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Opioid receptor blockade inhibits self-disclosure during a closeness-building social interaction

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ABSTRACT

Social ties are critical to human health and well-being; thus, it is important to gain a better understanding of the neurobiological mechanisms involved in the development of interpersonal closeness. Prior research indicates that endogenous opioids may play a role in social affiliation by elaborating feelings of social connection and warmth; however, it is not currently known whether opioids mediate affiliative behavior and emerging feelings of closeness in humans at the relationship initiation stage. This randomized, double-blind study examined opioidergic processes in the context of a naturalistic, face-to-face social interaction. Eighty pairs of unacquainted participants (final $N = 159$ due to removal of one dyad member from analysis) received either 50 mg of the opioid receptor antagonist naltrexone or placebo prior to completing a closeness-building exercise centered on escalating self-disclosure (sharing of personal information about the self). Compared to the placebo group, naltrexone participants held lower social reward expectations prior to the interaction, engaged in less intimacy-fostering behavior (self-disclosure) during the interaction, and reported wanting less closeness with their partner. Feelings of social connection were not significantly lower in the naltrexone group. However, placebo participants experienced improvements in mood after the closeness-building task whereas naltrexone participants did not. These findings suggest that endogenous opioids may contribute to behavioral, affective, and motivational processes related to the development of initial closeness.

1. Introduction

When asked to pinpoint the most positive emotional event of their lives, people commonly revisit moments of deepening intimacy (Jaremka et al., 2011), thus demonstrating the premium placed on social connection. Indeed, as humans have depended on each other for survival throughout evolutionary history, natural selection would have favored the emergence of neurobiological mechanisms that elaborate feelings of social pleasure and drive affiliative behavior, thus promoting the development of social connections (Baumeister and Leary, 1995). One such candidate mechanism is the endogenous opioid system – specifically, the μ-opioid receptor subtype and its ligands – which is a critical mediator of reward (Fields, 2007). Although non-human animal research has long implicated endogenous opioids in social bonding and attachment, research has only recently begun to investigate the role of opioids in human sociality, and questions remain about whether opioids exclusively mediate closeness in existing relationships or contribute to closeness-fostering processes in the early stages of relationship building.

The Brain Opioid Theory of Social Attachment (BOTSA; Panksepp, 1998) postulates that endogenous opioids mediate feelings of pleasure and security experienced in the presence of others, thus promoting the formation and maintenance of social bonds. Consistent with this theory, affiliative activities such as social play and grooming induce release of endogenous opioids in non-human animals (Keverne et al., 1989; Panksepp and Bishop, 1981) and opioid receptor antagonism diminishes the reward value of such interactions (Trezza et al., 2011). Accordingly, disruption of endogenous opioid activity inhibits development of social bonds in non-human animals. For example, opioid receptor antagonists such as naltrexone impede partner preference formation among monogamous prairie voles (Burkett et al., 2011) and disrupt development of maternal attachment in newborn lambs (Shayit et al., 2003).

Very little research to date has examined whether the initial development of social bonds in humans similarly relies on opioidergic processes. However, emerging evidence from studies using naltrexone to temporarily block opioid receptors suggests that opioids underlie feelings of social warmth and connection experienced in the context of

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existing attachment bonds both real (e.g., in response to warm written messages from, or images of, close others; Inagaki et al., 2016, 2019) and more abstract (e.g., films portraying intimacy-related themes; Depue and Morrone-Strupinsky, 2005). Similarly, imaging research has shown that μ-opioid receptor activation increases after imagining social acceptance (Hsu et al., 2013) and watching humorous videos with friends (Manninen et al., 2017); importantly, however, these studies are not able to provide causal evidence that opioids elaborate feelings of connection, and, in the case of the latter study, it is not clear to what extent opioid activation is related to engaging in an affiliative activity rather than a positive activity more generally. Opioid receptor blockade has also been shown to decrease social interest, as operationalized by less visual exploration of faces—and the eye-region specifically—in participants receiving naltrexone (Chelnokova et al., 2016). Notably, however, the only study to examine whether opioids play a role in the development of closeness with previously unknown individuals did not involve any actual social contact (participants were asked to dance side-by-side while wearing headphones); opioid receptor antagonism did not influence feelings of closeness towards group members (Tarr et al., 2017).

Thus, it is not currently known whether opioids contribute to the *initial* development of closeness among humans—or as Loseth et al. (2014) have phrased the question in their comprehensive review, whether endogenous opioids constitute a prerequisite or consequence of social bonding (or both). While Loseth et al. have suggested that, in positive social contexts, opioids may contribute to social exploration and formation of new social bonds, Inagaki (2018) recently argued that opioid processes may be uniquely engaged by intimate interactions with individuals with whom one is already bonded. However, the non-human animal literature has shown that the development of positive conditioned associations stemming from social play is reliant on opioid activity (Trezza et al., 2011) and that blockade of endogenous opioid receptors prevents new social attachments from developing (Burkett et al., 2011). Given the importance of social bonding for human well-being, this outstanding research question is important to address.

The current research extends the literature in two other significant ways. First, no prior work has examined the effects of opioid blockade on social behavior and affect in the context of naturalistic, real-time social interactions that can best support generalizability. Second, pharmacological studies on opioids and social affiliation have tended to focus on feelings of social reward, without examining concomitant effects of naltrexone on perceptions of social threat. BOTSA postulates that opioids inhibit feelings of separation distress and social pain, consequently contributing to a sense of psychological safety (Panksepp, 1998). To the extent that even positive social interactions may still carry a degree of vulnerability and risk, opioids may therefore promote affiliative behavior either by enhancing perceptions of reward or down-regulating perceptions of threat (or both); consequently, it is important that studies examining the effects of pharmacological agents acting on the endogenous opioid system take both social reward and social threat into account.

While social ties among non-human animals are largely reliant on tactile stimulation (Keverne et al., 1989), one important additional pathway toward closeness open to humans is self-disclosure, or sharing of information about the self – an intrinsically rewarding process (Tamir and Mitchell, 2012) that fosters feelings of liking, connection, and trust in both senders and receivers (Collins and Miller, 1994). Thus, in the current research, we used the intimate self-disclosure task developed by Aron and colleagues (1997) to examine whether opioids mediate developing closeness. This intimate question-and-answer task has been shown to lead to high levels of initial closeness (Aron et al., 1997), as well as subsequent development of friendships outside of the lab (Slatcher, 2010). We hypothesized that participant dyads who received naltrexone prior to completing this task would report lower social reward expectations before the social interaction, less self-disclosure and lower feelings of social connection during the interaction, as well as diminished desire for interpersonal closeness with the partner. We also hypothesized that participants receiving placebo, but not naltrexone, would experience increases in positive affect following the interaction.[1] Finally, even though the closeness task is designed to bolster feelings of social reward and acceptance, it still presents a degree of vulnerability and risk; thus, we conducted additional exploratory analyses examining whether naltrexone would increase perceptions of social threat leading to and following the social task.

2. Materials and methods

2.1. Sample size determination and stopping procedure

We planned to recruit 276 participants (138 dyads) based on a power analysis, conducted in G*Power (Faul et al., 2007) following the adjustments for dyadic data outlined by Kenny, Kashy, and Cook (2006), with the following parameters: Cohen's $d = 0.40$ (due to lack of research on this topic available at the time of study design we used a conservative estimate of a small to medium effect size), $\alpha = .05$, $\beta = .20$, intraclass correlation = .37 (e.g., Berry and Hansen, 1996). Due to financial constraints and personnel turnover over the two years it took to complete data collection, we had to terminate the study after collecting data from 170 participants. All analyses were conducted after data collection was complete.

2.2. Participants

Participants were recruited from the University of Toronto Introductory Psychology Participant Pool and the Greater Toronto Area via printed and online advertisements. Eligibility was assessed during a preliminary phone screening and an in-lab interview on the day of testing. Participants were considered eligible if they were between 18 and 27 years of age (inclusive), fluent in English, in good physical and mental health, not allergic to bovine milk proteins (included in the capsule filling), and free of contraindications for naltrexone administration (*Supplementary material: Methods*). Eleven participants were excluded prior to data analysis (*Supplementary material: Methods* and *Figure S1*); thus, the final sample consisted of 159[2] participants, of whom 84 received placebo and 75 received naltrexone. Due to a computer malfunction, one naltrexone participant's positive/negative affect data were missing at Time 2; therefore, that participant is not included in the repeated measures analyses of affect.

2.3. Study drug

Naltrexone is an opioid receptor antagonist that blocks the effects of exogenous and endogenous opioids by competitive binding at opioid receptors. We used a standard oral dose (50 mg), which has been shown to saturate brain opioid receptors within an hour of administration (Lee et al., 1988). The elimination half-life of naltrexone from plasma is approximately four hours; the half-time of naltrexone blockade of brain opioid receptors is 72 − 108 h (Lee et al., 1988).

Naltrexone (ReVia, Apotex Canada) was administered in a double-blind manner. Blinding was accomplished by over-encapsulating the naltrexone product and preparing matching lactose powder placebo capsules. At the end of the study, participants were asked to guess

[1] Although our focus was on social reward and self-disclosure, we also examined effects of naltrexone on state self-esteem, and general social goals; information about these analyses is included in *Supplementary material: Additional Analyses*.

[2] Where appropriate, we retained data from one of the partners even if the other partner's data were discarded (see *Supplementary Material* for more detail), thus resulting in an odd number of participants. Note: multilevel modeling allows for missing data for one member of the dyad (Kenny et al., 2006).

which substance they received. Among naltrexone participants, one participant did not answer, 32.4 % guessed that they received placebo, 29.7 % guessed naltrexone, and 37.8 % indicated "not sure" (percentages not significantly different from chance (33.3 %), $\chi^2(2, n = 74) = 0.76$, $p = .685$). In the placebo group, 54.8 % guessed placebo, 13.1 % guessed naltrexone, and 32.1 % indicated "not sure", $\chi^2(2, n = 84) = 21.93$, $p = .001$. Therefore, for all dependent variables, we conducted an additional series of analyses controlling for participants' condition guess. We do not report these analyses in the paper unless they influenced the original results.

2.4. Study overview

All study procedures were approved by the University of Toronto Office of Research Ethics. We used a randomized, double-blind, placebo-controlled, between-subjects design. Two previously unacquainted participants, henceforth referred to as "partners," were scheduled for each study session by an experimenter based on the participants' availability (i.e., participants were not matched on any predetermined criteria). The participants were not introduced to each other until the beginning of the closeness building task (see below). In order to maximize the strength of the drug effects and thus statistical power, both dyad members were assigned to the same drug condition. Each dyad was sequentially assigned to receive one of the coded treatments following medical screening according to a randomization plan created by the lead author.

Participants were recruited for a study investigating "how personality traits and endogenous opioid activity affect performance on mental tasks". Upon arrival at the laboratory, each participant was taken to a private room where they underwent a medical screening interview and completed the informed consent process; as part of this process, participants were informed about potential side effects of naltrexone (e.g., nausea; see *Supplementary material* for full list). Following provision of consent, participants were administered either naltrexone or placebo. Immediately following naltrexone/placebo administration and well before the drug had time to take effect, participants filled out individual difference questionnaires[3] including the Big Five personality traits (John et al., 1991), as well as a measure of affect (see below for details of all outcome measures).[4] As naltrexone takes approximately one hour to reach peak effect (Lee et al., 1988), we then had participants relax and watch a light, humorous cartoon[5] (The Simpsons) until this period elapsed.

Approximately 55 min after naltrexone/placebo administration, the experimenters informed each participant that, since more time was needed for the drug to reach effect, they could spend some of the remaining wait time helping the Arts and Science Students' Union pilot test some activities for Orientation Week that would involve interacting with another participant in the lab. Participants then filled out a brief measure assessing social reward and threat expectations about the upcoming interaction. Following the completion of this measure, the two participants were brought into the same room, introduced to each other, and given instructions for the closeness-building task (Aron et al., 1997). This task was described to participants as a "sharing game" where their goal is to get to know one another by taking turns answering a series of questions about themselves. Dyads received three sets of 12 questions that required gradually escalating intimacy of self-disclosure. Participants began, for example, by telling their partner whom, given the choice of anyone in the world, they would want to have as a dinner guest; later participants shared more personal information, such as their "most treasured memory" or the last time they cried in front of another person.

Partners were told to take their time answering the questions and to work through each set at a comfortable pace. They were not required to get through every question in a set, but rather to answer each question thoughtfully. Every 10 min, the experimenter entered the room and instructed the participants to move on to the next set of questions, thereby ensuring that each dyad had the chance to answer some of the more intimate questions. Due to time constraints, we allotted 10 min to each set of questions, rather than 15 min as in the original protocol. Afterwards, participants returned to their separate rooms and completed questionnaires assessing self-disclosure, feelings of social reward and connection, and evaluations of their partner's personality traits (Wiggins et al., 1988),[6] as well as the affect measure for a second time. Following completion of these measures, participants were debriefed, given compensation, and dismissed.

2.5. Outcome measures

2.5.1. Self-disclosure

Self-disclosure during the social task was assessed with the Self-Disclosure Index (Miller et al., 1983). Participants indicated how much they had disclosed on 10 different intimate domains (e.g., "what I like and dislike about myself," "what makes me the person I am," "my deepest feelings") using a 5-point scale (1 = *did not discuss at all*, 5 = *discussed fully and completely*). Participants also completed a second version of the scale asking how much they thought their partner had disclosed on the same topics.

2.5.2. Social threat and reward scale

We used the Social Threat and Reward Scale, adapted from Spielmann et al. (2012), to assess participants' perceptions of social reward and threat immediately before and after the closeness-building task. The wording of the items was altered between the first and second presentations of the scale to refer either to participants' expectations about the upcoming social interaction or to their actual experience during the interaction, respectively. Social reward refers to participants' perceptions of the potential for intimacy and interpersonal closeness. The social reward subscale includes five items such as "It will be (pre-measure)/was (post-measure) interesting to learn about my interaction partner" and "I think I could develop (pre-measure)/felt like I developed (post-measure) a meaningful connection with my interaction partner". Social threat refers to perceptions of the presence of, or the potential for, negative social evaluation and rejection. Thus, the social threat subscale includes five items such as "I'm concerned my partner won't (pre-measure)/didn't (post-measure) like me very much" and "I feel (pre-measure)/felt (post-measure) a little anxious about/during (pre-measure)/(post-measure) the interaction". All items were rated from 1 (strongly disagree) to 5 (strongly agree).

These two versions of the scale tap two different constructs: i.e., social reward/threat expectations (the extent to which participants thought the upcoming interaction with the partner they had not yet met would be rewarding or threatening) and actual social reward/threat experience (the extent to which participants found the dyadic interaction rewarding or threatening).

2.5.3. Inclusion of other in the self scale

The Inclusion of Other in the Self (IOS) scale (Aron et al., 1992) is a

[3] These measures were collected for exploratory analyses of potential moderator effects that will not be reported in the current paper; see *Supplementary material: Methods* for further information about measures collected.

[4] On average, participants took 10.44 minutes to complete the set of surveys ($SD = 3.61$).

[5] We opted for a humorous, rather than a more serious, video in order to reduce the likelihood of participants experiencing high levels of fatigue or boredom prior to the beginning of the closeness building task.

[6] Due to an error, not all items from this interpersonal circumplex scale were included and, as the included items did not factor together well, this scale was omitted from analysis.

single-item, pictorial measure of interpersonal closeness. It consists of seven pairs of partially overlapping, Venn diagram-like circles labeled *Self* and *Other*, which vary in the extent of their overlap. Participants selected the pair of circles that best represented their relationship with their interaction partner. We also included a variant of the measure (IOS-desired) asking participants which pair of circles best represented the relationship they *wished* they could have with their partner (Aron et al., 1997). By using these two different versions of the scale, we thus aimed to assess both *felt* closeness and *desired* closeness.

2.5.4. Subjective closeness index

The Subjective Closeness Index (Berscheid et al., 1989) asks participants how close they would characterize their relationship with their partner (1 = *least closeness,* 7 = *greatest closeness*) relative to 1) all of their other relationships, and 2) what they know about other people's close relationships.

2.5.5. Liking

Participants were asked three items assessing liking for their partner (Miller et al., 1983): a) how much do you like your partner?; b) How much would you like your partner as a close friend?; and c) How much would you like to see your partner again? Responses were rated on a scale ranging from 0 (not at all) to 9 (a great deal).

2.5.6. Connectedness

An eight-item questionnaire was used to assess feelings of connection following social interaction (Borsook and MacDonald, 2010). The questionnaire includes such items as "How close do you feel to your partner" rated on a scale from 1 (not at all) to 9 (very much).

2.5.7. Partner responsiveness

Participants' perceptions of partner responsiveness were assessed using 12 items from Cross et al. (2000). Participants indicated, on a scale of 1 (strongly agree) to 5 (strongly disagree), the extent to which their partner made them feel valued, cared for, and understood. For example, participants were asked to evaluate such statements as "my partner behaved warmly toward me".

2.5.8. Affect

We used the Positive and Negative Affect Schedule (Watson et al., 1988) to assess participants' affect at the start of the experiment (Time 1) and after the social interaction (Time 2). Participants rated how well 10 positive (e.g., enthusiastic) and 10 negative (e.g., upset) emotion adjectives described their current affect from 1 (very slightly or not at all) to 5 (extremely).

2.6. Statistical analyses

Analyses were conducted using SAS Studio for Linux (version 9.4; SAS Institute Inc., Cary, NC). Categorical predictors were dummy coded and all continuous predictors were grand mean centered in order to reduce multicollinearity and aid interpretation. Linear regression was used to compare naltrexone and placebo participants' social reward and threat expectation scores collected prior to the social interaction (as participants had not had any contact with each other at this point, they were not considered to be nested within the dyad for this measure). For all other outcome measures, multilevel modeling, implemented in PROC MIXED, was used to account for the nesting of participants within dyads (Kenny et al., 2006). All multilevel models were fitted with restricted maximum likelihood estimation, and we used Satterthwaite's approximation for degrees of freedom (which can yield fractional values) for calculating p-values. Repeated measures analyses (i.e., those investigating pre- and post-interaction affect) were conducted following the guidelines outlined in West (2013). We screened for the presence of outliers using boxplots (please see *Supplementary material* for graphs). For transparency, we report the results both with and without outliers.

In addition to models including condition as the sole predictor, we also fit a series of models with drug condition (placebo vs. naltrexone) and relevant covariate trait differences (see below) as predictors for each outcome variable. Covariates were retained if they predicted the outcome. Then, for all of our nested dependent measures, we examined whether the effect of naltrexone was moderated by the effects of gender and dyad-level gender composition using the Actor-Partner Interdependence Model (West et al., 2008) approach. This approach allows us to estimate each of the three possible gender effects – actor gender, partner gender, and the interaction between the two (which represents the dyad-level gender composition) – while controlling for the effects of the other two. For non-nested outcomes (i.e., social reward and threat expectations) we just looked at respondent gender. As the effect of naltrexone was not moderated by any of the gender variables, these analyses will not be discussed further but can be viewed at https://osf.io/4a382.

Reliabilities of all outcome measures are included in Table S1 in the *Supplementary material*.

3. Results

3.1. Preliminary analyses

3.1.1. Participant characteristics

The placebo and naltrexone groups did not differ on any demographic variables (Table S2) and the distribution of gender pairings was approximately equal across conditions (Table S3). However, the placebo group was significantly lower in agreeableness, $t(157) = -2.44$, $p = .016$, and marginally higher in neuroticism, $t(157) = 1.90$, $p = .059$. There were no group differences on any other trait variables (Table S2). As agreeableness and neuroticism have previously been found to be strongly related to our outcome measures (Cuperman and Ickes, 2009; Depue and Morrone-Strupinsky, 2005), these variables were included as covariates if they significantly predicted the dependent variable (nb: controlling for covariates is considered to be appropriate when it is evident that group differences on the covariate arose by chance, as is the case in the current study; Miller and Chapman, 2001).

3.1.2. Factor analysis of closeness measures

As we had included several measures assessing feelings of social reward and connection (Social Reward Experience, Inclusion of Other in Self – Felt Closeness, Connectedness, Liking, Partner Responsiveness, Subjective Closeness Index), we conducted an exploratory factor analysis to see if these measures could be reduced to a single factor separate from more behavioral measures of closeness (i.e., self-disclosure). We used iterated principal axis model fitting with promax rotation. A scree plot and a parallel analysis both indicated the presence of two factors. The rotated factor loadings showed a clear pattern, with self-disclosure and perceptions of partner self-disclosure loading on one factor (loadings were .83 and .90, respectively) without any cross-loading on the second factor (both loadings < .10). Scores on the Social Reward Experience, Inclusion of Other in Self – Felt Closeness, Connectedness, Liking, Partner Responsiveness, Subjective Closeness Index scales loaded on the second factor (loadings ranged between .63 and .97) without cross-loading on the first factor (all loadings < .22). Thus, we combined the closeness scales into a single composite by averaging together standardized scores for each measure. Treating this composite as a single scale with six subparts yielded a Cronbach's α value of .92. We also averaged the disclosure scores to create a single composite of disclosure ($\alpha = .88$). Descriptive statistics and correlations for these two composite scales and other dependent variables are reported in Table S4 in the *Supplementary material*.

Table 1
Estimation of naltrexone effects on evaluations of the dyadic interaction (full models).

Dependent variable	Parameter	Estimate	SE	95 % Confidence interval	*t*	df	*p*
Social reward expectations							
	Intercept	3.31	0.06	[3.19, 3.44]	54.09	156	< .001
	Agreeableness	0.24	0.07	[0.09, 0.38]	3.30	156	.001
	Condition	−0.20	0.09	[-0.38, -0.02]	−2.20	156	.029
Social threat expectations							
	Intercept	2.55	0.09	[2.37, 2.73]	28.09	156	< .001
	Neuroticism	0.38	0.08	[0.23, 0.53]	4.89	156	< .001
	Condition	−0.07	0.13	[-0.33, 0.20]	−0.50	156	.621
Self-disclosure (composite)							
	Intercept	3.08	0.08	[2.93, 3.24]	39.21	76.80	< .001
	Condition	−0.27	0.11	[-0.50, -0.04]	−2.38	77.30	.020
Feelings of closeness (composite)							
	Intercept	0.12	0.11	[-0.09, 0.33]	1.14	78.10	.259
	Agreeableness	0.41	0.09	[0.22, 0.59]	4.33	127.00	< .001
	Condition	−0.25	0.16	[-0.56, 0.06]	−1.60	79.80	.113
Desired closeness							
	Intercept	4.10	0.19	[3.72, 4.47]	21.90	78	< .001
	Agreeableness	0.64	0.19	[0.26, 1.02]	3.33	144.00	.001
	Condition	−0.62	0.27	[-1.17, -0.08]	−2.28	80.00	.025
Social threat perceptions							
	Intercept	2.52	0.06	[2.40, 2.65]	40.14	78.3	< .001
	Neuroticism	0.17	0.05	[0.06, 0.27]	3.07	156.0	.003
	Condition	0.01	0.09	[-0.17, 0.20]	0.13	79.6	.895

Table 2
Estimation of naltrexone effects on evaluations of the dyadic interaction without covariates.

Dependent variable	Parameter	Estimate	SE	95 % Confidence interval	*t*	df	*p*
Social reward expectations							
	Intercept	3.29	0.06	[3.16, 3.41]	52.50	157	< .001
	Condition	−0.14	0.09	[-0.32, 0.04]	−1.55	157	.123
Social threat expectations							
	Intercept	2.59	0.10	[2.40, 2.79]	26.86	157	< .001
	Condition	−0.16	0.14	[-0.44, 0.11]	−1.16	157	.248
Self-disclosure (composite)							
	Intercept	3.08	0.08	[2.93, 3.24]	39.21	76.80	< .001
	Condition	−0.27	0.11	[-0.50, -0.04]	−2.38	77.30	.020
Feelings of closeness (composite)							
	Intercept	0.07	0.11	[-0.14, 0.29]	0.69	76.90	.495
	Condition	−0.15	0.16	[-0.46, 0.16]	−0.96	77.40	.340
Desired closeness							
	Intercept	4.02	0.19	[3.65, 4.40]	21.29	76.70	< .001
	Condition	−0.47	0.28	[-1.02, 0.08]	−1.71	77.20	.091
Social threat perceptions							
	Intercept	2.54	0.06	[2.42, 2.67]	39.44	77.70	< .001
	Condition	−0.03	0.09	[-0.22, 0.16]	−0.33	78.30	.746

3.2. Social reward expectations

Agreeableness emerged as a significant predictor of social reward expectations in the initial model including potential covariates (i.e., agreeableness and neuroticism), $b = 0.23$, 95 % CI [0.08, 0.37], $t(155) = 3.08$, $p = .002$, and was therefore retained as a covariate. Controlling for agreeableness, social reward expectations were lower in the naltrexone group (adjusted $M = 3.12$) relative to the placebo (adjusted $M = 3.31$) group, $b = -0.20$, 95 % CI [-0.38, -0.02], $t(156) = -2.20$, $p = .029$, $d = -0.35$ (Table 1). However, this finding did not hold if condition guess was included in the model as an additional predictor, $b = -0.14$, 95 % CI [-0.33, 0.03], $t(153) = -1.58$, $p = .117$ or if agreeableness was removed as a covariate, $b = -0.14$, 95 % CI [-0.32, 0.04], $t(157) = -1.55$, $p = .123$, $d = -0.25$ (Table 2).[7]

3.3. Social threat expectations

Neuroticism emerged as a significant predictor of social threat expectations, $b = 0.36$, 95 % CI [0.20, 0.52], $t(155) = 4.50$, $p < .001$, was therefore included as a covariate. Controlling for neuroticism, there was no significant effect of naltrexone on social threat expectations ($M_{naltrexone} = 2.48$, $M_{placebo} = 2.54$), $b = -0.07$, 95 % CI [-0.33, 0.20], $t(156) = -0.50$, $p = .621$, $d = 0.08$ (Table 1).[8] Similarly, there was no effect of naltrexone on social threat expectations when neuroticism was removed as a covariate, $b = -0.16$, 95 % CI [-0.44, 0.11], $t(157) = -1.16$, $p = .248$, $d = -0.18$ (Table 2).

3.4. Self-disclosure

Participants in the naltrexone condition reported that their social

[7] Omitting outliers, the results of these analyses were as follows: a) model with condition only, $b = -0.15$, $t(152) = -1.88$, $p = .062$, b) model with condition and agreeableness, $b = -0.22$, $t(151) = -2.70$, $p = .008$, c) model with condition, agreeableness, and condition guess, $b = -0.19$, $t(148) = -2.28$, $p = .024$.

[8] Omitting outliers, the results of these analyses were as follows: a) model with condition only, $b = -0.08$, $t(154) = -0.62$, $p = .534$, b) model with condition and neuroticism, $b = -0.01$, $t(153) = -0.10$, $p = .918$.

interactions involved less intimate self-disclosure (as assessed with the self-disclosure composite; M = 2.81) compared to placebo participants (M = 3.08), b = -0.27, 95 % CI [-0.50, -0.04], $t(77.3)$ = -2.38, p = .020, d = -0.40 (Table 1).[9]

3.5. Feelings of closeness

Condition did not significantly predict scores on the closeness composite ($M_{placebo}$ = 0.07, $M_{naltrexone}$ = -0.08), b = -0.15, 95 % CI [-0.46, 0.16], $t(77.4)$ = -0.96, p = .340, d = 0.18 (Table 2). Agreeableness predicted feelings of closeness, b = 0.41, 95 % CI [0.22, 0.60], $t(122)$ = 4.22, p < .001 and was therefore included as a covariate. Controlling for agreeableness, naltrexone participants did not report statistically lower feelings of closeness toward their partner compared to participants receiving placebo, although the pattern of mean differences lay in the predicted direction ($M_{placebo}$ = 0.12, $M_{naltrexone}$ = -0.13), b = -0.25, 95 % CI [-0.56, 0.06], $t(79.8)$ = -1.60, p = .113, d = -0.30 (Table 1).[10]

3.6. Desired closeness

Participants in the naltrexone condition reported desiring somewhat less closeness (M = 3.55) with their partner relative to placebo participants (M = 4.02), but this difference did not reach statistical significance, b = -0.47, 95 % CI [-1.02, 0.08], $t(77.2)$ = -1.71, p = .091, d = -0.30 (Table 2). Agreeableness significantly predicted desired closeness in the initial covariate model, b = 0.66, 95 % CI [0.27, 1.05], $t(138)$ = 3.34, p = .001 and was therefore retained as a covariate. Controlling for agreeableness, participants in the placebo condition reported wanting to be closer to their partner relative to individuals receiving naltrexone ($M_{placebo}$ = 4.10, $M_{naltrexone}$ = 3.47), b = -0.62, 95 % CI [-1.17, -0.08], $t(80)$ = -2.28, p = .025, d = -0.40 (Table 1).

3.7. Social threat experience

There was no significant effect of naltrexone on social threat experience ($M_{naltrexone}$ = 2.54, $M_{placebo}$ = 2.51), b = -0.03, 95 % CI [-0.22, 0.16], $t(78.3)$ = -0.33, p = .746, d = -0.05 (Table 2). Neuroticism significantly predicted social threat in the full covariate model, b = 0.14, 95 % CI [0.03, 0.25], $t(155)$ = 2.49, p = .014; thus, we re-ran the analysis controlling for neuroticism. However, controlling for neuroticism did not alter the results for naltrexone, ($M_{placebo}$ = 2.52, $M_{naltrexone}$ = 2.54), b = 0.01, 95 % CI [-0.17, 0.20], $t(79.6)$ = 0.13, p = .894, d = 0.02 (Table 1).[11]

3.8. Affect

The repeated measures analysis of positive affect, revealed a significant time by condition interaction, b = -0.26, 95 % CI [-0.50, -0.01], $t(76)$ = -2.09, p = .040. Least square mean comparisons showed that there was no significant change in positive affect for naltrexone-treated participants between Time 1 (M = 2.73) and Time 2 (M = 2.85), M difference = 0.13, 95 % CI [-0.05, 0.30], $t(77)$ = 1.42, p = .161, while participants receiving placebo exhibited a significant increase in positive affect from Time 1 (M = 2.74) to Time 2 (M = 3.13), M difference = 0.38, 95 % CI [0.21, 0.55], $t(75)$ = 4.55, p < .001. Further, the placebo group reported marginally higher levels of positive affect at Time 2 relative to the naltrexone group, M difference = -0.27, 95 % CI [-0.56, 0.01], $t(84)$ = -1.91, p = 0.059. There was no difference between the two groups at baseline, M difference = -0.02, 95 % CI [-0.28, 0.23], $t(157)$ = 0.15, p = .885 (Table 3).

Neuroticism was a significant predictor of positive affect, b = -0.22, 95 % CI [-0.36, -0.07], $t(155)$ = -2.94, p = .004; thus we conducted a second analysis controlling for neuroticism. The results of this analysis were virtually identical, except that the difference in positive affect reported by the placebo and naltrexone groups at Time 2 was significant, M difference = -0.33, 95 % CI [-0.62, -0.04], $t(84)$ = 2.30, p = 0.024 (Fig. 1a, Table 4).[12]

Similar to the pattern of results for positive affect, there was a significant time by condition interaction in the model predicting negative affect, b = 0.19, 95 % CI [0.03, 0.36], $t(86.1)$ = 2.32, p = .023 (Table 3). Participants in the placebo group decreased in negative affect from Time 1 (M = 1.56) to Time 2 (M = 1.35), M difference = -0.21, 95 % CI [-0.32, -0.10], $t(85)$ = -3.69, p < .001, while naltrexone-treated participants did not show a significant change in negative affect from Time 1 (M = 1.39) to Time 2 (M = 1.37), M difference = -0.02, 95 % CI [-0.14, 0.10], $t(87)$ = -0.29, p = .770. However, negative affect was not significantly higher in the naltrexone group relative to the placebo group at Time 2, M difference = 0.02, 95 % CI [-0.13, 0.17], $t(81.9)$ = 0.26, p = .797. There was a marginal difference in negative affect between the two groups at baseline (with the placebo group reporting more negative affect), M difference = -0.17, 95 % CI [-0.35, 0.004], $t(157)$ = -1.93, p = .055.

Neuroticism was a significant predictor of negative affect, b = 0.18, 95 % CI [0.10, 0.27], $t(155)$ = 4.34, p < .001. Controlling for neuroticism, there was again a significant time by condition interaction, b = 0.19, 95 % CI [0.03, 0.36], $t(87.1)$ = 2.33, p = .022. Participants in the placebo group decreased in negative affect from Time 1 (M = 1.54) to Time 2 (M = 1.33), M difference = -0.21, 95 % CI [-0.32, -0.10], $t(86)$ = -3.74, p < .001, while naltrexone-treated participants did not show a significant change in levels of negative affect from Time 1 (M = 1.42) to Time 2 (M = 1.40), M difference = -0.02, 95 % CI [-0.14, 0.10], $t(88.1)$ = -0.32, p = .750. Negative affect was not significantly higher in the naltrexone group relative to the placebo group at Time 2, M difference = 0.07, 95 % CI [-0.08, 0.22], $t(82.4)$ = 0.89, p = .379. There was no baseline difference in negative affect between the two groups, M difference = -0.12, 95 % CI [-0.29, 0.04], $t(153)$ = -1.50, p = .136 (Fig. 1b, Table 4).[13]

4. Discussion

We found partial support for our hypothesis that opioid receptor blockade would inhibit the processes related to social bonding during an ecologically valid laboratory paradigm designed to create initial interpersonal closeness. Thus, while prior research has shown that opioids mediate feelings of closeness in established close relationships (Inagaki et al., 2019, 2016), this is the first study to provide evidence that opioidergic activity may underlie the *emergence* of social bonds in humans, paralleling findings in the non-human animal research domain (Burkett et al., 2011). Further, this is the first time that the effects of manipulating the opioid system have been examined in the context of naturalistic, face-to-face, real-time social interactions. Specifically, we found that, relative to the placebo group, participants who received naltrexone reported that their interaction involved less self-disclosure.

[9] Omitting outliers, the effect was b = -0.29, $t(77)$ = -2.70, p = .008.

[10] Omitting outliers, the results of these analyses were as follows: a) model with condition only, b = -0.23, $t(77.4)$ = -1.56, p = .122, b) model with condition and agreeableness, b = -0.30, $t(79.5)$ = -2.07, p = .042.

[11] Omitting outliers, the results of these analyses were as follows: a) model with condition only, b = -0.02, $t(76.4)$ = -0.22, p = .824, b) model with condition and neuroticism, b = 0.02, $t(78.5)$ = 0.31, p = .758.

[12] Removing outliers, the interaction terms were: a) model with condition only, b = -0.27, $t(76.9)$ = -2.81, p = .006, b) model with condition and neuroticism, b = -0.27, $t(76.5)$ = -2.82, p = .006.

[13] There were a lot of outliers (N = 16) in this analysis, as most participants showed very little change in negative affect. After these outliers were removed, there was no significant time by condition interaction, b = 0.05, $t(72.7)$ = 0.98, p = .330.

Table 3
Results of repeated measures models predicting positive and negative affect without covariates.

	Model predicting positive affect					Model predicting negative affect				
Predictor	*b*	SE	95 % Confidence interval	*t*(df)	*p*	*b*	SE	95 % Confidence interval	*t*(df)	*p*
Intercept	2.74	0.09	[2.57, 2.92]	30.65(157)	< .001	1.57	0.06	[1.44, 1.69]	25.26(157)	< .001
Time	0.38	0.08	[0.22, 0.55]	4.55(75)	< .001	−0.21	0.06	[-0.33, -0.10]	−3.69(85)	< .001
Condition	−0.02	0.13	[-0.28, 0.24]	−0.15(157)	.885	−0.17	0.09	[-0.35, 0.004]	−1.93(157)	.055
Time x Condition	**−0.26**	**0.12**	**[-0.50, -0.01]**	**−2.09(76)**	**.040**	**0.19**	**0.08**	**[0.03, 0.36]**	**2.32(86.1)**	**.023**

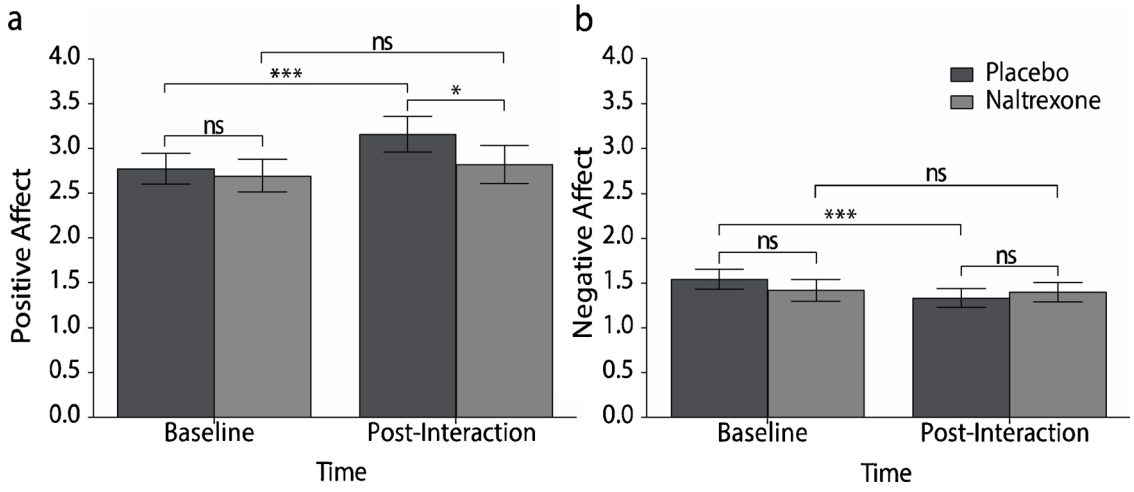

Fig. 1. Results of repeated measures dyadic analyses showing changes in positive (a) and negative (b) affect from baseline to post-interaction in the placebo and naltrexone groups (controlling for neuroticism). Error bars represent 95 % confidence intervals. *N* (dyads) = 80. ns = non-significant; * = significant ($p < .05$); *** = significant ($p < 0.001$).

Table 4
Results of full repeated measures models predicting positive and negative affect.

	Model predicting positive affect					Model predicting negative affect				
Predictor	*b*	SE	95 % Confidence interval	*t*(df)	*p*	*b*	SE	95 % Confidence interval	*t*(df)	*p*
Intercept	2.77	0.09	[2.60, 2.95]	31.96(156)	< .001	1.54	0.06	[1.43, 1.65]	27.08(152)	< .001
Neuroticism	−0.24	0.07	[-0.38, -0.10]	−3.36(156)	.001	0.19	0.04	[0.11, 0.28]	4.74(157)	< .001
Time	0.38	0.08	[0.22, 0.55]	4.54(74.5)	< .001	−0.21	0.06	[-0.32, -0.10]	−3.74(86)	< .001
Condition	−0.08	0.13	[-0.33, 0.17]	−0.63(156)	.533	−0.12	0.08	[-0.29, 0.04]	−1.50(153)	.136
Time x Condition	**−0.26**	**0.12**	**[-0.50, -0.01]**	**−2.08(75.6)**	**.041**	**0.19**	**0.08**	**[0.03, 0.36]**	**2.33(87.1)**	**.022**

The sharing of personal feelings and experiences lies at the very crux of emerging intimacy; it both fosters and communicates the discloser's liking for the recipient of the disclosure, engenders resonant feelings of liking in the partner, tests and expands the boundaries of trust, and shapes decisions about how the relationship should progress (Laurenceau et al., 1998). Interestingly, our observation that naltrexone inhibited self-disclosure also dovetails with earlier behavioral and neuroimaging work suggesting that self-disclosure is an intrinsic reward comparable with primary rewards such as food and sex (Tamir and Mitchell, 2012). Thus, our study advances a potential neurochemical substrate that may underlie the pleasure of self-disclosure. Consistent with our finding that naltrexone inhibited affiliative behavior, we also found that, compared to participants given placebo, naltrexone participants held lower social reward expectations before the interaction (e.g., expectations that they would like their partner and develop a meaningful connection with them) and reported desiring less interpersonal closeness with their partner after the interaction.

Our findings showing lower affiliative behavior and desire for interpersonal closeness in the naltrexone condition are consistent with one of the predictions made by the State-Dependent μ-Opioid Modulation of Social Motivation model (Loseth et al., 2014), which attempts to reconcile conflicting findings in the non-human animal literature showing that opioid receptor antagonism can lead both to *increases* and *decreases* in socially-motivated behavior (e.g., Fabre-Nys et al., 1982; Trezza et al., 2011) depending on the prevailing socio-emotional context. This model predicts that decreased opioid activity will inhibit social motivation in a positive emotional context, when affiliation motives revolve around the pursuit of pleasure, reward, and exploration (including formation of new social bonds), but increase seeking of safe social contact during distress, when affiliation motives revolve around pursuit of safety and comfort. Notably, as few previous studies on opioids have examined socially-motivated behavior in humans, these hypotheses have remained largely untested. Although this study was not intended to provide a test of the full model, our findings provide support for the prediction that opioid blockade should diminish social motivation during a positive emotional state.

There was no significant effect of naltrexone on feelings of closeness in the current study, although the effect was in the predicted direction and had an effect size comparable to the effect sizes for the other dependent variables. Significantly, however, placebo, but not naltrexone, participants exhibited increases in positive affect after the bonding task, suggesting that naltrexone participants may not have found the

interaction as enjoyable. Importantly, prior work shows that high levels of positive emotion experienced at the onset of a relationship predict the subsequent development of closeness later on in the relationship, as well as more complex understanding of the partner (Waugh and Fredrickson, 2006). Thus, based on the current data, it is possible that opioids may play a part in this process as relationships unfold; this may be a fruitful avenue for further research.

Naltrexone did not appear to have any effect on perceptions of social threat, either prior to or following the social interaction (and, in contrast to the closeness finding, the effect sizes for these variables were negligible). This finding was unexpected, as μ-opioids are known to have anxiolytic and pain-relieving effects (Colasanti et al., 2011; Fields, 2007); thus, prior research has linked variation in the μ-opioid receptor gene with sensitivity to rejection or hurtful interpersonal behavior (Tchalova et al., 2019; Way et al., 2009). Importantly, however, the closeness-building task used in the current study was designed to bolster feelings of acceptance and minimize threat (Aron et al., 1997); consequently, it is possible that effects of opioids on threat-inhibition may not be detectable at such low levels of threat. Nonetheless, we hope this study will encourage future work in the field to examine opioidergic regulation of social reward and social threat simultaneously across a variety of social contexts. If this finding proves to be replicable, it would suggest that, in social situations dominated by the presence of social reward, μ-opioids may exert their primary influence on affiliative behavior via reward-enhancing pathways, without engaging threat-inhibiting pathways. This contrasts with earlier theoretical perspectives arguing that inhibitions in social play under opioid antagonism may be due to increases in feelings of vulnerability (e.g., Panksepp et al., 1985). An alternative explanation, however, is that the lack of an increase in social threat perceptions may be attributable to the potential anxiolytic κ-opioid receptor antagonist effects of naltrexone. Although naltrexone has the highest affinity for μ-opioid receptors, it may also bind to κ-opioid receptors (Raynor et al., 1994), which are thought to be involved in processing social threat and aversion (Resendez and Aragona, 2013). Indeed, earlier research has shown that naltrexone selectively slows identification of sadness and fear (but not, however, anger) facial expressions—an effect that is more consistent with κ-, rather than μ-, opioid receptor blockade (Wardle et al., 2016). Future research on this topic may benefit from strategic combination of pharmacological agents targeting opioid receptors and/or neuroimaging methods in order to delineate the relative contributions of μ- and κ-opioid receptors.

This study has several limitations. Due to logistical constraints, we were unable to recruit as many participants as planned, thus reducing statistical power. This may help explain why the effect of naltrexone on feelings of social closeness, although lying in the direction consistent with our prediction and the overall pattern of findings, was not statistically significant (especially considering the trade-off between increased ecological validity and increased noise inherent in naturalistic designs). As a related issue, even though the naltrexone dose used in the current study has been shown to effectively saturate brain μ-opioid receptors (Lee et al., 1988), it is also possible that administration of naltrexone over several consecutive days (e.g., Inagaki et al., 2016) may yield stronger effects.

Relatedly, we made the decision to place both dyad members in the same treatment condition for the purpose of maximizing power; however, a limitation of this approach is that it is not possible to determine from the current data whether naltrexone differentially affected sending and receiving of disclosures. Further, we did not video record the participant interactions, which would have provided more objective ratings of self-disclosure. Future research could also incorporate other measures of closeness, such as nonverbal communication and behavioral or psychophysiological synchrony.

Although participants were instructed to notify the experimenter if they felt unwell and were queried about feelings they experienced during the study at the debriefing interview, we did not obtain a quantitative measure of physical symptoms, and thus were unable to control for this variable in our analyses. Such analysis is important for ruling out the possibility that physical symptoms are contributing to decreases in affiliation. However, we think it is unlikely that the psychosocial effects observed in this study were driven by naltrexone participants feeling unwell, as a) only one participant reported feeling ill, b) participants receiving naltrexone were not able to guess which substance they had received above chance levels, and c) there was no difference in levels of negative affect between the placebo and naltrexone groups, nor was there an increase in negative affect following drug administration in the naltrexone group. Further, it is not clear why physical side effects, if present, would influence measures related to affiliation and positive affect but not social threat. Finally, prior research involving naltrexone administration in healthy participants has typically found either no differences between naltrexone and placebo groups in symptom levels (Mallik et al., 2017; Murray et al., 2014; Yeomans and Gray, 1997) and feelings of well-being (Chelnokova et al., 2016), or very low levels of symptoms that do not impact the socio-affective measures being assessed (Inagaki et al., 2019; Wardle et al., 2016).

We should further acknowledge some of the noise and issues present in our data. First, when examining the effectiveness of the blind, we saw unexpectedly that while naltrexone participants seemed to be guessing their condition at random, placebo participants were somewhat more likely to guess that they were in the placebo condition. One speculation is that because placebo participants on average appeared to have a more enjoyable experience, to the extent that drug side effects are typically thought of as negative, the positive experience would have seemed incongruent with drug side effects that participants were cautioned about during the informed consent process. Further research will be needed to establish whether this finding occurred by chance or whether it is a structural feature of naltrexone research. Importantly, however, none of our participants were able to accurately guess the study hypotheses during debriefing, which speaks against the possibility that participants were conforming to our expectations. Furthermore, inclusion of condition guess as a variable in the analyses did not significantly influence any of the findings other than reward expectations. Second, there were some differences between the experimental groups in the prevalence of personality traits relevant to the task; specifically, the placebo group was higher in neuroticism and lower in agreeableness relative to the naltrexone group. Thus, the personality differences may have obscured some of the effects of the drug. Finally, there were a number of outliers in many of the analyses that also seemed to obscure some of the drug effects. As we previously mentioned, while the naturalistic design employed in this study is one of its major strengths, such designs involve a lot of noise. Future research may also benefit from assessment of other variables that may help explain some of the heterogeneity in responses to naltrexone, such as variation at the μ-opioid receptor gene.

This work holds significance for several lines of further inquiry. Greater understanding of opioid involvement in affiliative behavior and affect may yield insight into psychiatric conditions marked by social anhedonia, withdrawal, and other deficits in interpersonal functioning (Trezza et al., 2011). The current research also has timely implications for clinical applications of opioid receptor antagonists like naltrexone. In recent years, researchers and physicians have shown growing interest in using naltrexone for the treatment of substance dependence (Sudakin, 2016); however, the psychosocial effects of naltrexone have received little research attention and are consequently poorly understood. The current study's focus on naltrexone effects at the relationship initiation stage may be particularly significant in this context, as the formation of new friendships is a critical factor in recovery from addiction – especially as previous friendship networks frequently become strained or eroded over the course of addiction and the recovery process (Laudet et al., 2004). Furthermore, the ability to forge a strong therapeutic alliance with a clinician is also a strong predictor of drug

treatment outcomes (Meier et al., 2005). Thus, this current research showing that naltrexone may impede the development of new intimate relationships suggests that future clinical work on this topic may be warranted.

The idea that social attachment resembles opiate addiction is a longstanding literary and cultural trope (Panksepp, 1998); a newly emerging body of evidence suggests that there may be substance to this metaphor by showing that endogenous opioids indeed contribute to feelings of social connection in humans. Building on this literature, we found that opioid receptor blockade diminished self-disclosure, desire for interpersonal closeness, social reward expectations, and positive affect during an initial, face-to-face dyadic encounter designed to foster intimacy, thus suggesting that opioids may play an important role in the development of the social relationships that are so necessary for humans to thrive.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Kristina Tchalova: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Geoff MacDonald:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision.

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Appendix A. Supplementary data

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