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Endogenous mu-opioid modulation of social connection in humans: a systematic review and meta-analysis

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Social bonding, essential for health and survival in all social species, depends on mu-opioid signalling in non-human mammals. A growing neuroimaging and psychopharmacology literature also implicates mu-opioids in human social connectedness. To determine the role of mu-opioids for social connectedness in healthy humans, we conducted a preregistered (https://osf.io/x5wmq) multilevel random-effects meta-analysis of randomised double-blind placebo-controlled opioid antagonist studies. We included data from 8 publications and 2 unpublished projects, totalling 17 outcomes (N = 455) sourced from a final literature search in Web of Science, Scopus, PubMed and EMBASE on October 12, 2023, and through community contributions. All studies used naltrexone (25–100 mg) to block the mu-opioid system and measured social connectedness by self-report. Opioid antagonism slightly reduced feelings of social connectedness (Hedges' g [95% CI) = −0.20] [−0.32, −0.07]. Results were highly consistent within and between studies ($I^2 = 23\%$). However, there was some indication of bias in favour of larger effects among smaller studies (Egger's test: $B = -2.16$, $SE = 0.93$, $z = -2.33$, $p = 0.02$), and publication bias analysis indicated that the effect of naltrexone might be overestimated. The results clearly demonstrate that intact mu-opioid signalling is not essential for experiencing social connectedness, as robust feelings of connectedness are evident even during full pharmacological mu-opioid blockade. Nevertheless, antagonism reduced measures of social connection, consistent with a modulatory role of mu-opioids for human social connectedness. The modest effect size relative to findings in non-human animals, could be related to differences in measurement (subjective human responses versus behavioural/motivation indices in animals), species specific neural mechanisms, or naltrexone effects on other opioid receptor subtypes. In sum, these results help explain how mu-opioid dysregulation and social disconnection can contribute to disability, and conversely—how social connection can buffer risk of ill health.

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INTRODUCTION

Affiliative behaviours are life-sustaining in social animals across taxa [1]. In humans, social relationships are key to physical and mental health [2] and quality of life [3]. While loneliness increases the risk of both mental and physical health problems, strong relationships build resilience and reduce mortality [4].

To promote resilience, we must uncover the neurobiological mechanisms linking social relationships to health and wellbeing. Non-human animal findings indicate that affiliative behaviours are supported by much the same neurochemical processes that drive motivation for and pleasure from food consumption and mating [5]. Similarly, neural responses to social rejection and isolation have been associated with pain and threat-responsive systems [6–8]. While several neurochemical systems, notably dopamine and oxytocin, can promote affiliation, the experience of affiliative reward has so far primarily been linked to mu-opioid receptor signalling [9, 10].

According to the influential Brain Opioid Theory of Social Attachment, endogenous mu-opioid signalling promotes social bonds by mediating feelings of pleasure and security in presence of others [11]. Conversely, social isolation is theorised to reduce opioid receptor activation and induce withdrawal-like feelings of despair [11]. Decades of research in non-human mammals support this notion [10]. For instance, mu-opioids are necessary for mouse pups to form a normal preference for their mother over a stranger [12] and for prairie voles to form a partner pair-bond [13]. Across species, mu-opioid modulation is observed in a state-dependent pattern that suggests involvement in regulation of both negative and positive social feelings [14].

A growing body of literature implicates opioids in social processes relevant for feeling socially connected [15–17]. PET studies using mu-opioid selective ligands have shown differences in receptor binding related to feeling accepted or rejected by others [16, 18] and linked attachment styles to mu-opioid receptor availability at rest [19]. A hypothesis derived from the Brain Opioid Theory of Social Attachment is that blocking opioid receptors would reduce feelings of connection in humans. Several human studies have used opioid antagonists such as naltrexone to test this hypothesis. For instance, Inagaki et al. [20] found increased diary ratings of feeling disconnected from others after naltrexone compared to placebo. Tchalova and MacDonald [21] reported that while feelings of social closeness was not significantly reduced in participants pre-treated with naltrexone, they disclosed less in a self-disclosure task designed to facilitate bonding between strangers and the mood improvement

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evident in the placebo group following this task was absent in the naltrexone group.

The endogenous mu-opioid system is reported to be disrupted in a range of mental and physical health conditions, notably chronic pain with [22] and without chronic opioid treatment [23–26], alcohol [27–29] and substance use disorder [30–32], behavioural addictions [33, 34], schizophrenia [35] and Parkinson's dyskinesia [36, 37]. Disruptions in endogenous mu-opioid signalling could disturb behaviours important for forming and maintaining social connection and thereby contribute to disability in these populations.

To determine how important endogenous mu-opioids are for experiences of social connection in humans, we conducted a systematic review of randomised double-blind placebo-controlled studies and used meta-analysis to estimate the effect of pharmacological mu-opioid receptor blockade on social connection and accompanying ratings of mood in healthy humans.

METHODS

This systematic review and meta-analysis was preregistered on the Open Science Framework (https://osf.io/x5wmq, [37]) and follows the PRISMA 2020 guidelines for reporting systematic reviews [38]. Data and code are available on the Open Science Framework (https://osf.io/5f6ej). Deviations from the preregistration include (1) recording whether the included studies were preregistered, (2) visualising individual study quality with traffic light and risk of bias summary plots, (3) determining the achieved mu-opioid receptor blockade in the included studies, (4) conducting power analysis of the included studies, (5) using aggregated outcomes within studies for the trim-and-fill analysis, (6) using the GRADE approach to assess overall certainty in evidence [39], and (7) conducting a reviewer-suggested meta-regression to assess whether the effect of naltrexone on social connectedness depends on relationship type.

Eligibility criteria

Original studies were eligible if they surveyed generally healthy humans who were not described as patients and had collected any measure of social bonding or connectedness, including self-report and behavioural observations, after drug administration. A centrally active mu-opioid antagonist (e.g., naltrexone or naloxone) and an inert substance (i.e., placebo) had to be administered to two separate groups or on two separate occasions. Treatment allocation or order had to be described as randomised, and the drug administration had to be described as double-blind. No other drugs could be administered before or together with the study drug (antagonist/placebo), or between the administration of the study drug and the following outcome assessment.

Information sources

We searched the databases Web of Science, Scopus, PubMed, and EMBASE (via Ovid) to ensure high coverage of relevant literature [40]. All searches were conducted between February 21, 2022 and October 12, 2023.

Search strategy

Exact search strings are available in the supplement. The searches used a combination of the following terms, including synonyms and related terms, and subject headings when applicable: (1) Centrally active mu-opioid antagonist, (2) placebo, and (3) social bonding/connectedness. Records tagged as review articles were excluded from each search. No other restrictions were imposed on the literature searches.

Selection process

We used Mendeley Desktop [41] to automatically remove duplicate records and to merge records identified as close duplicates. This method has been shown to yield accurate deduplication [42]. Remaining duplicates were identified and removed manually. Two researchers independently evaluated each identified record against the eligibility criteria (agreement = 100%). Eligibility was primarily determined by screening the title and abstract. When more information was necessary to reach a conclusion, the author accessed and screened the full text, including associated supplementary information and pre-registrations.

Data collection process

One author (MT) extracted data manually from the full-texts, supplementary materials, and preregistrations. When necessary, we used WebPlotDigitizer [43] to extract data from figures as this tool is reliable and easy to use and produces valid data [44–46]. We contacted authors to obtain both data missing from published records and unpublished data.

Data items

We extracted the following data from the included records:

1. Record information, including author names, publication year, record title, and journal name.
2. Drug administration information, including design (between-subjects, within-subjects), mu-opioid antagonist name and dose, and administration route, and intersession interval when applicable.
3. Context information, including the context (task/activity/event/stimuli) in which the outcome was assessed, the time between drug administration and engagement in this context, and what type of relationships (e.g., new or established) the participants were likely considering when providing outcome ratings.
4. Outcome assessment information, including the time between drug administration and the outcome assessment, and the measurement type (self-report, behaviour).
5. Outcome information (social bonding/connectedness) and covariate (positive mood, and negative mood) per drug condition (antagonist, placebo), including the number of participants, mean and standard deviation, outcome interpretation, and whether the outcome was baseline corrected. For within-subjects design, we extracted the correlation between outcome scores and covariates in the antagonist and placebo condition, or converted it from *t*- or *F*-values [47]. When means and/or standard deviations were missing, we extracted Cohen's *d* for the difference between the drug conditions.
6. Sample characteristics, including the total number of participants, the number and percentage of male and female participants, and the mean and standard deviation for age.

Effect size measures

Effect sizes were calculated as the standardised mean difference in outcome scores (social bonding/connectedness) and covariates (positive mood, and negative mood) between the antagonist and the placebo condition. Specifically, we used the formulas for Hedges' *g* in Borenstein et al. [48]. Calculation of Hedges' *g* is similar to that of Cohen's *d* but includes the application of a multiplicative correction factor that reduces overestimation of the standardised mean difference when the sample size is small. Hedges' *g* was computed so that negative values indicated lower social bonding/connectedness, positive mood, and negative mood in the antagonist condition than in the placebo condition. Conversely, positive values indicated higher social bonding/connectedness, positive mood, and negative mood in the antagonist condition than in the placebo condition.

Synthesis methods

Studies for which we could calculate Hedges' *g* for social bonding/connectedness were included in the statistical analyses. Random-effects models were implemented in *R* [49] using the *metafor* package [50]. We specified a three-level model with random intercepts for studies and outcomes nested within studies to

account for statistical dependencies arising from reporting of multiple outcomes per study [51, 52]. In the primary analysis, we simply computed the average Hedges' g for social bonding/connectedness across studies and visualised the results in a forest plot. In secondary analyses, we ran four separate models with Hedges' g for positive mood, negative mood, quality score, and likely relationships as moderators to assess the contribution of these variables to the effect of mu-opioid antagonism on social bonding/connectedness. Studies for which moderator data were unavailable were excluded from these analyses. The results of secondary analyses were visualised in scatter plots. Heterogeneity was assessed by computing the standard deviation between studies (σ_{study}) and between outcomes within studies ($\sigma_{study/outcome}$), by computing I^2 for these two variance components, and by conducting a Cochran's Q test. Results were considered statistically significant whenever $p < 0.05$ or the 95% CI did not include 0.

Study quality assessment

To evaluate the quality of the included studies, we used the Oxford quality scoring system, i.e., the Jadad scale [53]. Although brief, this checklist covers key sources of bias, such as treatment randomisation and blinding procedures, and participant dropout. Quality scores range from 0 to 5, with lower scores indicating lower quality or higher risk of bias.

We also used the *R Shiny* app *plantrexone* and its accompanying recommendations [54] to determine the achieved mu-opioid receptor blockade at the time of outcome assessment in the included studies.

Finally, we calculated the statistical power of each included study to detect the average effect size obtained in the primary analysis assuming $\alpha = 0.05$. The function *mpower* from the package *metapower* [55] was used to estimate the sample size needed per study for the meta-analysis to have 80% power to detect this average effect size at the same alpha level.

Reporting bias assessment

To evaluate the risk of reporting bias, we assessed the relationship between individual outcomes and their precision. First, we visually inspected standard and contour-enhanced funnel plots for asymmetry. Next, we formally tested the relationship between outcome and precision by conducting an Egger's test [56]. Finally, we used the trim-and-fill method to estimate the average Hedges' g for social bonding/connectedness under a symmetrical funnel plot [57]. Because the trim-and-fill method has yet to be generalised to three-level models, we used the *aggregate* function from the *metafor* package [50] to aggregate outcomes within studies before applying this method.

Overall certainty in evidence assessment

We used the GRADE approach to rate the overall certainty in evidence [39].

RESULTS

Study selection

A detailed overview of the study selection process is available in the PRISMA flowchart, Supplementary Fig. 1 (Supplementary Materials). The literature search returned 410 records, and we obtained details of 2 unpublished studies from authors. Of these 412 records, 159 were identified as duplicates. A total of 10 records met the inclusion criteria [20, 21, 58–65]. These records reported 17 outcomes from 8 studies (N = 455, 276 women, 179 men). All relevant outcomes from all studies were included in the primary analysis.

One double-blind, randomised, placebo-controlled study with 25 mg naltrexone appeared to meet inclusion criteria, but was excluded due to the measure of social bonding/connectedness being collected only prior to drug administration [66].

Study characteristics

Characteristics of individual studies are available in Table 1. On average, participants were 22 years old (range 20–43). The gender distribution was uneven in all studies, with the percentage of women ranging from 6% to 100% ($M = 61\%$).

Participants in the included studies rated their feelings of social connectedness during or following a variety of tasks and activities, such as participating in a yoga session, a silent disco session, or a religious ritual; viewing images of close others, reading messages from strangers and close others, having a structured conversation with a stranger, preparing for a stressful event together with a close other, experiencing physical pain together with another participant, holding cold, warm or neutral objects, or simply going about their daily lives.

Social bonding/connectedness was exclusively measured with self-report. Questionnaire items mainly assessed feelings of connection with or disconnection from others, liking of others, commonalities or similarities with others, and inclusion of others in the self, and were rated on Likert scales ranging from either 1–5, 1–7, 1–9, or 0–9.

Positive and negative mood was either measured with the Positive and Negative Affect Schedule [21, 58, 64], Profile of Mood States [65] or custom questionnaires [20, 59].

Results of individual studies

Figure 1 presents the results of individual studies. In total, 12/17 outcomes (71%) showed a negative effect of naltrexone on social connectedness, while the remaining 5/17 (29%) indicated a positive effect. When measured on a 1–7 Likert scale, the reported social connectedness in the included studies was 1.12 points lower to 0.33 points higher after naltrexone than after placebo. Hedges' g ranged from −2.50 to 0.35. See Table 1 for aggregated outcomes within studies.

Results of syntheses

All outcomes ($k_{outcomes} = 17$) from all studies ($k_{studies} = 8$) were included in the primary analysis. This analysis showed that on average, there is a statistically significant negative effect of naltrexone on social connectedness (Fig. 1). The mean effect size was small (Hedges' g [95% CI] = −0.20 [−0.32, −0.07]).

There was significant heterogeneity in the reported outcomes, Q (16) = 28.47, $p = 0.03$. However, the amount of heterogeneity was small ($I^2 = 23\%$) and driven by variance in outcomes within studies ($I^2_{within} = 23\%$, $I^2_{between} = 0\%$). The estimated standard deviation was 0.12 Hedges' g units for outcomes within studies, and 0.00 Hedges' g units between studies.

Across individual outcomes, reductions in social connectedness following treatment with naltrexone tended to be accompanied by reductions in positive mood ($k_{studies} = 6$, $k_{outcomes} = 8$, $B = 1.02$, $SE = 0.52$, $z = 1.97$, $p < 0.05$, see Fig. 2F) and increases in negative mood ($k_{studies} = 5$, $k_{outcomes} = 6$, $B = -3.62$, $SE = 1.55$, $z = -2.33$, $p = 0.02$, see Fig. 2G). However, the relationship with negative mood changes was primarily driven by an outlier ($k_{studies} = 4$, $k_{outcomes} = 5$, $B = 0.75$, $SE = 4.01$, $z = 0.19$, $p = 0.85$).

Quality scores did not significantly predict the reported effect of naltrexone on social connectedness ($k_{studies} = 8$, $k_{outcomes} = 17$, $B = -0.01$, $SE = 0.12$, $z = -0.08$, $p = 0.93$, see Fig. 2E).

The effect of naltrexone on social connectedness was non-significantly higher when participants were likely considering established (e.g., close others) versus new (e.g., strangers) relationships ($k_{studies} = 8$, $k_{outcomes} = 17$, $B = -0.30$, $SE = 0.16$, $z = -1.91$, $p = 0.06$). Exploratory removal of an outlier shifted the statistics slightly ($k_{studies} = 7$, $k_{outcomes} = 16$, $B = -0.33$, $SE = 0.16$, $z = -2.11$, $p = 0.04$).

Table 1. Study characteristics.

Study	Demographics		Treatment		Social connectedness				Mood		Quality (0–5)
	N (W:M)	Mean age (SD)	Design (ISI)	Dose (N)	Context	Relationship type	Effect size	Power	Effect size (positive mood)	Effect size (negative mood)	
Inagaki et al. [20, 59][P]	31 (21:10)	21.55 (3.34)	WS (10 days)	50 mg (31)	Holding warm vs neutral object	Unspecified	−0.34 [−0.58, −0.09]	0.35	−0.13 [−0.41, 0.15]	---	4
					Holding cold vs neutral object	Unspecified					
				Placebo (31)	Reading messages from close others	Established					
					Daily life	Unspecified					
Tarr et al. [64]	76 (57:19)	21.17 (3.60)	BS	100 mg (25)	Silent disco with strangers	New	0.08 [−0.35, 0.51]	0.15	−0.25 [−0.66, 0.15]	0.27 [−0.12, 0.66]	3
				50 mg (28)							
				Placebo (23)							
Inagaki et al. [60, 61] & Ross et al. [62][P]	80 (48:32)	22.39 (3.36)	BS	50 mg (40)	Reading messages from close others	Established	−0.19 [−0.39, 0.02]	0.47	---	---	5
					Reading messages from strangers	New					
					Holding warm object	Unspecified					
				Placebo (40)	Holding cold object	Unspecified					
					Viewing images of close others	Established					
					Daily life	Unspecified					
Charles et al. [58, Study 1][P]	9 (9:0)	25.80 (11.70)	BS	100 mg (4)	Yoga session	New	−2.50 [−4.16, −0.84]	0.06	−0.43 [−1.62, 0.77]	0.82 [−0.41, 2.05]	5
				Placebo (5)							
Charles et al. [58, Study 2][P]	24 (16:8)	42.70 (15.30)	BS	100 mg (11)	Religious ritual	Established	−0.79 [−1.63, 0.05]	0.07	−0.63 [−1.44, 0.18]	0.21 [−0.60, 1.02]	4
				Placebo (13)							
Tchalova & MacDonald [21]	159 (98:61)	19.80 (2.22)	BS	50 mg (75)	Structured conversation with stranger	New	−0.18 [−0.57, 0.22]	0.16	−0.33 [−0.67, −0.02]	0.35 [0.04, 0.66]	4
				Placebo (84)							
Tchalova et al. [17][U]	34 (2:32)	21.10 (3.09)	BS	50 mg (16)	Stress preparation with close other	Established	0.21 [−0.49, 0.91]	0.08	−0.14 [−0.82, 0.53]	0.24 [−0.42, 0.90]	5
				Placebo (18)							
Rütgen & Lamm [63][U]	42 (25:17)	24.05 (3.24)	WS (7 days)	50 mg (42)	Pain empathy task	New	0.05 [−0.36, 0.46]	0.15	---	---	5
				Placebo (42)							

Mean effect size per study is reported here; effect sizes per activity are listed in the forest plot (Fig. 1). All studies were randomised, double-blind, and placebo-controlled. All studies used oral naltrexone. All studies measured social connectedness by self-report. Effect size = standardised mean difference (Hedges' g) and 95% confidence interval. Negative effect sizes indicate lower social connectedness/positive mood/negative mood after administration of naltrexone than after administration of placebo. Effect sizes within studies were aggregated in R [49] using the aggregate function from the metafor package [50]. Power = probability of finding a significant effect size of Hedges' $g = -0.20$ (i.e., the average effect size obtained with the three-level random-effects meta-analysis) given study precision (i.e., standard error) and $\alpha = 0.05$. Quality = Jadad Scale score (possible range = 0–5) [53]. --- = Not applicable.

N number of participants, *W* women, *M* men, *SD* standard deviation, *WS* within-subjects, *BS* between-subjects, *ISI* intersession-interval, *Context* the context in which social connectedness ratings were recorded, *Relationship type* our categorisation of the 'target' of the social connectedness rating as an established (e.g., close others) or new relationship (strangers).

[P]Preregistered.

[U]Unpublished.

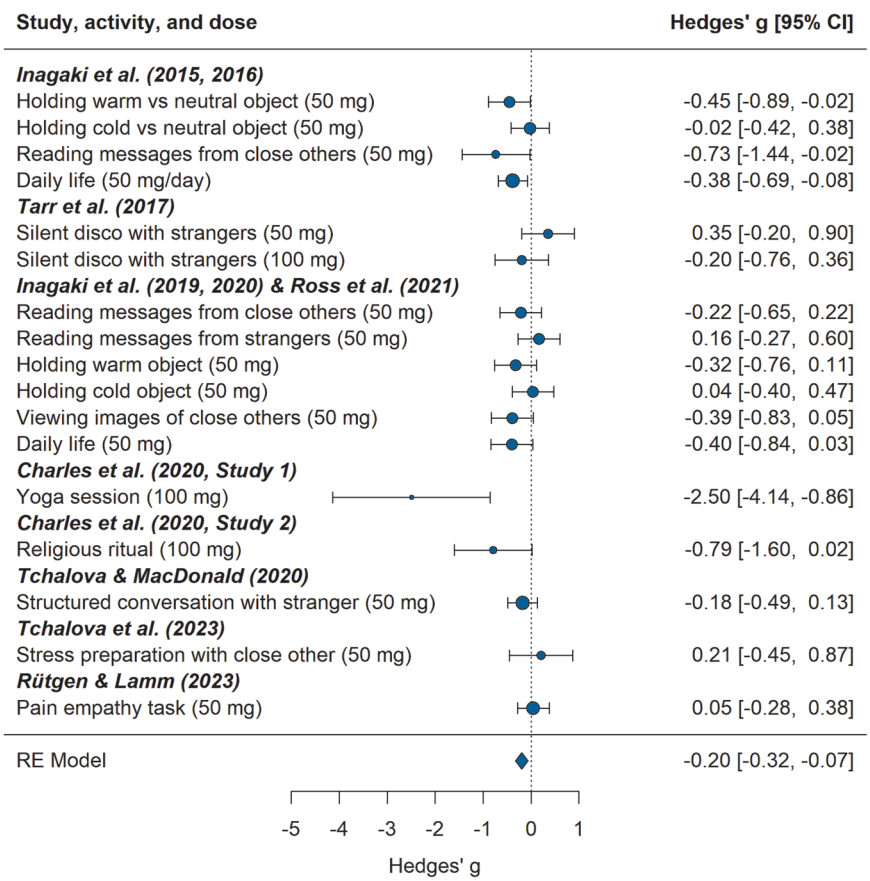

Fig. 1 Forest plot. Hedges' g is the effect size and indicates the standardised mean difference in social connectedness between the naltrexone and placebo conditions. Circles indicate individual study effects and error bars indicate their corresponding 95% confidence intervals. The diamond indicates the average effect size and corresponding 95% confidence interval obtained with the three-level random-effects meta-analysis. Negative effect sizes indicate lower social connectedness after administration of naltrexone than after administration of placebo. The vertical dotted line indicates an effect size of Hedges' $g = 0$ (i.e., no difference in social connectedness between the naltrexone and placebo conditions).

Quality of individual studies

Four out of the eight included studies (50%) were preregistered. Quality scores for each included study are available in Table 1. In line with the strict inclusion criteria, quality scores were relatively high for all studies (range 3–5, $M = 4.38$), indicating low risk of bias associated with blinding and randomisation procedures, and participant dropout. However, detailed descriptions of exact blinding and randomisation procedures were sometimes missing (see Risk of bias assessment based on Jadad Scale scores in Supplementary Fig. 2), and quality scores do not reflect the statistical power of the individual studies.

Power analysis indicated that all the included studies were underpowered (median power = 0.15) to detect the average effect size of $g = -0.20$ at $\alpha = 0.05$ (Firepower plot, Supplementary Fig. 3). The estimated number of participants per study required for a random-effects meta-analysis to have 80% power to detect this effect size at the same alpha level was 120 (60 in each drug condition). In the included studies, the median number of participants was 38 (range = 9–159) with a median of 36 participants in the naltrexone conditions (range = 4–75) and 27 in the placebo conditions (range = 5–84).

Full mu-opioid receptor blockade was likely achieved at some point in all the included studies as they used oral doses of 50–100 mg naltrexone. When administered orally, a dose of 50 mg naltrexone produces full (>90%) mu-opioid receptor blockade within 2 h and maintains this level of blockade for at least 49 h [54, 67]. Inagaki et al. [20, 59]. used a daily dosing schedule starting at 25 mg for the first two days, then increased to 50 mg on the next two days. We include measures only from the days with 50 mg naltrexone in the meta-analysis.

Social connectedness was often assessed 60–95 min after administration [20, 21, 59, 60, 63, 64]. It is likely that mu-opioid receptor blockade would be adequately high at this time point, although it is uncertain whether mu-opioid receptor blockade had reached >90% since stable PET data on mu-opioid receptor blockade with oral naltrexone are available only from 2 h post-ingestion [54, 67]. Charles et al. [58], Inagaki et al. [20, 21], Ross et al. [62], and Tchalova et al. [65]. assessed social connectedness 2–24 h after naltrexone administration and therefore likely under full mu-opioid receptor blockade.

The blockade half-life of oral naltrexone is 72 h [67], meaning that it takes at least 15 days for the blockade to be eliminated [54], i.e., five times the half-life [68]. The intersession intervals in the included within-subjects studies were 7 [63] and 10 days [20, 59], which would not be sufficient to completely eliminate the mu-opioid receptor blockade produced by naltrexone. Residual mu-opioid receptor blockade in participants who received daily naltrexone before their first session could be contributing to the significantly lower social connectedness ratings observed in the second session compared to the first session in the study by Inagaki et al. [20].

Reporting bias

Visual inspection of standard (Fig. 2A) and contour-enhanced funnel plots (Fig. 2C) suggested asymmetry. Egger's test indicated that this asymmetry was statistically significant ($k_{studies} = 8$, $k_{outcomes} = 17$,

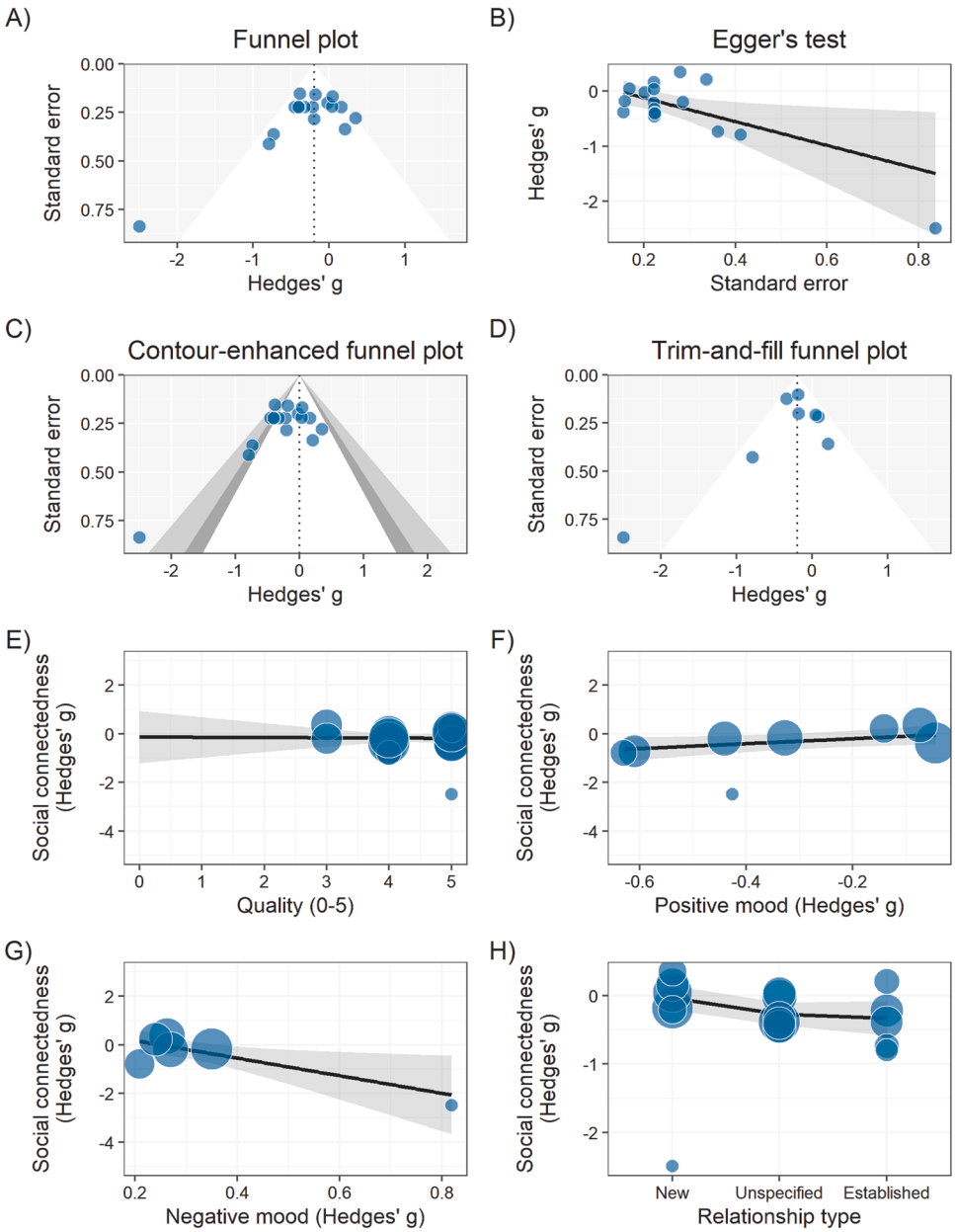

Fig. 2 Small-study effects and meta-regressions. In all plots, Hedges' *g* is the effect size and indicates the standardised mean difference between the naltrexone and placebo conditions in ratings of social connectedness (**A**–**E**), positive mood, and negative mood (**F**, **G**). Negative effect sizes indicate lower social connectedness/positive mood/negative mood after administration of naltrexone compared to placebo. **A** Funnel plot. The vertical dotted line indicates the average effect size of $g = -0.20$ obtained with multilevel random-effects meta-analysis. White shading indicates the 95% confidence interval (CI) around this average effect size at various levels of precision (i.e., standard error). **B** Egger's test. Meta-regression assessing the relationship between effect size and precision. The medium grey band is the 95% confidence band around the solid black regression line. **C** Contour-enhanced funnel plot. The vertical dotted line indicates an effect size of $g = 0$ (i.e., no difference in social connectedness between the naltrexone and placebo conditions). White, dark grey and medium grey shading indicates the 90%, 95%, and 99% CI (respectively) around this null-effect at various levels of precision. **D** Trim-and-fill funnel plot. Because the trim-and-fill method has not been generalised to multilevel random-effects meta-analysis, this method was applied to aggregated study effect sizes. Effect sizes within studies were aggregated in R using the aggregate function from the *metafor* package [50]. The vertical dotted line indicates the adjusted average effect size of $g = -0.20$ obtained with the trim-and-fill method. White shading indicates the 95% CI around this adjusted average effect size at various levels of precision. Circles indicate aggregated observed effect sizes. **E**–**G** Meta-regressions assessing predictors of the effect of naltrexone (vs placebo) on social connectedness. These predictors include (**E**) study quality as assessed with the Jadad Scale (possible range = 0–5) [53]; (**F**) the effect of naltrexone (vs placebo) on positive mood; (**G**) the effect of naltrexone (vs placebo) on negative mood; and (**H**) the likely type of relationships (new, unspecified or established) considered by participants when rating their feelings of social connectedness. The medium grey band represents the 95% confidence interval around the solid black regression line. Individual effect sizes are scaled according to their relative weight in each model, with larger circles indicating greater relative weight.

$B = -2.16$, $SE = 0.93$, $z = -2.33$, $p = 0.02$, see Fig. 2B). When we restored funnel plot symmetry with the trim-and-fill method, the average effect of naltrexone on social connectedness was not reduced and still statistically significant (Hedges' g [95% CI] $= -0.20$ [−0.32, −0.07], see Fig. 2D). The estimated number of missing studies was 0 ($SE = 2$). Together, these results indicate that the

average effect size of $g = -0.20$ could be a slight overestimate.

Overall certainty in evidence

The overall certainty of the evidence was judged as low (see Table 1 in Supplementary Materials for full GRADE evidence profile), primarily due to indirectness (i.e., use of a non-selective opioid antagonist to infer functions of a specific opioid receptor subtype) and imprecision (i.e., insufficient statistical power). There were only some concerns about bias due to insufficient details about blinding ($k = 2$) and randomisation procedure ($k = 2$) and participant dropout ($k = 1$). Risk of bias was otherwise judged as low in line with the strict inclusion criteria used in this systematic review.

Heterogeneity was low ($I^2 = 23\%$) and the 95% CIs of most individual observed effect sizes were overlapping. All studies surveyed healthy volunteers, administered the same opioid antagonist (i.e., oral naltrexone), used questionnaires consisting of similar types of questions to measure social connectedness, measured social connectedness in at least one context in which participants spent ($k = 6$) or could have spent ($k = 2$) time with other people, and measured social connectedness at a time point when the administered dose of naltrexone (50–100 mg) would likely have produced full (i.e., >90%) mu-opioid receptor blockade.

Naltrexone's high affinity for both mu-opioid and kappa-opioid receptors precludes the assessment of their unique contributions to social connectedness. Consequently, while the certainty in evidence for the effect of oral naltrexone compared to placebo on social connectedness in healthy volunteers is moderate, the certainty in evidence for the effect of mu-opioid receptor blockade compared to no mu-opioid receptor blockade on social connectedness in healthy volunteers is low.

All studies were underpowered to detect a significant average effect size of $g = -0.20$. Only $k = 1$ study included more than 120 participants, which is the estimated number of participants per study required for a random-effects meta-analysis to have 80% power to detect a significant average effect size of $g = -0.20$ given $\alpha = 0.05$ [55].

There was a tendency for less precise individual observed effect sizes to be of greater negative magnitude. While this could indicate publication bias or other forms of reporting bias, no studies were estimated to be missing ($k = 0$), and adjustments for this asymmetry resulted in no change in the average effect size (g [95% CI] $= -0.20$ [−0.32, −0.07]).

DISCUSSION

This systematic review and meta-analysis found modest reductive effects of opioid antagonism on feelings of social connectedness observed across tasks and contexts as varied as diary reports, reading messages from close others, engaging with strangers in a religious ritual, and performance in a structured self-disclosure task. Moreover, naltrexone had a comparable impact on ratings of social connection collected in the lab and in daily life through diary measures, suggesting that the laboratory findings might generalise to daily life. While the included studies used opioid antagonist doses estimated to cause full (>90%) blockade of mu-opioid receptors [54], the average effect was a reduction of ~1 point or less on a 7-point scale. The most parsimonious interpretation of these findings is that feelings of social connection in humans are fine-tuned by - but not dependent on - endogenous mu-opioid signalling [69, 70].

The modest effect size of systemic opioid antagonism on feeling connected to others reported here is broadly consistent with the magnitude of modulatory effects reported in laboratory studies of other rewards, e.g., pleasantness of pain relief [71], photos of rewarding faces and bodies [15, 72, 73], monetary reward [74] and taste reward [75, 76]. Small (or null) effects are also often reported in opioid antagonist studies of socially relevant behaviours such as emotion perception [77–79], facial mimicry [80], responses to music [81–83] and stroking touch [84, 85]. Consistent with this literature – though perhaps more surprising – are studies reporting small or even null effects of opioid antagonism on experimental [86, 87] and clinical pain [88, 89]. The abundance of modest opioid antagonist effects in the literature contrasts to more dramatic reports, such as naloxone-reversible insensitivity to pain in people and mice [90, 91], or the lack of social preference formation after mu-opioid silencing in mice and prairie voles [12, 13, 92, 93].

Although the preclinical evidence indicates that opioid antagonist treatment impedes *formation* of social preference in non-human animals, many social behaviours remain intact. For instance, Burkett et al. [13] reported that repeated systemic naltrexone effectively eliminated the usual pair-bonding (partner preference) triggered by huddling and mating in prairie voles. Not a single animal treated with repeated doses of naltrexone preferred their partner over a stranger. Yet, these animals continued to huddle and mate, suggesting that social and reproductive behaviours were not directly impeded. Other social behaviours such as social exploration, reproductive and maternal behaviour, are also not reliant on opioid signalling [93, 94]. Furthermore, grooming and huddling solicitations typically *increase* after opioid antagonism when the animal is stressed. These behaviours are directed towards individuals with whom the stressed animal has an established bond, suggesting that their social preference, perhaps reflecting trust and attachment, remains intact after mu-opioid blockade (see Løseth et al. [14] for a review). Mu-opioid blockade could increase social comfort seeking both via direct effects on the experience of social connection, and indirectly by interfering with stress coping [95]. Future studies in humans could disentangle this by assessing opioid antagonist effects on connectedness and coping in response to stress. The meta-regression results indicating a somewhat larger effect of naltrexone on feelings of connectedness in established relationships are in line with the suggestion that opioids play a central role for maintenance of the long-term bonds typical in humans and primates [10]. Since stress appears to enhance social motivation targeted towards established bonds, a stress context could be a good setting for testing potential differences in opioid involvement of social connectedness related to relationship types.

Small effects may become important if they accumulate over time [96]. Considering the results of this meta-analysis, one could speculate that the healthy mu-opioid system promotes behaviours that foster feelings of connection, intimacy and trust, allowing strong attachments to build over time. Conversely, disruptions in mu-opioid functioning related to drug use, pharmacological treatment or physical and mental ill health might trigger a negative feedback loop contributing to a growing sense of social disconnection. For instance, the decreased amount of self-disclosure in the naltrexone group reported by Tchalova & MacDonald [21] indicates a subtle disruption in a behaviour key to forming new relationships. In rodents, partial reductions in mu-opioid signalling impaired reciprocal social interaction as well as social preference formation (Toddes et al. [93]). In humans, altered mu-opioid responses to social rejection and acceptance in people with major depression were linked to reduced social motivation [18]. Reduced ability to experience social connection could contribute to disability by negatively affecting the individual's mood [6, 97, 98] and coping with pain [99] or inflammation [100], over time leading to attrition of social relationships and reduced resilience [101].

In contrast to the reports from acute opioid antagonism, prolonged naltrexone treatment of alcohol or opioid use disorder

has not been associated with social impairments. An early report found that switching from opioid maintenance treatment to antagonist treatment with naltrexone led to an improvement in depression symptoms and increased social functioning over time [102]. Naltrexone-treated patients are able to form and maintain social relationships, and some report even stronger feelings of social connection while on long-term naltrexone treatment [103]. When opioid pathways are disrupted, compensatory neurobiological and psychological mechanisms are triggered. Emery and Akil use the metaphor of the endogenous opioid system as a spinning plate, acutely sensitive to disruption [70]. Hence, naltrexone treatment may restore rather than disrupt opioid function in addiction.

The meta-analysis and included studies have some important limitations. Firstly, the certainty of evidence was judged low due to imprecision (underpowered studies). Secondly, the use of a general opioid antagonist means that we cannot differentiate the role of the various opioid receptor types. While the naltrexone doses and timings of outcome assessments in the studies reviewed here are broadly consistent with full mu-opioid blockade, naltrexone also produces substantial blockade at the kappa opioid receptor [54]. Simultaneous blockade of mu- and kappa opioid receptor signalling could conceivably cancel out behavioural sequelae of silencing each receptor system, due to opposite effects on behaviour. For instance, kappa activity has been shown to have both pronociceptive [104] and social-aversion-like [105] effects in preclinical studies, contrasting with antinociceptive [106] and prosocial [107] effects of mu-opioid binding. The study of kappa-selective medications and kappa-opioid neural processing in humans is still in its infancy [108, 109]. We note however that the few published studies employing a mu-opioid selective antagonist, reported behavioural and neural effects broadly consistent with the effects of non-selective antagonists [110, 111]. Further complicating the interpretation of opioid antagonist studies in humans is the preclinical finding that partial reductions in mu-opioid signalling ability can have larger effects than full (genetic) blockade [93].

A third limitation pertains to side effects of opioid antagonism, e.g., nausea, which could interfere with social connection ratings directly via a "gut feeling" or indirectly via distress and/or impaired mood. In studies where physical side effect symptoms were measured, naltrexone caused a modest increase in symptoms and symptom-related distress [60–62]. Another study reported severe gastrointestinal discomfort in three female participants, who were excluded from further participation [59]. While Inagaki et al. [60] report that adjusting for side effect symptoms did not change their key findings, we note that some included studies did not assess side effects. Future studies should carefully consider the actions of medications over time in the brain and body as well as their interactions and effects on mood. The use of Western, Educated, Industrialised, Rich and Democratic (WEIRD) and/or convenience samples is also frequently observed in the literature to date, limiting generalisability [112].

Finally, note that most of the studies included in this meta-analysis did not involve stress, threats or reward tasks. Exceptions are the unpublished datasets included here, where feelings of social connection were collected while participants were preparing for a stress task [65] and during a pain empathy task [63]. As the opioid system is thought to "come into action" once an organism is exposed to significant threats or rewards [70, 113], it is conceivable the mu-opioid system is key for generating and modulating social feelings when social homoeostasis is truly disrupted. Future studies should assess the role of opioids in situations dominated by psychosocial stress, loneliness or other social threats, or in the context of immediate opportunities for attractive social rewards such as establishment of new connections.

CONCLUSION

In sum, we report that pharmacological opioid blockade causes a modest reduction in feelings and behaviours related to healthy human social connection. When considered in conjunction with the alterations in endogenous mu-opioid receptor binding reported in samples of patients with common mental or physical conditions, this finding highlights endogenous mu-opioid function as a putative mechanism contributing to impairment and social difficulties in clinical populations. Future studies should aim to detect small effect sizes, use active rather than inert placebo controls, tailor tasks and stimuli to individuals and their social environments, target established connections, and design inclusion strategies to enhance the generalisability of findings.

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AUTHOR CONTRIBUTIONS

GL and SL conceptualized the study. GL, MT, and SL wrote the preregistration. MT conducted the literature search, study selection, and analyses. GL, MT, and SL wrote the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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