

Relationships Between Early Maternal Warmth and Social Connection: A Randomized Clinical Trial With Naltrexone

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ABSTRACT

Objective: Early experiences of having received maternal warmth predict responses to opportunities to connect with others later in life. However, the understanding of neurochemical mechanisms by which such relationships emerge remains incomplete. Endogenous opioids, involved in social connection in both animals and humans, may contribute to this link. Therefore, the current study examined a) relationships between early maternal warmth and brain and self-report responses to novel social targets (i.e., outcomes that may promote social connection) and b) the effect of the opioid antagonist, naltrexone, on such relationships.

Methods: Eighty-two adult participants completed a retrospective report of early maternal warmth. On a second visit, participants were randomized to 50 mg of oral naltrexone ($n = 42$) or placebo ($n = 40$), followed by a magnetic resonance imaging scan where functional brain activity in response to images of novel social targets (strangers) was assessed. Approximately 24 hours later, participants reported on their feelings of social connection since leaving the scanner.

Results: In the placebo condition, greater early maternal warmth was associated with less dorsal anterior cingulate cortex, anterior insula, ventral striatum, and amygdala activity in response to images of novel social targets (r values ≥ -0.360 , p values $\leq .031$), and greater feelings of social connection ($r = 0.524$, $p < .001$) outside of the laboratory. The same relationships, however, were not present in the naltrexone condition.

Conclusions: Results highlight relationships between early maternal warmth and responses to the social world at large and suggest that opioids might contribute to social connection by supporting the buffering effects of warm early life experiences on social connection later in life.

Trial Registration: Clinical Trials NCT02818036.

Key words: maternal care, social exploration, social approach, naltrexone, brain opioid theory of social attachment.

INTRODUCTION

Feeling socially connected to others has significant health implications. A lack of social connection predicts and exacerbates disease such as cardiovascular disease and some cancers, and is its own clinical end point (1,2). Early social experiences may influence social connection later in life such that nurturing, warm experiences predict greater feelings of social connection (3,4). Because early social relationships may provide a foundation to connect with others in adulthood, understanding neurochemical mechanisms and supporting such experiences remain topics of considerable scientific interest. Endogenous opioids have been theorized to support the initiation and maintenance of social connection in humans and social approach behavior in animals (5). Furthermore, individual differences in attachment style, which stem from early experiences with the caregiver, modulate the sensitivity of the endogenous opioid system (6,7). Therefore, opioids may contribute to the link between early warmth (defined as nurturing, affectionate care that is responsive to one's needs) and later social connection. The current study examined the role of opioids in linking

retrospective reports of having received maternal warmth early in life with neural responses to social targets and feelings of social connection.

Early Warmth and Social Connection

Correlational evidence suggests that early maternal warmth affects later social connection, potentially by reducing barriers to approaching opportunities for connection. For instance, retrospective reports of early maternal warmth have been associated with less feelings of loneliness (8) and lower sensitivity to social rejection (negative social expectations including fear that interactions will result in rejection; (9)). Early maternal warmth has also been related to clinical disorders characterized by social disconnection and withdrawal from novel social situations such that a lack of

AI = anterior insula, BCa = bias-corrected and accelerated percentile bootstrap method, CI = confidence interval, DACC = dorsal anterior cingulate cortex, fMRI = functional magnetic resonance imaging, PBI = Parental Bonding Instrument, ROI = region of interest, VS = ventral striatum

SDC Supplemental Digital Content

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Received for publication March 30, 2020; revision received February 4, 2021.

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DOI: 10.1097/PSY.0000000000000986

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warmth predicts social phobia, social anxiety, and depression (10–13). Similarly, prospective evidence shows that maternal warmth increases coping behavior during childhood (14) and reduces the risk of clinical disorders in adulthood among children high in anxiety and withdrawal (e.g., fearfulness, shyness in novel social contexts; (15)). Thus, early maternal warmth is associated with greater approach toward opportunities for social connection in adulthood, suggesting that early warmth may leave its mark on social connection later in life.

Opioids and Social Connection

The endogenous opioid system has long been theorized to contribute to social connection (5). Specifically, endogenous opioids may be released from the central nervous system (brain) during social interaction to facilitate social connection (e.g., (16)). Blocking the central action of opioids pharmacologically prevents binding to opioid receptors, particularly μ -receptors, and may disrupt social connection and related behavior (for a review, see Ref. (17)). Relevant to the current hypotheses, opioid antagonism (versus placebo or control) decreased bonding behavior in animals (18–20) and increased barriers to social connection (distress vocalizations during social interaction, (21)). Similar effects have emerged in humans. Naltrexone (versus placebo) decreased interest for attractive strangers (22), feelings of social connection toward strangers in laboratory settings (23–25), and daily feelings of social connection outside of the laboratory (26), suggesting that opioids support social connection toward a range of possible opportunities to connect. Whether opioids support positive associations between early warmth and later opportunities for social connection has not been examined.

The current study hypothesizes that early maternal warmth will relate to processes that support social connection later in life. Of particular interest are neural regions that encode socioemotional information that may be a barrier to social connection, including the dorsal anterior cingulate cortex (DACC), anterior insula (AI), ventral striatum (VS), and amygdala. All four regions have been identified as key hubs of the brain's response to emotional content, regardless of valence, in meta-analyses (27–30) and consistently activate to personally relevant social information (31,32). The DACC and AI also integrate stimuli from the environment to help an organism decide how to act next, such as when approaching new social targets (33). Most relevant to the current study goals, the ACC, AI, VS, and amygdala are densely concentrated with μ -opioid receptors (34) and have been shown to reduce μ -receptor availability (indicating a release of endogenous opioids relative to baseline) to novel social targets in positron emission tomography imaging (35). Therefore, DACC, AI, VS, and amygdala activity to novel social targets may be a) related to social connection and b) supported by endogenous opioids.

Consistent with this notion, results from patient samples with symptoms characterized by social disconnection and withdrawal show *increased* activity in the DACC, AI, VS, and amygdala to novel social targets relative to nonpatient controls (36–38). For example, anxiety-prone individuals, relative to nonanxious controls, show increased AI and amygdala activity in response to viewing emotional faces, including angry, fearful, and happy expressions (37). Similarly, increased activity to social stimuli in these regions is associated with greater social anxiety symptoms (39,40). Thus,

heightened activity may indicate less social approach. In turn, dampening activity in these regions in response to new opportunities for connection may facilitate exploration of the social world more broadly. To the extent that early maternal warmth promotes approach toward social connection later in life, higher levels of maternal warmth may be associated with less activity in these regions in response to novel social targets.

The current study examined relationships between retrospective reports of early warmth; brain activity in the DACC, AI, VS, and amygdala to novel social targets (i.e., strangers); and feelings of social connection outside of the laboratory. In addition, the causal influence of opioids, previously implicated in social connection in animals and humans, on links between early warmth and social connection was evaluated with a pharmacological manipulation. Three hypotheses were tested. First, greater perceptions of early warmth were hypothesized to be associated with reduced brain activity to strangers. Second, following previous correlational findings between maternal warmth and social connection (8), greater perceptions of early warmth were hypothesized to relate to greater feelings of social connection. Finally, should endogenous opioids support long-term buffering effects of warm early life experiences on social connection later in life, the same relationships were not expected in the naltrexone condition.

METHODS

Participants and Screening

In a randomized, double-blind, placebo-controlled clinical trial, 82 participants were administered 50 mg of oral naltrexone or placebo. A target sample size of 80 participants was determined after a power analysis ($\beta = 0.80$, $\alpha = .05$) using effect sizes from prior research on the effect of pharmacological challenges on feelings of social connection (26,41). Two participants from the naltrexone condition did not complete the functional magnetic resonance imaging (fMRI) scan, leaving a final sample of 80 participants (see Table 1 for demographics and Figure 1 for CONSORT flow diagram).

Recruitment took place via flyers and posting to Pitt + Me, a voluntary research registry. Interested individuals underwent a two-stage screening process beginning with a telephone interview followed by an in-person visit with the study physician (C.A.). Inclusion criteria were good self-reported health, fluency in English, and age between 18 and 35 years. Participants

TABLE 1. Sample Demographics

	Placebo (<i>n</i> = 40)	Naltrexone (<i>n</i> = 40)
Age, <i>y</i>		
Mean (SD)	22.88 (3.20)	21.90 (3.49)
Range	18–31	18–31
Sex, %		
Female	52.5	67.5
Male	47.5	32.5
Ethnicity, %		
Asian	30	25
Black	5	2.5
White	57.5	67.5
Other	5	5
Missing	2.5	0

SD = standard deviation.

CONSORT Flow Diagram

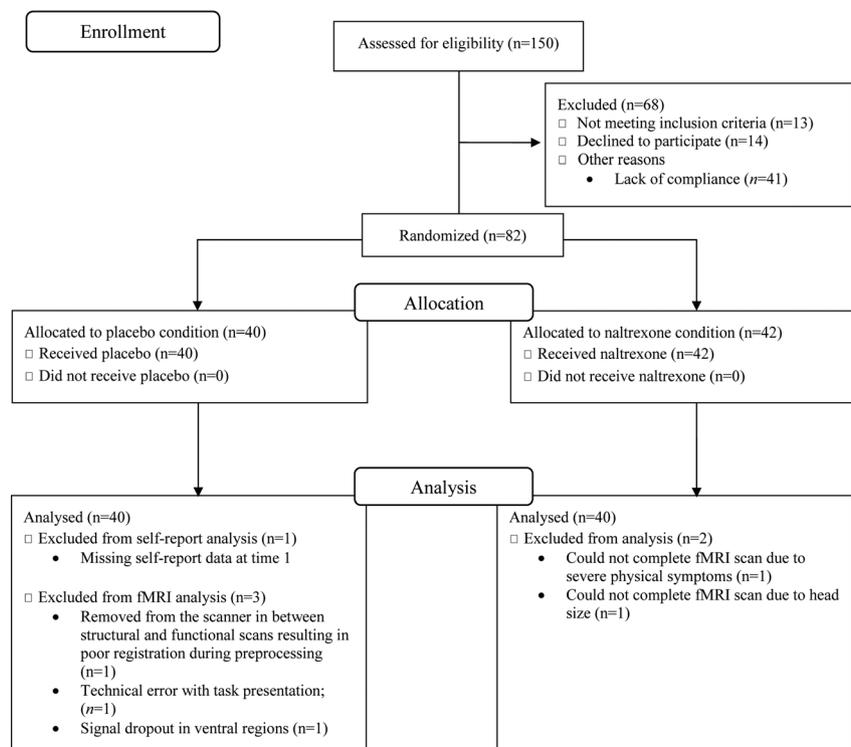


FIGURE 1. CONSORT flow diagram depicting participant recruitment through data analysis.

were excluded for contraindications for naltrexone or MRI, and general health: a positive urine pregnancy or drug test result (opiates, tetrahydrocannabinol, cocaine, amphetamines, methamphetamines); medication use other than birth control; depressive symptoms above a 9 on the Patient Health Questionnaire-9 (42); alcohol use more than 14 drinks/week or 4 drinks/occasion for men and 3 drinks/occasion for women (following current Centers for Disease Control and Prevention guidelines); self-reported mental or physical illness, including hepatic illness; body mass index greater than 35 kg/m²; nonremovable MR-incompatible metal in the body; or claustrophobia.

The study was run between September 2016 and June 2018 after approval from the University of Pittsburgh's Human Research Protection Office and registration as a clinical trial on the US National Institutes of Health Clinical Trials registry (NCT02818036: An fMRI study of opioid-related changes in neural activity). Participants provided written consent before commencing procedures and received \$90 in exchange for completing the study.

Hypothesis generation occurred before secondary data analyses on an existing data set, but after the publication of results from the primary aims (43,44). Detailed descriptions of the experimental visit (time 2) have been reported in prior publications but are summarized here. The current data have not been reported previously. However, other results from the current study have been reported, including physical symptoms in response to the drug manipulation at time 2 (43,44). Results are separated because each article tests separate theoretical questions.

Time 1: Maternal Warmth

To assess perceptions of early maternal warmth, participants completed the care subscale of the Parental Bonding Instrument (PBI; (13)), a widely used measure to assess early warmth. Previous findings suggest that perceptions of mothers, more than fathers, are associated with social connection (12);

therefore, participants were asked about perceptions of their mothers only. Ratings of the mother during childhood up until age 16 years were made on a 0–3 scale anchored by “very unlikely” and “very like.” Sample items include “spoke to me in a warm and friendly voice” and “could make me feel better when I was upset.” The PBI was missing from one participant in the placebo condition. There were no differences in perceptions of maternal warmth between drug condition ($t(77) = 0.736, p = .46$). Scores on the PBI were high such that the average score in the current sample was above the cutoff for high warmth as outlined by Parker et al. (13) (mean [standard deviation], or M [SD] = 29.899 [6.113], $\alpha = .921$).

Time 2: Drug Administration and Brain Activity to Novel Social Targets

Upon arrival to the experimental session, participants were administered either placebo or naltrexone in a parallel design using block randomization (blocks of four) by an individual unassociated with the study. To maintain the study's double blind, study drugs were packaged in identical, indistinguishable capsules. Naltrexone is a Food and Drug Administration-approved drug used in maintenance treatment for addiction, but is also used off-label for research purposes and is ideal for testing the current hypotheses because it is a full opioid antagonist that crosses the blood-brain barrier to causally change opioid receptor binding in the DACC, AI, VS, and amygdala (45). When combined with neuroimaging methods, effects of naltrexone can be isolated to central (brain) effects and, when combined with a placebo condition, allows for causal inference. Furthermore, naltrexone is safe and well tolerated.

Sixty minutes after drug administration, when naltrexone shows peak effects (46), participants completed an MRI scan. Brain activity associated with processing social targets was evaluated with a task commonly used to assess neural correlates of viewing novel and familiar social targets (41,47–49).

In a block design, participants viewed images of smiling strangers and in separate blocks, sex, race, and age-matched familiar people. The additional standard control condition for this task is mental serial subtraction (e.g., count back by 7's from 1753). The inclusion of serial subtraction is meant to "erase" any carryover feelings from viewing the social targets and is commonly used as a comparison condition (41,48,49). Eight 16-second blocks (four stranger, four familiar social targets) separated by a 1-second fixation crosshair, interleaved with 12-second blocks of serial subtraction were presented via E-Prime 3.0 software (Psychology Software Tools, Pittsburgh, Pennsylvania).

The primary goal of the current analyses was to examine associations between early maternal warmth and brain activity to novel social targets as a correlate of approach toward new opportunities for social connection. Therefore, we examined DACC, AI, VS, and amygdala activity in response to images of strangers (compared with baseline and compared with the serial subtraction condition). For associations between maternal warmth and brain activity to familiar social targets, see Table S1, Supplemental Digital Content 1, <http://links.lww.com/PSYMED/A766>. Three participants from the placebo condition were excluded from imaging analyses (Figure 1).

Time 3: Feelings of Social Connection Outside of the Laboratory

Although the half-life of naltrexone is ~4 hours, the drug does not fully metabolize until ~48 hours after ingestion and remains in the plasma at measurable concentrations through 12 hours after administration (46). Therefore, the day after the MRI session, participants reported on how they felt over the past 24 hours since leaving the scanner. Feelings of social connection were measured via responses to the following two items on a 1 (not at all) to 7 (very) scale: "I felt accepted by others and connected to them." and "I felt out of touch and disconnected from others" (reverse coded). The items were taken from previous studies examining feelings of social connection outside of the laboratory setting (49,50). Responses were averaged.

fMRI Data Acquisition

Scanning took place on a Siemens 3 T MAGNETOM Prisma MRI Scanner housed at the University of Pittsburgh's MR Research Center. Scans began with a magnetization-prepared rapid gradient-echo scan (repetition time/echo time = 5000/2.97 milliseconds, flip angle = 4 degrees, 256 × 256 matrix, 177 sagittal slices, field of view = 258, 1 mm thick) followed by functional scans. Participants completed one run of the task (4 minutes, 23 seconds, T_2^* -weighted gradient echo covering 60 axial slices; repetition time/echo time = 1000/28 milliseconds, flip angle = 55 degrees, 112 × 112 matrix, field of view = 220 mm, 2 mm thick). In addition, participants completed a messages task and a temperature task. Results from both tasks are reported separately (43,44).

Data Analyses

Neuroimaging Data

Preprocessing for imaging data occurred via Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) procedure in SPM8 (Wellcome Department of Imaging Neuroscience, London, United Kingdom). Images were motion corrected, realigned, normalized to the magnetization-prepared rapid gradient-echo scan, warped into Montreal Neurologic Institute space, and smoothed with an 5-mm Gaussian kernel, full width at half maximum. For the current aims, the focus was on linear contrasts for the comparison of strangers versus baseline and strangers versus serial subtraction. Contrasts were computed at the single-subject level and then brought to the group level for analyses. Although serial subtraction and implicit baseline (i.e., fixation crosshair) are imperfect comparisons for assessing activity over and above viewing faces or social stimuli, the current aims are focused on differences between drug conditions and on associations between early maternal warmth and social connection-related

outcomes. Both contrasts were examined and are included in all reporting as evidence of the consistency of associations.

Region-of-Interest Analyses

Given the a priori hypotheses regarding brain activity to novel social targets, we examined activity in the DACC, and bilateral AI, VS, and amygdala, regions that have previously been shown to activate to socioemotional information (27–32,36,51) and that are densely concentrated in μ -opioid receptors (34,45,52). Regions of interest (ROIs) were structurally defined using the Automated Anatomical Labeling atlas (53). The DACC was further constrained at $32 < y < 0$ on the basis of a previous review of the cingulate cortex (54). We divided the insula at $y = 8$, the approximate boundary between the dysgranular and granular sectors to constrain analyses to the anterior portion. Finally, the VS was further constrained at $-10 < x < 10$, $4 < y < 18$, $-12 < z < 0$ after the previous use of this ROI to the same scanner task (41,48).

Relationships Between Maternal Warmth and Social Connection

The current hypotheses are that early maternal warmth will be related to reduced DACC, AI, VS, and amygdala activity to novel social targets and greater feelings of social connection. To test the hypotheses, we ran separate Pearson correlations between scores on the care subscale of the PBI and DACC, AI, VS, and amygdala activity to images of strangers (versus baseline and versus serial subtraction) and then feelings of social connection outside of the laboratory in the placebo group. Ninety-five percent confidence intervals (CIs) were estimated using the bias-corrected and accelerated percentile bootstrap method (BCa) with 1000 random samples with replacement. Significance was determined at an α of .05, two tailed, and/or a BCa 95% CI excluding 0.

Effect of Naltrexone on Brain Activity and Feelings Outside of the Laboratory

To assess the effect of naltrexone (versus placebo) on DACC, AI, VS, and amygdala activity to strangers and feelings of social connection outside of the laboratory, parameter estimates from each ROI for the stranger blocks (versus baseline and versus serial subtraction) and feelings of social connection collected 24 hours after drug administration were evaluated with independent-samples t tests.

Relationships Between Maternal Warmth and Social Connection in Naltrexone Condition

We also hypothesized that relationships between early maternal warmth and social connection in the placebo condition would not be present in the naltrexone condition. Pearson correlations between scores on the care subscale of the PBI and DACC, AI, VS, and amygdala activity in response to images of strangers (versus baseline and versus serial subtraction) and feelings of social connection outside of the laboratory were therefore run again in the naltrexone group. To assess the strength of any drug effect, the significance of the difference between correlations in each drug condition was assessed by Fisher r -to- z transformations of the correlation coefficients.

Raw data and syntax can be found on the Open Science Framework at: <https://osf.io/x8sqe/>.

RESULTS

Relationship Between Maternal Warmth and Brain Activity to Novel Social Targets

The current theoretical perspective suggests that early warmth may predict greater social connection later in life. Therefore, we examined the relationship between early maternal warmth and brain activity to novel social targets as a correlational test of this notion. As

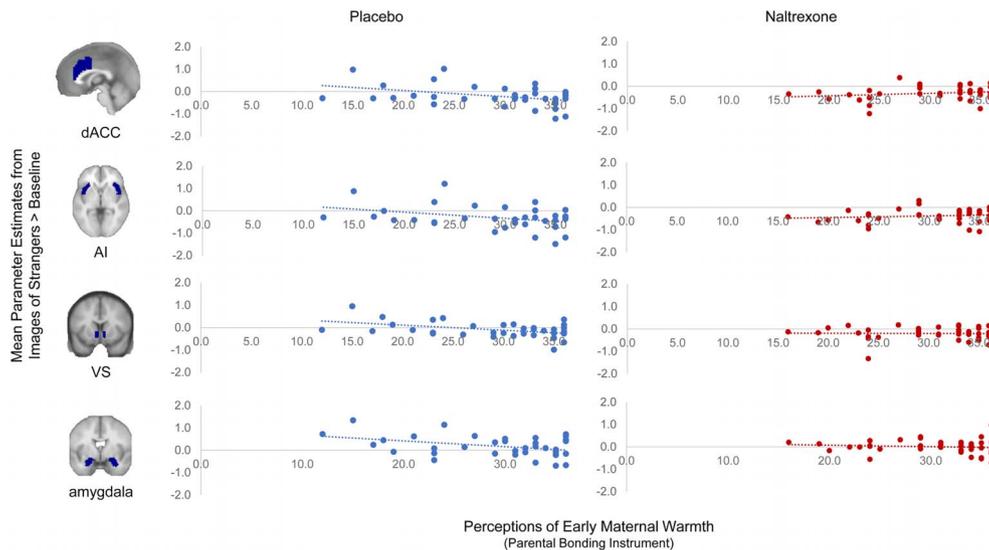


FIGURE 2. Relationships between maternal warmth and brain activity to strangers in each drug condition separately. Greater perceptions of early maternal warmth were associated with less dorsal anterior cingulate cortex (DACC), anterior insula (AI), ventral striatum (VS), and amygdala activity to strangers (versus baseline [pictured above] and versus serial subtraction) in the placebo group. The same relationships between maternal warmth and brain activity were absent in those who took naltrexone. Color image is available online only at www.psychosomaticmedicine.org.

TABLE 2. Associations Between Retrospective Perceptions of Early Maternal Warmth as Assessed by the PBI and Brain Activity to Novel Social Targets (i.e., images of strangers)

	<i>r</i>	<i>p</i>	BCa 95% CI
Placebo			
Strangers > baseline			
DACC	-0.403	.015*	-0.646 to -0.123
AI	-0.360	.031*	-0.583 to -0.112
VS	-0.449	.006*	-0.701 to -0.116
Amygdala	-0.383	.021*	-0.641 to -0.041
Strangers > serial subtraction			
DACC	-0.394	.017*	-0.637 to -0.118
AI	-0.375	.024*	-0.620 to -0.101
VS	-0.369	.027*	-0.678 to -0.011
Amygdala	-0.304	.071*	-0.564 to -0.001
Naltrexone			
Strangers > baseline			
DACC	0.199	.21	-0.118 to 0.476
AI	0.133	.41	-0.125 to 0.397
VS	-0.018	.91	-0.356 to 0.276
Amygdala	-0.127	.43	-0.420 to 0.139
Strangers > serial subtraction			
DACC	-0.049	.76	-0.337 to 0.235
AI	0.108	.50	-0.174 to 0.362
VS	-0.236	.14	-0.545 to 0.067
Amygdala	-0.226	.16	-0.527 to 0.134

PBI = Parental Bonding Instrument (13); DACC = dorsal anterior cingulate cortex; AI = anterior insula; VS = ventral striatum; BCa = bias-corrected and accelerated percentile bootstrap method; CI = confidence interval.

* *p* < .05, two tailed, and/or BCa CI excluding 0.

hypothesized, in the placebo group, there was a negative correlation between perceptions of maternal warmth and DACC, AI, VS, and amygdala activity to strangers (versus baseline and versus serial subtraction) such that greater retrospective reports of maternal warmth at time 1 were associated with less brain activity to images of strangers at time 2 (Figure 2, Table 2).

In a pattern consistent with the suggestion that the brain activity evaluated for the current study is a barrier to social connection, DACC and AI activity in response to images of strangers (versus baseline) and feelings of social connection outside of the laboratory were negatively correlated in the placebo group (Table 3). VS and amygdala activities were also negatively correlated with feelings of social connection at a statistically marginal level. That

TABLE 3. Associations Between Brain Activity in Response to Images of Strangers and Feelings Collected Outside of the Laboratory in Those Administered Placebo

	<i>r</i>	<i>p</i>	BCa 95% CI
Feelings of social connection			
Strangers > baseline			
DACC	-0.348	.035*	-0.531 to -0.104
AI	-0.321	.052*	-0.527 to -0.062
VS	-0.297	.074	-0.566 to 0.034
Amygdala	-0.296	.076	-0.528 to 0.004
Strangers > serial subtraction			
DACC	-0.383	.019*	-0.599 to -0.114
AI	-0.362	.028*	-0.593 to -0.072
VS	-0.231	.16	-0.546 to 0.152
Amygdala	-0.229	.17	-0.546 to 0.119

DACC = dorsal anterior cingulate cortex; AI = anterior insula; VS = ventral striatum; BCa = bias-corrected and accelerated percentile bootstrap method; CI = confidence interval.

* *p* < .05, two tailed, and/or BCa CI excluding 0.

is, greater DACC, AI, VS, and amygdala activities to strangers were associated with lower feelings of social connection.

Relationship Between Maternal Warmth and Feelings of Social Connection Outside of the Laboratory

Again, consistent with the hypotheses, maternal warmth (time 1) was positively correlated with feelings of social connection (time 3). Those who perceived greater maternal warmth early in life also reported greater feelings of social connection outside of the laboratory setting ($r = 0.524, p < .001$, BCa 95% CI = 0.135–0.796).

Effect of Naltrexone on Social Connection

Naltrexone (versus placebo) reduced amygdala activity to strangers (versus baseline only, $M [SD]$ placebo = 0.184 [0.460]; $M [SD]$ naltrexone = 0.002 [0.315]; $t(75) = 2.036, p = .045$, BCa 95% CI = 0.004–0.360). Unexpectedly, there was no effect of naltrexone on DACC, AI, or VS activity (p values $> .16$). However, in replication of previous findings (26), naltrexone (versus placebo) decreased feelings of social connection outside of the laboratory setting ($M [SD]$ placebo = 5.888 [0.937]; $M [SD]$ naltrexone = 5.450 [1.197]; $t(78) = 1.820, p = .073$, BCa 95% CI = 0.007–0.888).

Maternal Warmth and Brain Activity to Novel Social Targets in Naltrexone Condition

Because of their theorized involvement in social connection in humans and animals, opioids may support associations between early maternal warmth and later social connection. Indeed, reports of early maternal warmth collected at time 1 were not related to DACC, AI, VS, or amygdala activity to strangers in those who had taken naltrexone at time 2 (Figure 2, Table 2). The correlation in the placebo group was different from that in the naltrexone group for the DACC (versus baseline: $z = 2.360, p = .009$; versus serial subtraction: $z = 1.530, p = .12$), AI (versus baseline: $z = 2.130, p = .033$; versus serial subtraction: $z = 2.100, p = .036$), and VS (versus baseline: $z = 1.940, p = .052$; versus serial subtraction: $z = 0.610, p = .54$), suggesting that naltrexone moderated the early warmth–brain relationship for these regions. Correlations with amygdala were not different between drug conditions (versus baseline: $z = 1.190, p = .23$; versus serial subtraction: $z = 0.350, p = .72$).

Maternal Warmth and Feelings of Social Connection Outside of the Laboratory in Naltrexone Condition

Maternal warmth and feelings of social connection were not related in those who took naltrexone ($r = 0.114, p = .48$, BCa 95% CI = –0.171 to 0.400). The correlation present in the placebo group was significantly different from the correlation in the naltrexone group suggesting a comparatively strong drug effect ($z = 2.000, p = .046$).

DISCUSSION

Prior work suggests that early maternal warmth may have lasting effects on social connection later in life such that a warm, nurturing mother facilitates greater social connection and a lack of warmth produces the opposite effects (3,4,55). In support of the current hypotheses, greater perceptions of early maternal warmth were associated with less activity in the DACC, AI, VS, and amygdala to novel social targets and greater feelings of social connection outside of the laboratory. The same relationships, however, were not present in those administered the opioid antagonist, naltrexone. Results highlight the endogenous opioid system as a potential

contributor to positive effects of an early warm relationship on later social connection.

Early Warmth and Social Connection

Outside of the well-known links between early warmth and stress-related outcomes in vulnerable populations, less is known about how and whether early warmth relates to social connection absent a stressful context (e.g., (56–59)). The current results broaden understanding for links between early warmth and later social connection by demonstrating that, in the placebo group, perceptions of early maternal warmth are associated with less DACC, AI, VS, and amygdala activity to novel social targets and greater feelings of social connection outside of the laboratory. Patterns support perspectives that early warmth molds an individual for later socializing, but extend these perspectives to show that the imprint left by early warmth also relates to social connection beyond the more well-known contexts of stress and threat, and further still beyond adult romantic relationships (55,60,61). Indeed, the current results suggest that warmth is so critical early in life that it may lay the foundation for later behavior toward new opportunities for social connection.

The correlational patterns in the current study highlight a potential path by which early warmth and social connection are related. Specifically, DACC, AI, VS, and amygdala activity in response to novel opportunities to socialize, such as with a stranger, may be a barrier to social approach behavior (36–40). In the current study, feelings of connection were related to less activity in the same regions, principally the DACC and AI. Perceptions of early warmth were similarly related to less activity in the DACC, AI, VS, and amygdala in response to novel social targets. To the extent that early maternal warmth assists one in approaching opportunities for social connection later in life, the correlational patterns suggest the following: decreasing activity in the DACC, AI, VS, and amygdala to novel opportunities to socialize, in and of itself, may also increase social connection, and/or that early warmth may set or contribute to the threshold at which one approaches strangers. Lack of warmth may lead to a lower threshold to approach, whereas high warmth may lead to a higher threshold.

However, the current results are correlational, and therefore, we can only conjecture based on previous theoretical models as to the causal direction of early warmth on brain activity to strangers and new experiences of social connection (57,60). Future longitudinal studies could incorporate measures of social connection toward a broader range of social targets or could compare those who perceive high versus low warmth to better understand whether caregiver warmth, as measured early in life, relates to social connection, as measured later in life.

Opioid Contribution to Early Warmth and Social Connection

Endogenous opioids support the initiation and maintenance of social connection in humans (6,23) and, as an extension of this theory, may maintain the positive relationships between early social experiences and later social connection. In replication of previous findings, naltrexone (versus placebo) decreased feelings of social connection outside of the laboratory (26). Furthermore, both the early warmth–brain and early warmth–affective experience relationships in the placebo group were not present in those who had been administered naltrexone. To our knowledge, these are the first results to suggest that naltrexone can alter social connection, potentially by disrupting the foundation from which individuals who grew up in warm, caring environments approach the social world.

Although naltrexone decreased feelings of social connection outside of the laboratory, no differences between drug conditions were found for DACC, AI, or VS activity to strangers. Unexpectedly, naltrexone decreased, rather than increased, amygdala activity to viewing images of strangers, although only to the comparison of strangers versus implicit baseline. Additional research is needed to replicate this effect before firm conclusions can be made about the effect of naltrexone on brain activity to new opportunities for social connection. Previous research outside the brain suggests that the effect of naltrexone on social responding can depend on state-level factors like the salience of the targets (17) and desire to interact with someone new, as well as trait-level personality factors (23). Such moderators will be important to explore in future research. In addition, future research that adjusts for general or trait levels of social connection is needed when replicating naltrexone's effect on state-level feelings of social connection.

Limitations are noted. Causal inference of maternal warmth on later social connection is not possible given that the correlational nature of the findings and the use of retrospective reports of warmth may suffer from recall bias (62–64). Although there was no difference between drug conditions in perceptions of early warmth at time 1, future research would benefit from tighter control over individual differences by using a crossover, rather than between-subject, drug manipulation. Viewing static images of strangers only approximates real-world social interaction. Future work would benefit from enhanced instructions (“imagine meeting this person”) or the use of video stimuli to better mirror the intended social experience. Finally, the focus of the current study was on the mother, but other individuals can be equally influential and integral to a child's upbringing and may similarly influence later social connection. Caregivers identified as primary early relationships should be measured in future studies assessing the effects of early social experience on social connection later in life.

CONCLUSIONS

The current study revealed relationships between perceptions of early maternal warmth and social connection later in life. Greater maternal warmth was related to less DACC, AI, VS, and amygdala activity to strangers and greater feelings of social connection outside of the laboratory, relationships that were not present in those administered naltrexone. Results have implications for connection with new opportunities for social interaction and suggest that opioids contribute to the broader experience of social connection by supporting the positive effects of early life experience on social connection later in life.

We thank the University of Pittsburgh Investigational Drug Service, members of the Social-Health and Affective Neuroscience Lab for their assistance in running the study, and Edward Orehek for assistance with drug randomization and the study blind.

Source of Funding and Conflicts of Interest: The study was supported by a National Alliance for Research on Schizophrenia and Depression Young Investigator Grant from the Brain & Behavior Research Foundation (T.K.L.), National Institute of Mental Health grants R01MH108509 and R01MH076079 (C.A.), and National Institutes of Health grant UL1TR001857. The authors declared no conflicts of interest.

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