



Short Communication

Naltrexone increases negatively-valenced facial responses to happy faces in female participants



Isabell M. Meier^{a,*}, Peter A. Bos^a, Katie Hamilton^b, Dan J. Stein^c, Jack van Honk^{a,c,d}, Susan Malcolm-Smith^b

^a Department of Experimental Psychology, Utrecht University, Utrecht, The Netherlands

^b Applied Cognitive Science and Experimental Neuropsychology Team, Department of Psychology, University of Cape Town, Cape Town, South Africa

^c Department of Psychiatry and Mental Health, Groote Schuur Hospital, MRC Unit on Anxiety & Stress Disorders, University of Cape Town, Cape Town, South Africa

^d Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa

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ABSTRACT

Positive social cues, like happy facial expressions, activate the brain's reward system and indicate interest in social affiliation. Facial mimicry of emotions, which is the predominantly automatic and unconscious imitation of another person's facial expression, has been shown to promote social affiliation. It has been demonstrated repeatedly that the opioid system is vital to social affiliation in rodents, but there is less evidence in humans. We investigated whether a 50 mg administration of naltrexone, an opioid antagonist with highest affinity for the mu-opioid system, modulates emotional mimicry. A passive viewing task with dynamic facial expressions was used in a randomized placebo controlled between-subjects design. Mimicry was measured with electromyography (EMG) on three facial muscles, the corrugator supercilii and the depressor jaw muscle, associated with negatively-valenced emotions, and the zygomaticus major, which is activated during smiling. The results demonstrate an increase of negatively-valenced facial responses (corrugator and depressor) to happy facial expressions after naltrexone compared to placebo, consistent with lowered interest in social interaction or affiliation. Our findings provide evidence for a role of the opioid system in modulating automatic behavioral responses to cues of reward and social interaction, and translate to rodent models of the mu-opioid system and social affiliation.

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1. Introduction

Social affiliation processes, the formation of strong emotional bonds with individuals in our social environment, are crucial in our everyday life. The absence of positive social contact and isolation has been shown to negatively affect health and well-being (Cacioppo et al., 2015). A pivotal social reward cue that signals interest in social affiliation, indicates social approval and that has been shown to activate the brain's reward system, is happy facial expressions (Spreckelmeyer et al., 2009). Facial mimicry, the predominantly unconscious and automatic activation of facial muscles in response to emotional expressions (Dimberg et al., 2002), towards happy faces has been referred to as 'social glue', due to its properties of promoting affiliation and binding individuals

together (Hess and Fischer, 2014; Lakin et al., 2003). Congruent facial mimicry can therefore be considered a measure for social affiliative behavior in humans.

The opioid system represents one of the underlying neurobiological factors of social affiliation. The attractiveness and pursuit of a rewarding stimulus is driven by several aspects: the motivational 'wanting' of the reward, the hedonic 'liking' of the reward and the associative 'learning' of the context in which a reward cue appears. The opioid system has been shown to especially contribute to the hedonic value ('liking') of rewarding stimuli (Trezza et al., 2011). Further research demonstrated that an increase of 'liking' mediated by the opioid system, may in consequence enhance the motivational 'wanting' of a reward (Syal et al., 2015). Supportive evidence derives from studies demonstrating the role of opioid receptor activity in the nucleus accumbens (NAc), a main structure of the neural reward circuitry, in the attribution of positive value to social interaction in rodents (Trezza et al., 2011) and humans (Hsu et al., 2013). Additionally, in direct relation to affiliative processes,

* Corresponding author at: Department of Experimental Psychology, Utrecht University, Heidelberglaan 1, 3584 CS, Utrecht, The Netherlands.

E-mail address: I.M.Meier@uu.nl (I.M. Meier).

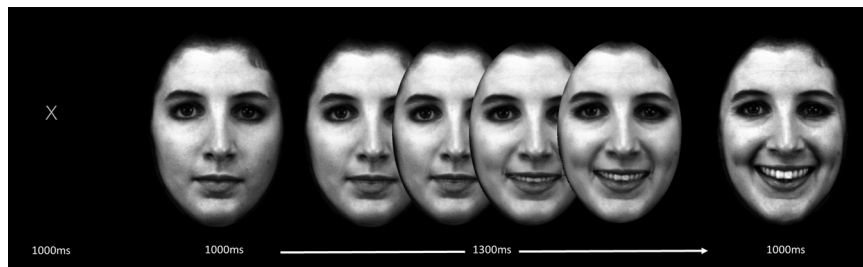


Fig. 1. Schematic view of a single trial. Fixation cross 1000 ms, followed by 1000 ms baseline (neutral face), 1300 ms of morphing into one of the emotional expressions, which remained on the screen for another 1000 ms.

a recent study showed that the mu-opioid system modulates the feeling of social connection in humans (Inagaki et al., 2016).

Naltrexone is an opioid antagonist, which is most selective to the mu-opioid system and which binds competitively at the opioid receptors in the brain (Lee et al., 1988). In the present study naltrexone was administered to investigate if blocking the opioid system would attenuate social affiliative behavioral responses indexed by emotional mimicry to emotional facial expressions. Typically, the zygomaticus major, a muscle that forms a smile by lifting the corners of the mouth, is activated in response to happy faces. The corrugator supercilii, a muscle that produces a frown by drawing the eyebrows together, shows an increase of activation in response to angry faces and a decrease in activation in response to happy faces. The depressor jaw muscle, which pulls the corners of the mouth down is activated for sad faces (Dimberg et al., 2002). Naltrexone was administered in a randomized, double-blind, placebo controlled design. Based on the literature on the opioid system and social affiliation, we expected that naltrexone compared to placebo would disrupt the social affiliative response to happy faces resulting in a decrease in zygomaticus activity. For the depressor activity in response to sad faces two competing hypotheses may be considered. On the one hand, we could expect naltrexone administration to result in an increase of depressor activity, reflecting increased shared pain with others, in line with the potential efficacy of mu-opioids in the treatment of depression (Panksepp and Watt, 2011; Stein et al., 2007). On the other hand, we might expect a decrease of depressor activity in response to sad faces with naltrexone compared to placebo, since mimicry of a sad face can reflect a social affiliative response. From this perspective, a decrease in depressor activity would be in line with our predictions about happy faces, in that blocking the mu-opioid system disrupts socially affiliative responses. Angry facial expressions served as a control measurement.

2. Methods

2.1. Participants

36 female students were recruited at Cape Town University to participate in the study. Only female participants were included because women have been shown to display more robust facial mimicry than men (Dimberg and Lundquist, 1990). Participants were all of South African nationality, Caucasian, right handed, with a mean age of 20.7 years ($SD=2.11$), and were screened for any history of psychopathology. Exclusion criteria also contained use of alcohol or painkillers in the last 24 h, or the general use of psychotropic medication. The experimental protocol was approved by the Human Research Ethics Committee (HREC) of the University of Cape Town, in accordance with the latest declaration of Helsinki. Participants gave written informed consent prior to participation and received payment afterwards.

2.2. Drug administration

Either placebo or 50 mg of naltrexone, an opioid antagonist, were administered orally, in a randomized, double-blind and counter-balanced manner. Naltrexone has higher selectivity for mu-opioid receptors, compared to kappa- and delta- opioid receptors and is therefore an adequate choice for investigating the role of the mu-opioid system in social affiliation. The mimicry task started 69 min after administration and was completed 7 min later, to coincide with the central effects of naltrexone (Lee et al., 1988).

2.3. Material & procedure

Upon arrival participants signed informed consent and received naltrexone or placebo in a randomized, double-blind manner. Short video clips of dynamic facial expressions were presented (Hofman et al., 2012) using e-prime version 2.0 (Psychology Software Tools, Pittsburgh, PA) and displayed on a 47 cm screen. Participants were positioned 70 cm distant from the screen. Before the start of the task, participants were informed that they would see faces with different emotions and instructed to look at the faces, to sit still and move to the head as little as possible, while focusing on the center of the screen. One trial was composed of a fixation cross (1000 ms), followed by the dynamic face video clip which was displayed for 3300 ms. The video clip included 1000 ms neutral facial expression (baseline), 1300 ms of morphing, with the last frame showing the full emotion expression for 1000 ms (cf. Fig. 1). The inter-stimulus interval lasted 4000 ms. All 24 stimuli were displayed twice in a randomized manner, resulting in a total of 48 trials and a task duration of seven minutes. Electromyography (EMG) responses were measured on three muscles, the corrugator supercilii, the zygomaticus major and depressor jaw muscle (cf. Hofman et al., 2012). Ag/AgCl electrodes were used in a bipolar electrode set up (www.biosemi.com). Mood was assessed with a computerized version of the Positive Affect Negative Affect Scale (PANAS; Watson et al., 1988).

2.4. Data reduction and statistical analysis

The electrophysiological data was processed offline with Brain-VisionAnalyzer 2.0. Trials were selected -1000 ms to $+2500$ ms around the reference marker, filtered, rectified, baseline corrected, and segmented in 14 bins of 250 ms per trial (cf. Hofman et al., 2012). The first four bins containing neutral expressions were excluded from statistical analysis. Where sphericity was violated, Huynh-Feldt corrections were applied. In total three participants had to be excluded from analysis, one due to high depression scores and two due to measurement related problems.

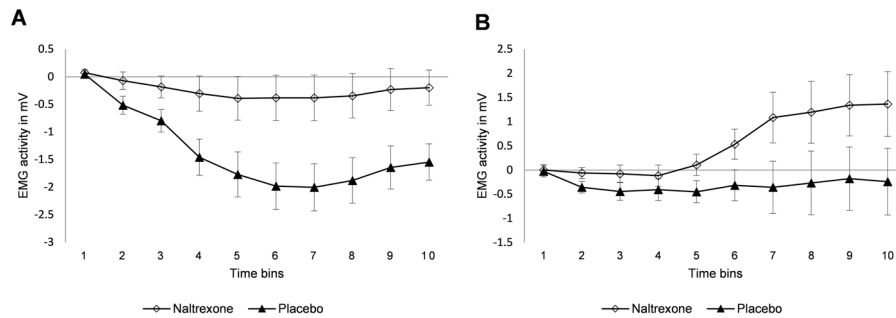


Fig. 2. Averaged EMG activity in microvolt (mV) of corrugators muscle for happy faces (A) and depressors activity for happy faces (B), over time (bin 1–6 morph; 6–10 full emotional expression). Standard error indicated.

3. Results

3.1. Mood and task validation

To test for a possible effect of medication on mood ratings, a 2 (naltrexone, placebo) \times 2 (positive affect, negative affect) repeated measures ANOVA was performed. There was no effect of medication ($F(1,30)=2.04$, $p=0.164$, $P\eta^2=0.06$), nor any significant interaction of mood by medication ($F(1,30)=2.81$, $p=0.104$, $P\eta^2=0.09$). We conducted a $3 \times 3 \times 10$ (emotion \times muscle \times time) repeated measures ANOVA in the placebo condition to validate the task. The three way interaction of emotion \times muscle \times time showed to be significant ($F(5.2, 78.74)=2.8$, $p=0.017$, $P\eta^2=0.16$), as well as the interaction of emotion \times muscle ($F(2.9, 43.26)=5.01$, $p=0.005$, $P\eta^2=0.25$). These interactions show that the muscles responded differently over time to the distinct emotions, thus demonstrating facial mimicry.

3.2. Mimicry

A $2 \times 3 \times 10$ three-way repeated measures ANOVA (medication \times emotion \times time) with medication as a between subject factor and emotion and time as within subject factors was conducted per muscle to test for the effect of naltrexone on emotional mimicry.

3.2.1. Corrugator supercilii

There was a significant interaction of emotion \times medication on mimicry ($F(1.39, 43.1)=3.69$, $p=0.048$, $P\eta^2=0.11$) indicating that the corrugator muscle showed a different response to the three emotions depending on drug administrations. There was no main effect of time ($F(1.63, 50.6)=0.94$, $p=0.383$, $P\eta^2=0.03$), nor any interaction of time with emotion and condition ($F(2.98, 92.3)=2.0$, $p=0.120$, $P\eta^2=0.06$). The main effect of medication was not found to be significant ($F(1, 31)=2.34$, $p=0.136$, $P\eta^2=0.07$).

To break down the interaction, three separate 2×10 (medication \times time) repeated measure ANOVAs were conducted per emotion. Results showed a significant main effect of medication for happy faces ($F(1,31)=7.3$, $p=0.011$, $P\eta^2=0.19$), but not for angry ($F(1,31)=0.33$, $p=0.572$, $P\eta^2=0.01$) or sad faces ($F(1,31)=0.03$, $p=0.855$, $P\eta^2=0.001$). Crucially, naltrexone administration, compared to placebo resulted in a significant increase in corrugator activity (cf. Fig. 2A). The mean activation of the corrugator during happy faces increased from $M=-1.36$ ($SE=0.3$) in placebo condition, to $M=-0.24$ ($SE=0.29$) in the naltrexone condition.

3.2.2. Depressor jaw muscle

Trend level effects were shown for both the two way interaction of emotion \times medication ($F(1.5, 46.4)=2.63$, $p=0.097$, $P\eta^2=0.08$), and the three way interaction of emotion \times medication \times time ($F(2.43, 75.2)=2.48$, $p=0.080$, $P\eta^2=0.07$). The main effect of medication was not significant ($F(1, 31)=0.17$, $p=0.682$, $P\eta^2=0.005$). To

investigate the effect of medication per emotion, three 2×10 (medication \times time) repeated measures ANOVA's were conducted. The analysis showed a near significant effect of naltrexone for the depressor in happy faces ($F(1, 31)=3.93$, $p=0.056$, $P\eta^2=0.11$), pointing to an increase of depressor activity after naltrexone administration (cf. Fig. 2B). No effect of naltrexone was found for sad ($F(1, 31)=1.06$, $p=0.311$, $P\eta^2=0.03$) and angry faces ($F(1, 31)=0.15$, $p=0.705$, $P\eta^2=0.005$).

3.2.3. Zygomaticus major

The ANOVA did not reveal a significant interaction of emotion \times medication ($F(1.23, 38.1)=0.058$, $p=0.859$, $P\eta^2=0.002$) nor of emotion \times medication \times time ($F(1.67, 51.7)=0.23$, $p=0.759$, $P\eta^2=0.007$). Also, the main effect of medication was not significant ($F(1, 31)=0.02$, $p=0.890$, $P\eta^2=0.001$).

4. Discussion

The literature indicates that congruent facial mimicry in response to happy faces in terms of increased zygomaticus and decreased corrugator activity promotes affiliative interest (Hess and Fischer, 2014). The current findings suggest that naltrexone automatically lowers motivation for social affiliation, as indicated by increased negatively-valenced facial responses (corrugator and depressor activity) to these affiliative facial cues. There was significant increase of activation in the corrugator in response to happy faces during naltrexone, compared to relaxation during placebo, and a near-significant increase of depressor activity for happy faces. The latter findings may correspond to evident negative relationships between opioids and depression, and antidepressant effects of opioid agonist buprenorphine (Panksepp and Watt, 2011). However, while naltrexone increased negatively-valenced facial responses to happy faces, it should be noted that the opioid antagonist did not induce expected decreases of zygomaticus activation for happy faces or increases of activation in the depressor muscle in response to sad faces. In other words, the results demonstrated that by blocking the mu-opioid system, social reward cues like happy faces received greater negative valence.

There are several human studies demonstrating the involvement of the mu-opioid system in motivational and hedonic aspects of social reward behavior (Chelnokova et al., 2014; Syal et al., 2015). The present study extends these findings to social affiliation by demonstrating that the opioid system modulates the automatic, unconscious behavioral response towards rewarding social stimuli like happy faces. Since these positive facial expressions indicate social acceptance and promote affiliative behavior, our findings suggest that mu-opioid antagonism in humans results in reduced affiliative behavior. Our results are also in line with findings indicating that mu-opioid receptor activation in the ventral striatum after positive social feedback is predictive for desire of social interaction in humans (Hsu et al., 2013). Further supporting evidence is

provided by the study of Inagaki et al. (2016), which showed that regular intake of naltrexone over 4 days resulted in a decrease in the experience of social connection, on the basis of daily reports and in a laboratory setting.

As a limitation to the present study it must be mentioned that the effect on the depressor was only near significant, which might be due to the use of a relatively small sample size. Furthermore, although naltrexone shows highest sensitivity for the mu-opioid system, we cannot disregard the possibility of effects via the kappa- or delta-opioid receptor systems. Finally, only females were included in the study due to the fact that females show more robust facial mimicry than males (Dimberg and Lundquist, 1990). To validate and extend the current results further testing is required, which should include a male sample.

In conclusion, we suggest that the mu-opioid system has a pivotal role in the underlying mechanisms that regulate the appetitive response to social reward cues, like happy faces. We show that naltrexone administration results in increases in negatively-valenced facial responses during the presentation of happy faces. This finding corresponds to the role of the mu-opioid system in social interaction and affiliation, and in adaptive socio-emotional behavior.

Contributors

Isabell M. Meier, Peter A. Bos, Katie Hamilton, Dan J. Stein, Jack van Honk & Susan Malcolm-Smith. Author PAB, JvH & SMS designed the study and wrote the protocol. Author KH conducted the experiment. Author IMM and PAB managed the literature searches and facilitated data analyses. Authors IMM and PAB undertook the statistical analysis, and authors IMM, PAB, DJS, JvH & SMS contributed to the writing of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

In the past 3 years, Dr. Stein has received research grants and/or consultancy honoraria from AMBRF, Biocodex, Cipla, Lundbeck, National Responsible Gambling Foundation, Novartis, Servier, and Sun.

Role of the funding source

The funding sources had no role in: study design; the collection, analysis and interpretation of the data; the writing of the report, and the decision to submit the paper for publication.

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References

- Cacioppo, J.T., Cacioppo, S., Capitanio, J.P., Cole, S.W., 2015. The neuroendocrinology of social isolation. *Annu. Rev. Psychol.* 66, 733–767.
- Chelnokova, O., Laeng, B., Eikemo, M., Riegels, J., Løseth, G., Maurud, H., Willoch, F., Leknes, S., 2014. Rewards of beauty: the opioid system mediates social motivation in humans. *Mol. Psychiatry* 19, 746–747.
- Dimberg, U., Lundquist, L.O., 1990. Gender differences in facial reactions to facial expressions. *Biol. Psychol.* 30, 151–159.
- Dimberg, U., Thunberg, M., Grunedal, S., 2002. Facial reactions to emotional stimuli: Automatically controlled emotional responses. *Cogn. Emot.* 16, 449–471.
- Hess, U., Fischer, A., 2014. Emotional mimicry: why and when we mimic emotions. *Soc. Personal. Psychol. Compass* 8, 45–57.
- Hofman, D., a, Bos P., Schutter, D.J.L.G., van Honk, J., 2012. Fairness modulates non-conscious facial mimicry in women. *Proc. R. Soc. B Biol. Sci.* 279, 3535–3539.
- Hsu, D.T., Sanford, B.J., Meyers, K.K., Love, T.M., Hazlett, K.E., Wang, H., Ni, L., Walker, S.J., Mickey, B.J., Korycinski, S.T., Koeppe, R.A., Crocker, J.K., Langenecker, S.A., Zubietta, J.-K., 2013. Response of the μ -opioid system to social rejection and acceptance. *Mol. Psychiatry* 18, 1211–1217.
- Inagaki, T.K., Ray, L.A., Irwin, M.R., Way, B.M., Eisenberger, N.I., 2016. Opioids and social bonding: naltrexone reduces feelings of social connection. *Soc. Cogn. Affect. Neurosci.*
- Lakin, J.L., Jefferis, V.E., Cheng, C.M., Chartrand, T.L., 2003. The chameleon effect As social glue: evidence for the evolutionary significance of nonconscious mimicry. *J. Nonverbal Behav.* 27, 145–161.
- Lee, M.C., Wagner, H.N., Tanada, S., Frost, J.J., Bice, N., Dannals, R.F., 1988. Duration of occupancy of opiate receptors by naltrexone. *J. Nucl. Med.* 29, 1207–1211.
- Panksepp, J., Watt, D., 2011. Why does depression hurt? ancestral primary-process separation-distress (PANIC/GRIEF) and diminished brain reward (SEEKING) processes in the genesis of depressive affect. *Psychiatry* 74, 5–13.
- Spreckelmeyer, K.N., Krach, S., Kohls, G., Rademacher, L., Irmak, A., Konrad, K., Kircher, T., Gründer, G., 2009. Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Soc. Cogn. Affect. Neurosci.* 4, 158–165.
- Stein, D.J., van Honk, J., Ipser, J., Solms, M., Panksepp, J., 2007. Opioids: from physical pain to the pain of social isolation. *CNS Spectr.* 12, 512–517.
- Syal, S., Ipser, J., Terburg, D., Solms, M., Panksepp, J., Malcolm-Smith, S., a, Bos P., Montoya, E.R., Stein, D.J., van Honk, J., 2015. Improved memory for reward cues following acute buprenorphine administration in humans. *Psychoneuroendocrinology* 53, 10–15.
- Trezza, V., Damsteegt, R., Achterberg, E.J.M., Vanderschuren, L.J.M.J., 2011. Nucleus accumbens μ -opioid receptors mediate social reward. *J. Neurosci.* 31, 6362–6370.
- Watson, D., Clark, L., a Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J. Pers. Soc. Psychol.* 54, 1063–1070.