference of
435 same-sex touch in females than males (Stier & Hall, 1984; Suvilehto et al., 2015). Participants
436 were tested during the luteal phase of their menstrual cycle, as assessed by self-report. All
437 participants reported to be right-handed, to smoke less than ten cigarettes per week, to have no
438 history of current or former drug abuse, to have a BMI between 17 and 35, and to be free of
439 psychiatric or neurological disorders. Other exclusion criteria were: single or repeated use of any
440 strong opioids in the last two years, use of hormonal contraceptives, regular intake of medications,

[3] Due to technical problems, EMG data from 6 (4 MORPH) participants and HR data from 1 participant (MORPH) were not recorded. Saliva samples from one participant (MORPH) are also missing.

441 current pregnancy or breastfeeding, suffering from impaired respiratory functions, respiratory
442 weakness or lung disease, injury/disease of the arms (making it impossible to squeeze with the
443 right hand and to be caressed on the left forearm). Participants were instructed to refrain from
444 eating, brushing their teeth and consuming caffeinated beverages, juices, and chewing gum in the
445 two hours preceding the test, as well as from smoking, doing physical activity and intaking alcohol
446 and medications in the 24 hours preceding the test. The two experimental groups did not differ
447 significantly in terms of age, BMI, autistic traits (short version of the German Autism Spectrum
448 Quotient, AQ-k; Freitag et al., 2007), general (State-Trate Anxiety Inventory, STAI; Spielberger
449 et al., 1970) and social (Liebowitz Social Anxiety Scale, LSAS; Heimberg et al., 1999) anxiety,
450 and social touch appreciation (Social Touch Questionnaire, STQ; Wilhelm et al., 2001) (Table 1).
451 The study was approved by the Ethics Committee of the Medical University of Vienna (EK
452 1393/2017) and was performed in line with the Declaration of Helsinki (World Medical
453 Association, 2013). All participants signed a consent form before taking part in the study.

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

	MORPHINE	PLACEBO	*p* value
N	40	40	---
Age (years)	23.08 (3.08)	23.88 (3.86)	0.31
BMI (kg/m^2)	21.37 (3.38)	22.26 (2.66)	0.19
Autism (AQ-k)	6.45 (3.81)	5.65 (3.58)	0.34
Anxiety (STAI)	38.13 (9.43)	35.73 (8.27)	0.23
Social Anxiety (LSAS)	36.73 (17.87)	33.18 (19.02)	0.39
Social Touch Preferences (STQ)	25.33 (9.53)	27.10 (7.67)	0.36
Drug use (% lifetime – last year)			
Cannabis	47.5 – 25	60 – 32.5	---
Tranquilizers	7.5 – 5	5 – 2.5	---
Stimulants	25 – 10	17.5 – 7.5	---
Opiates	7.5 – 0	2.5 – 0	---
Hallucinogens	12.5 – 2.5	12.5 – 2.5	---

Other	5 – 2.5	2.5 – 0	---

455 **Procedure**

456 The study was conducted at the Department of Psychiatry and Psychotherapy of the Medical
457 University of Vienna. After completing an online survey to assess their eligibility, potential
458 participants were first invited to a health screening (~45'), including blood examination,
459 electrocardiogram, blood pressure measurement, and psychiatric interview (Mini-International
460 Neuropsychiatric Interview; Sheehan et al., 1998). Eligible participants were then invited to the
461 experimental session (~210'), which always started between 11:30 and 12:30 in order to control
462 for cortisol diurnal fluctuations (Labuschagne et al., 2019). At the beginning of the session, urine
463 drug and pregnancy tests were administered. After baseline mood and physiological measures were
464 collected, participants received a standardized snack, and took the assigned capsule. Throughout
465 the session, mood and physiological measures were obtained at regular intervals. The experimental
466 tasks were completed between 60 and 160 min after drug administration, and included economic
467 decision making, facial mimicry, emotion recognition, stress induction and social reward
468 processing (see Fig.1A for an overview of the session timeline). Here we will focus on the last
469 two, while the others will be reported elsewhere. Approximately 180 min. after pill administration,
470 a blood sample was taken to confirm drug uptake (see Table S2 of the *Supplementary Material*).
471 After completing the experimental session, participants were debriefed and received a financial
472 compensation of 65€. Half of the sample was tested before and half during the COVID-19
473 pandemic (see *Supplementary Material* for details regarding the employed safety measures and
474 additional statistical analyses to assess possible effects of the pandemic and safety measures on
475 the results).

Drug administration

Ten mg of morphine sulfate (Morapid®) were administered per oral to stimulate the activity of the MOR system with minimal subjective 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 & Kern, 2002). Placebo consisted of capsules containing 650 mg of mannitol (sugar), visually identical to the ones containing morphine.

Stress induction

In order to induce a stress reaction in the participants, the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) was employed. In the TSST, participants were given 3 minutes to prepare a 5-minute speech for a mock-job interview, followed by a 5-minute arithmetic task, in which they were asked to count backwards from 2043 in steps of 17 as fast and as accurate as possible. The speech and arithmetic tasks were completed in front of an evaluating panel (one male and one female confederates). Participants were told that these tasks would be video recorded via a camera located next to the examiners (no video was actually taped).

Social Reward task

Stimuli

Gentle caresses in three different speeds (CT-optimal: 6 cm/s, non-CT-optimal: 21 cm/s and 27 cm/s) were used as social rewards of different level of pleasantness (high, low, very low). Pleasantness of touch is high between 1 and 10 cm/s, and decreases between 10 and 30 cm/s (Löken et al., 2009) and CT-optimal touch has been shown to have a stress buffering effect, reducing arousal (Pawling et al., 2017) and distress following social exclusion (von Mohr et al., 2018), and increasing heart rate variability (Triscoli et al., 2017). The suitability of these stroking speeds has been confirmed in three previous independent studies from our group (Korb,

499 Götzendorfer, et al., 2020; Korb, Massaccesi, et al., 2020; Massaccesi et al., 2021). Caressed were
500 delivered over a previously-marked nine–cm area on participants' left forearm (measurement
501 started from the wrist towards the elbow) by a female experimenter, moving her index and middle
502 fingers back and forth in the marked area of the forearm (Figure 1B). Touch delivery was guided
503 by auditory rhythms, which matched the frequency of the stimulation, over headphones. The
504 experimenter administering the touch was seated on the other side of a curtain, used to limit the
505 participants' field of view to the monitor (Figure 1B). All experimenters were presented as trained
506 masseurs, wore standardized clothes (white t-shirt and beige trousers) to minimize differences in
507 their appearance, and underwent extensive training on the tactile stimulation delivery.

508 ***Task***

509 The Social Reward task (Korb, Götzendorfer, et al., 2020; Massaccesi et al., 2021) consisted of
510 two blocks of 16 trials, separated by a 5-minute break. To avoid habituation to the touch, the site
511 of application (left or right area of the forearm) was alternated within the two blocks, in a counter-
512 balanced order. Before starting the task, participants experienced each type of touch once and
513 performed two training trials. Each trial was structured as follow (see Figure 1C): i) announcement
514 of the best attainable reward (high or low, 16 trials each, 3s); ii) rating of subjective wanting via a
515 VAS ranging from -10 (not at all) to +10 (very much) (no time limit); iii) effort task (4s), requiring
516 to squeeze a hand-dynamometer (HD-BTA, Vernier Software & Technology, USA) with the right
517 hand, in order to obtain the announced reward – the applied force, displayed via an online visual-
518 feedback, was expressed as percentage of the participants' MVC, measured immediately before
519 the task, and translated into the probability of obtaining the announced reward (0–100%); iv)
520 announcement of the reward obtained (high, low, or – if insufficient force had been exerted – very
521 low; 2s); v) reward delivery (6s); vi) relax phase (5s); vii) rating of subjective liking via a VAS

522 ranging from -10 (not at all) to +10 (very much) (no time limit). At the end of the task, participants'
523 MVC was measured again.

524 The task was implemented in MATLAB 2014b (MathWorks, Inc) and presented on an LCD
525 monitor with a resolution of 1280 × 1024 pixels.

526 **Facial EMG**

527 Facial EMG was recorded throughout the Social Reward task, using a g.USBamp amplifier (g.tec
528 Medical Engineering GmbH) and the software Matlab (MathWorks, Inc). Participants' face areas
529 were prepared using alcohol, water and an abrasive paste. Reusable Ag/AgCl electrodes were then
530 attached bipolarly according to guidelines (Fridlund & Cacioppo, 1986) on the left corrugator
531 supercilii (corrugator), and zygomaticus major (zygomaticus) muscles. A ground electrode was
532 attached to the participants' forehead and a reference electrode on the left mastoid. The EMG data
533 were sampled at 1200 Hz with impedances below 20 kΩ. Data preprocessing included filtering
534 with a 20 to 400 Hz bandpass filter, rectification and smoothing with a 40 Hz low-pass filter.

535 Each trial was divided in 4 epochs: Anticipation Pre-Effort (announcement of best attainable
536 reward, 3s), Anticipation Post-Effort (announcement of attained reward, 2s), Delivery (touch
537 administration, 6s), and Relax (relax phase after reward delivery, 5s). EMG was first averaged
538 over 1s time-windows and then over the epoch total duration. For each trial, values in the four
539 epochs were expressed as percentage of the average amplitude during the fixation cross at the
540 beginning of that trial (baseline, 2s). Outliers in baseline (defined as values more than 3 SDs away
541 from the subjects' average baseline) were substituted with the average amplitude of the baseline
542 preceding and following that trial. The extracted epochs were visually inspected in order to identify
543 signal artifacts which were then removed (33 epochs for corrugator and 51 epochs for zygomaticus

across 5 participants). Because of data skewness and to reduce the effect of non-experimental movements, for each subject, epochs over the subject's mean ± 3 SD were removed (average removed epochs per subject: corrugator: $M = 2.4$, $SD = 1.2$; zygomaticus: $M = 3.1$, $SD = 1.1$), and the remaining data were transformed using natural logarithmic transformation.

Subjective measures of stress and mood

During the session, participants completed self-report questionnaires assessing their mood and subjective state at regular intervals. Happiness, calmness, relaxation, feeling good, as well as stress, tension, anxiety and feeling bad were assessed via visual analogue scales ranging from +1 ("not at all") to +101 ("very much") at 7 time points (T1-T7; see Figure 1A). Positive and negative mood items were averaged to constitute the "Positive mood" and "Negative mood" scales used for statistical analyses. The German short version Profile of Mood States (POMS; Albani et al., 2005), consisting of 4 subscales for current mood (depression, vigor, fatigue, and displeasure), was administered at 5 time points (T1, T2, T3, T5, T6; see Figure 1A). During the preparation phase of the TSST (T4), anticipatory cognitive appraisal (PASA; Gaab et al., 2005) was also assessed. Lastly, after completion of the TSST (T5), participants' satisfaction towards their performance at the speech and math tasks was assessed on a VAS scale ranging from 1 ("not at all") to +101 ("very much").

Physiological measures of stress

Heart rate was recorded using a chest strap (Polar H10; Polar Electro Oy, Kempele, Finland). Data were collected over a 10-minute period at baseline, during TSST, and during the Social Reward task. Values in each time window were then averaged for statistical analyses.

565 Saliva samples were collected via passive drool method using Salicaps (IBL, Hamburg, Germany)
566 at 6 time points (T1, T2, T3, T5, T6, T7; see Figure 1A). Free cortisol concentration in saliva was
567 determined by using commercial luminescence immunosorbent assay (LUM; IBL, Hamburg,
568 Germany). Salivary alpha-amylase activity was measured using a kinetic colorimetric test and
569 reagents obtained from DiaSys Diagnostic Systems (Holzheim, Germany). For heart rate, salivary
570 cortisol and alpha-amylase analyses, outliers were defined as subjects with a baseline value (T1)
571 3 SDs over the mean baseline of the sample. This procedure led to the exclusion of two participants
572 for cortisol (1 MORPH, 1 PLB) and of one participant for alpha-amylase (MORPH).

573 **Drug effects on cognitive functions and side-effects**

574 To assess potential drug effects on cognitive functions, participants completed the Trail Making
575 Test (TMT; Reitan, 1958) and the Digit Symbol Substitution Test (DSST; Wechsler, 1939) 55 min
576 after drug administration. Regarding subjective drug effects, participants filled out a self-report
577 questionnaire assessing nausea, dry mouth and other 24 possible side-effects on a 4-point Likert
578 scale (with the anchors 1 = "not at all" and 4 = "very much") at baseline (T1), as well as 50 min
579 (T2) and 160 min (T7) after drug administration (see Figure 1A).

580 **Statistical analyses**

581 Statistical analyses were conducted in R (R Core Team, 2019). Drug effects on subjective and
582 physiological state measures were analyzed using LMMs with Drug (MORPH, PLB) and Time as
583 fixed effects and by-subject random intercepts. Drug effects on ratings of wanting and liking, and
584 force exerted were analyzed with LMMs including Drug (MORPH, PLB) and Reward Level (high,
585 low, and very vow in the case of liking) as fixed effects, and by-subject random intercepts and
586 slopes for Reward Level. For EMG data, LMMs for each muscle and task phase were fitted,
587 including Drug (MORPH, PLB) and trial-by-trial Wanting (for anticipation) or Liking (for

consumption) as fixed effects, and by-subject random intercepts and slopes for Wanting/Liking. In case of model unconvergence or singularity, random effects with the lowest cumulative variance were removed and transformed into the corresponding complex random intercept (CRI; Scandola & Tidoni, 2021). Group differences in age, BMI, and personality traits, as well as drug effects on executive functions, PASA, satisfaction for the TSST performance and side-effects were assessed using independent two-sided t-tests.

LMMs were computed using the lmer() function of the *lme4* package (Bates et al., 2015). Type-III F-tests were computed with the Satterthwaite degrees of freedom approximation, using the anova() function of the *lmerTest* package (Kuznetsova et al., 2017). Significant interactions were further analyzed with multiple comparisons using the function emmeans() from the homonymous package (Lenth, 2021). Results from all LMMs and multiple comparisons were controlled for the false discovery rate (FDR) associated with multiple testing using the Benjamini–Hochberg method (Benjamini & Hochberg, 1995). Data and analysis scripts are available online (https://osf.io/gbd24/).

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Authors contribution

CM: Conceptualization of the study, Data curation, Software, Formal analysis, Supervision, Investigation, Visualization, Methodology, Project administration, Funding acquisition, Writing - original draft, review and editing; MW: Contribution to the conceptualization of the design, Project administration, Medical testing, Funding acquisition, Writing - review and editing; BBQ: Contribution to the conceptualization of the design, Writing - review and editing; UMN: Contribution to the conceptualization of the design, Curation of saliva analysis, Writing - review and editing; CL: Contribution to the conceptualization of the design, Writing - review and editing; DM: Curation of blood analyses; GS: Conceptualization of the study, Supervision, Methodology, Funding acquisition, Project administration, Writing - review and editing.

All authors approved the final version of the manuscript.

Competing interests

No competing interests declared.

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Supplementary Material

Enhanced negative response to stress following morphine administration increases wanting of social reward

C. Massaccesi, M. Willeit, B. B. Quednow, U. M. Nater, C. Lamm, D. Mueller, G. Silani

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1. Effects of COVID-19 pandemic

Half of the sample was collected after the COVID-19 pandemic outbreak. The implemented safety measures, as well as the statistical analyses conducted to assess the possible effects of the pandemic on the study dependent variables are described below.

a. Safety measures

After the COVID-19 pandemic outbreak the following safety measures were implemented:

- All experimenters wore face masks. The evaluating panel of the TSST wore a special face mask with a clear plastic insert on the mouth region in order to allow the participant to see the "absence of facial feedback" (crucial for stress induction) during the stress paradigm.
- Participants were provided with clear mouth visors resting on the chin in order to minimize the contact with the face and avoid disturbances during facial electromyography (EMG).

In order to assess participants reaction towards these safety measures, they were asked to answer the following questions at the end of the experimental session:

1) "How well/comfortable did you feel during the study?" rated on a VAS ranging from 1 (not all) to 101 (very much).
2) "How high do you rate the risk of infection during the study?" rated on a VAS ranging from 1 (very high) to 101 (very low).
3) "Were you afraid of being infected with COVID-19 during the study?", Yes/No
4) "How comfortable did you feel with the research team wearing a mask during the study?" rated on a VAS ranging from 1 (not all) to 101 (very much).

As shown in Figure S1, participants did not report to feel threatened by COVID-19 infection during the study, and to feel comfortable during the session.

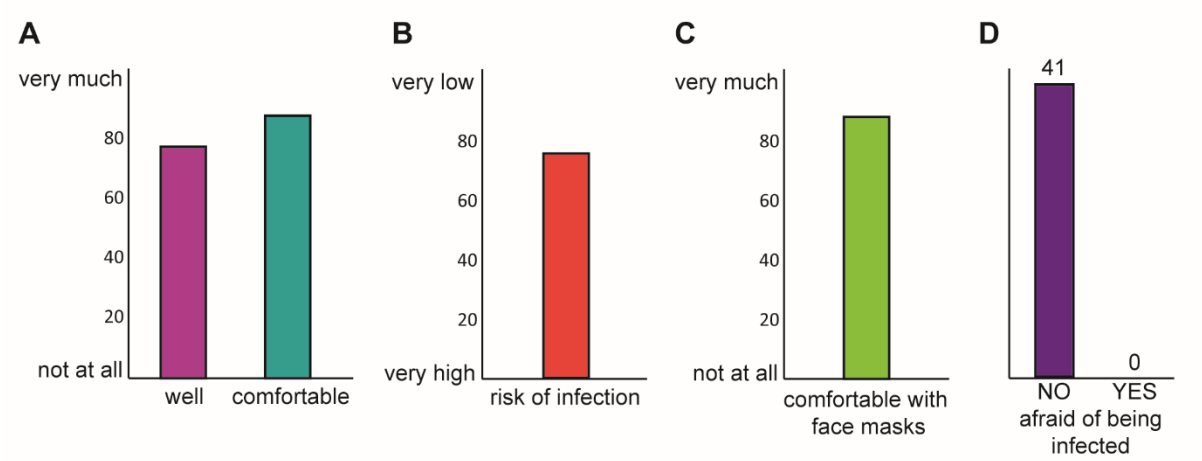

Figure S1. Participants' attitudes toward COVID-19 pandemic and safety measures during the study. (A) Ratings of wellness and comfort. (B) Perceived risk of COVID-19 infection during the study. (C) Ratings of comfort related to use of face masks during the study. (D) Perceived fear of having been infected with COVID-19 during the study.

b. Additional analyses to assess the effects of the COVID-19 pandemic and employed safety measures on responses to social rewards

We tested for possible effects of the pandemic and related implemented safety measures on the subjective stress response (positive and negative mood, POMS subscales), as well as on the ratings of wanting and liking, on the force exerted to obtain the social rewards, and on facial EMG data, by adding the covariate "COVID-19" (2 levels: pre-covid19, covid19) to the statistical models. No changes in the pattern of results were observed.

2. Drug effects on cognitive functions

Table S1. Mean (SD) scores at the Trial Making Test (TMT) part A and part B, and at the Digit Symbol Substitution Test (DSST) across drug groups.

	MORPHINE	PLACEBO	*p* value
TMT A	26.33 (8.02)	26.40 (8.60)	0.97
TMT B	57.25 (33.05)	58.93 (21.94)	0.79
DSST	54.20 (8.99)	54.10 (9.32)	0.96

3. Drug side-effects

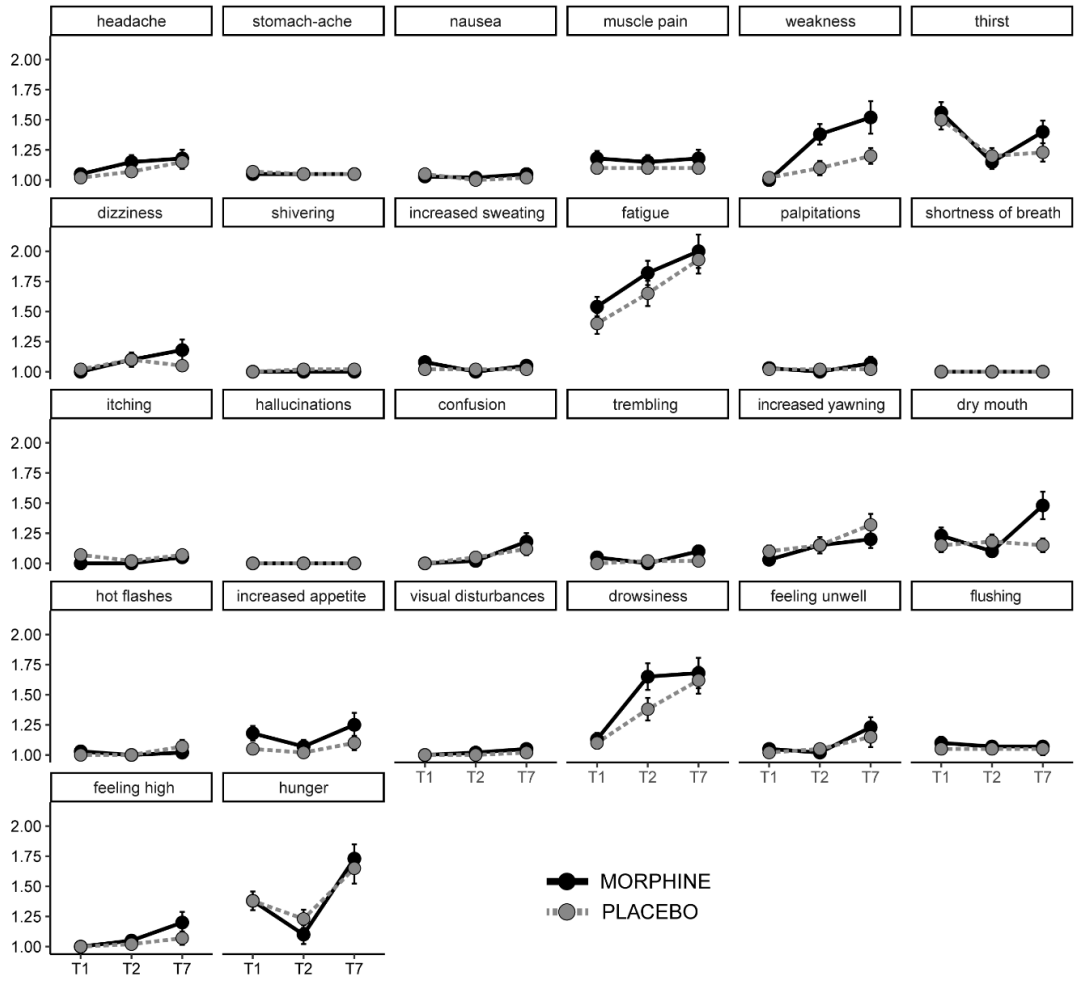

Figure S2. Drug side-effects assessed at baseline (T1), 60 min (T2) and 160 min (T7) after drug administration using a 4-point Likert scale (with the anchors 1 = "not at all" and 4 = "very much").

4. Serum levels of morphine and its metabolites

A blood sample was drawn at the end of the session (~180 min after drug administration). Analyses were performed at the Institute of Clinical Chemistry, University Hospital Zurich, using liquid chromatography coupled to mass spectrometry (LC-MS) to identify serum levels of morphine and its two major metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Blood samples from 3 participants could not be obtained and 10 samples were lost because of

961 storage problems. Results from the available samples confirmed drug uptake, as shown in *Table*
962 *S2*.

963 *Table S2.* Serum levels (nmol/l) of morphine and its major metabolites at the end of the
964 experimental session (~180 min after drug administration). M3G & M6G = morphine-3/6-
965 glucronide.

	M	**SD**
Morphine	12.63	6.82
M3G	394.79	179.46
M6G	84.63	44.32

966