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Neurobiological Bases of Social Connection

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Neurobiological Bases of Social Connection

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in Psychology

by

Tristen Kimiko Inagaki

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ABSTRACT OF THE DISSERTATION

Neurobiological Bases of Social Connection

by

Tristen Kimiko Inagaki

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2014

Professor Naomi I. Eisenberger, Chair

Social connection, the affectively pleasant experience of being close to and bonded with others, is a ubiquitous and critical experience for continued social bonding, immediate and long-term health, and overall well-being. However, for such an important experience, few have experimentally examined the mechanisms by which we connect with others. The strongest insights into social affiliation and bonding come from work in animals showing that the maintenance and monitoring of social relationships rely on many of the same systems that support basic sensory and motivational circuits. With this literature as a starting foundation, the following dissertation aims to examine the neurobiological mechanisms underlying social connection in humans with an emphasis on the specific contributions of thermoregulatory and reward-related systems. To begin, paper 1 examines the potential shared neural mechanisms that contribute to social connection and physical warmth with a sample of 20 participants who read

positive, loving messages written by their friends and family and separately, held a warm pack (to increase physical warmth) while lying in the fMRI scanner. Paper 1 revealed, for the first time, that an experience of social connection shares overlapping neural activity with an experience of physical warmth lending support to the description of social affiliation as "heartwarming." Next, in one of the first tests of the brain opioid theory of social attachment in humans, paper 2 pharmacologically manipulated the endogenous opioid system with an opioid-antagonist, naltrexone, to uncover the importance of opioids to feelings of connection both in the laboratory and in the real-world using daily diary assessments. Finally, paper 3 follows up on the results from paper 1 to show that opioids are also involved in the feelings of connection from physical warmth. Collectively, the results from this dissertation add to existing models of social bonding as a basic need on its own and provide a basis for understanding how to help those lacking social connections.

The dissertation of Tristen Kimiko Inagaki is approved.

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University of California, Los Angeles

2014

To Kay Shiota, for saying it like it is

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Publications and Presentations

Inagaki, T. K., Irwin, M. R., & Eisenberger, N. I. (2014). Neural mechanisms underlying social approach and withdrawal: The role of inflammation. Paper presentation at the American Psychosomatic Society (APS) Conference, March 2014, San Francisco, CA.

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Invited Talks and Colloquia

Cornell University, Social Psychology Colloquium, 2013
Cornell University, Psychology Department Colloquium, 2013
University of Pittsburgh, Psychology Department Colloquium, 2013
University of California, Merced, Psychology Department Colloquium, 2013
University of California, Los Angeles, Health Psychology Brown Bag, 2011
University of California, Los Angeles, Social Psychology Colloquium, 2010

INTRODUCTION

"We are like islands in the sea, separate on the surface but connected in the deep."

-William James

The importance of making and maintaining connections with other people cannot be overstated. In fact, research on animals and humans from almost every subfield of psychology, psychiatry, anthropology, and public health converge to highlight the importance of having and maintaining nurturing, affiliative bonds for normal functioning, overall well-being and happiness (Baumeister & Leary, 1995; Bowlby, 1988; Czikszentmihalyi & Hunter, 2003; Diener & Seligman, 2002; House, Landis, Umberson, 1988; Harlow, 1958; Taylor, 2007; Panksepp, 1998). Beyond being a purely hedonic experience, feeling connected to others serves other functions such as strengthening the bond between two individuals (Gable, Gonzaga, & Strachman, 2006), increasing long-term physical and mental health (Charles & Carstensen, 2010; Diener, Suh, Lucas, & Smith, 1999; Holt-Lundstad, Smith, & Layton, 2010), reducing biological and psychological responses to acute stress (Kiecolt-Glaser & Newton, 2001; Taylor, 2007; Uchino, Cacioppo, & Kiecolt-Glaser, 1996), and contributing to normal physical and psychological development (Bowlby, 1988; Harlow, 1958; Hofer, 2006; Zhang & Meaney, 2010). Conversely, a lack of connections leads to a number of negative outcomes such as a higher mortality risk, accelerated cancer progression and even increased suicide rates (Durkheim, 1897/1951; House et al., 1988; Holt-Lundstad et al., 2010; Lutgendorf & Sood, 2011).

However, relative to its importance in the literature, not much research has focused on the mechanisms underlying social connection in humans. In particular, little is known about how we remain socially connected or the neural or neurochemical mechanisms that underlie this

psychological experience. In an attempt to fill this gap in the literature, the following presents three papers in support of a neurobiological system underlying social connection, the affectively pleasant experience of being close to and bonded with others. Using a combination of experimental, neuroimaging, pharmacological, and daily diary techniques, this dissertation focuses on the role of primitive emotional systems, common to all warm-blooded mammals, that help guide and support social connections with others. Here, the goal of each paper is briefly outlined.

Paper 1: Shared Neural Mechanisms Underlying Social Warmth and Physical Warmth

Paper 1 begins to answer the question of what the subjective experience of connecting with others feels like and the neural mechanisms associated with social connection by exploring the contributions of physical experiences, such as warmth, to the more abstract psychological experience of connecting with close others. Based on the theory that basic homeostatic mechanisms involved in temperature perception and regulation are involved in monitoring for and reinforcing social connection (Panksepp, 1998; Panksepp, Nelson, & Bekkedal, 1997) and recent evidence that physical warmth can increase perceptions of social warmth (Williams & Bargh, 2008, Ijzerman & Semin, 2009), this study had two main goals. First, we aimed to test whether experiencing social warmth would increase feelings of warmth and whether physical warmth would increase feelings of social connection. Second, the potential neural overlap between physical and social warmth were explored. Using a novel paradigm designed to elicit feelings of social connection, 20 participants read loving messages written by their closest friends and family members while they were lying in the fMRI scanner and, in a separate task, also held a warm pack (to elicit increases in physical warmth) and neutral object. Establishing a neural overlap would push our understanding of what contributes to feelings of social connection

and help us understand why and how social relationships have come to be so important. Furthermore, this study will attempt to bridge abstract psychological feelings with experiences rooted in the physical world in order to shed light on how relationships are regulated and maintained from the perspective of the brain.

Paper 2: Opioids and social bonding: The effect of naltrexone on feelings of social connection

To further understand the mechanisms underlying social bonding and as a direct test of the brain opioid theory of social attachment, paper 2 used a randomized double-blind placebo-controlled crossover design with the opioid-antagonist, naltrexone, in order to assess whether the feelings associated with social connection are opioid-mediated. Based on a substantial animal literature and emerging work from humans on the importance of μ-opioids to social bonding, we expected naltrexone (vs. placebo) to decrease feelings of social connection to an experience with close others. To test this possibility, 31 participants took both naltrexone and placebo (for 4 days each) and completed an experimental lab session once while on naltrexone and once while on placebo. Additionally, participants completed a daily diary while they were on both naltrexone and placebo in order to examine the effect of opioid-antagonism on feelings of social connection in the real-world. Together, results from this study have the potential to uncover one of the basic pathways that mediate social attachments and further inform a larger neurobiological model of social connection in humans. Furthermore, results may validate any findings from the experimental lab task by assessing the effect of a pharmacological manipulation on feelings of social connection during real-world interactions.

Paper 3: Naltrexone reduces warmth-induced feelings of social connection

As a second aim of the pharmacological manipulation outlined in paper 2, we sought to further examine the theory that social and physical warmth share similar neurobiological

mechanisms. Based on findings that physical warmth can lead to increases in perceptions of social warmth (Williams & Bargh, 2008, Ijzerman & Semin, 2009) and that opioids are involved in temperature regulation (Adler, Geller, Roscow, & Cohin, 1988), paper 3 explored the role of opioids in feelings of social connection elicited by physical warmth. We hypothesized that naltrexone (vs. placebo) would reduce feelings of social connection to physical warmth, but would not alter perceptions of warmth. To test the hypothesis, participants simply held a warm pack, a cold pack, and a neutral object, both while on naltrexone and placebo and then rated their feelings of social connection to holding each item. These findings could lend further support to the theory that social and physical warmth share neurobiological mechanisms (Panksepp, 1998) by uncovering a potential neurochemical substrate and more broadly, help us understand how physical experiences, such as warmth, contribute to abstract psychological feelings.

Overarching goal

Together, these three papers will help inform our understanding of how an individual might remain connected to others by examining the contribution of basic neurobiological processes to social connection. This line of research is pursued in the hopes that the results will guide future research on interpersonal processes, especially with those we are closest to, and ultimately provide the foundation to help those lacking high quality social connections.

Paper 1:

Shared Neural Mechanisms Underlying Social Warmth and Physical Warmth

Tristen K. Inagaki and Naomi I. Eisenberger

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Abstract

Many of people's closest bonds grow out of socially warm exchanges and the warm feelings associated with being socially connected. Indeed, the neurobiological mechanisms underlying thermoregulation may be shared by those that regulate *social warmth*, the experience of feeling connected to other people. To test this possibility, we placed participants in a functional MRI scanner and asked them to (a) read socially warm and neutral messages from friends and family and (b) hold warm and neutral-temperature objects (a warm pack, a ball, respectively). Findings showed an overlap between physical and social warmth: Participants felt warmer after reading the positive (compared with neutral) messages and more connected after holding the warm pack (compared with the ball). In addition, neural activity during social warmth overlapped with neural activity during physical warmth in the ventral striatum and middle insula, but neural activity did not overlap during another pleasant task (soft touch). Together, these results suggest that a common neural mechanism underlies physical and social warmth.

The ability to connect and maintain deep emotional bonds with other people is fundamental to a happy and fulfilled life. However, even though close relationships are known to be critical for survival early in life and for health and well-being later on (Bowlby, 1988; House, Landis, & Umberson, 1988; Taylor, 2007), the experience of feeling socially connected has received little empirical attention thus far. In particular, little is known about the neural mechanisms that underlie feelings of social connection.

One proposal is that being socially integrated is so crucial to survival that it is necessary to have a neurobiological system in place that leads individuals to seek out social connection and reinforces these experiences to ensure that they continue. Indeed, it has been suggested that the basic homeostatic mechanisms involved in temperature perception and regulation may be involved in monitoring for and reinforcing social connection (Panksepp, 1998; Panksepp, Nelson, & Bekkedal, 1997). That is, the neural circuitry underlying thermoregulation, the processes associated with maintaining people's relatively warm core body temperature (including the motivation to seek out warm stimuli and the perceived pleasantness of physical warmth; Rolls, Grabenhorst, & Parris, 2008), may have been coopted to maintain *social warmth*, the experience of feeling loved by and connected to other people. According to this view, the neural systems in place to detect signs of social connection may have borrowed from the neural systems that detect physical warmth, which sheds light on one reason why connecting with other people is often described as "heartwarming."

Even before birth, warmth and connection develop concurrently, initially in the warm, protected environment of the mother's womb. Following birth, infant-caregiver interactions, such as being held or rocked to sleep, are characterized by increases in external physical warmth from the close proximity of a caregiver. From these early interactions, warmth may have come to

signal that one is socially connected and cared for (Panksepp, 1998). This overlap between physical and social warmth may have been either selected for over the course of our evolutionary history or learned associatively across an individual's life span. As evidence of the critical role of warmth in early life, pups placed in a warm environment after being deprived of maternal care, food, and water continue to develop normally and even survive longer relative to those in cold environments (Stone, Bonnet, & Hofer, 1976). Furthermore, pups removed from their mothers and placed in warm cages show fewer signs of distress than those placed in relatively cold or hot cages (Blumberg, Efimova, & Alberts, 1992). Thus, in some cases, physical warmth may serve as a proxy for closeness to the caregiver. Finally, in Harlow's (1958) famous study of infant macaques and their surrogate cloth or wire mothers, the cloth mothers were also heated by a 100 W light bulb, which made them not only a source of contact comfort but also of physical warmth. Hence, the observed preference for a soft cloth mother cannot be disentangled from the preference for a warm mother.

Similar to nonhuman mammals, human infants require both physical warmth (Costeloe, Hennessy, Gibson, Marlow, & Wilkinson, 2000; Day, Caliguiri, Kamenski, & Ehrlich, 1964; Silverman, Fertig, & Berger, 1958) and nurturing care for normal development (Bowlby, 1988). For instance, premature infants placed in relatively warmer incubators for the first 5 days of life were more likely to survive than those placed in cooler incubators (Silverman et al., 1958), and many children raised in institutional settings without the presence of a nurturing figure show stunted physical, cognitive, and socioemotional development (Gunnar, Bruce, & Grotevant, 2000). These early experiences may provide the building blocks for detecting social warmth later in life.

More recent research from the embodied-cognition literature supports this association between social and physical warmth in humans. Holding warm compared with cold stimuli led participants to rate a fictional target as interpersonally warmer (Williams & Bargh, 2008) and to rate themselves as psychologically closer to an experimenter and a friend (Ijzerman & Semin, 2009). Furthermore, as evidence that feeling cold is associated with a lack of social connection, holding a cold (vs. a warm or neutral) pack led to increases in self-reported loneliness (Bargh & Shalev, 2012). Moreover, participants who were socially excluded reported a room to be colder than did included participants (Zhong & Leonardelli, 2008). Collectively, these results suggest that there is an overlap between the experience of social connection and physical warmth.

Although such evidence points to the possibility that feelings of social connection and feelings of physical warmth are interrelated, no studies have focused on whether experiences of physical and social warmth activate overlapping neural regions (although see Kang, Williams, Clark, Gray, & Bargh, 2011, for a study on the neural mechanisms linking temperature perception with subsequent trust behavior). The few studies to assess neural activity to innocuous, warm (vs. neutral) thermal stimuli have found increased activity in the insula, a region associated with processing interoceptive cues (Becerra et al., 1999; Craig, 2003; Davis, Kwan, Crawley, & Mikulis, 1998; Olausson et al., 2005; Rolls et al., 2008; Verhagen, Kadohisa, & Rolls, 2004). Indeed, lesions to the insula can result in selective loss of nonpainful thermal sensation (Cattaneo, Chierici, Cucurachi, Cobelli, & Pavesi, 2007). Additionally, the ventral striatum (VS), pregenual anterior cingulate cortex (pACC), and orbitofrontal cortex show more activity the more pleasant a warm stimulus is rated, which suggests that these regions may code for the rewarding component of warmth (Rolls et al., 2008).

Although to our knowledge, no imaging studies have explored the general experience of connecting with other people in the absence of stress or pain, some have assessed neural responses to viewing pictures of loved ones. Viewing a romantic partner (vs. a friend) or one's own child (vs. a familiar but unrelated child) leads to increased activity across a broad array of neural regions, including the caudate, middle insula, VS, ventral tegmental area, pACC, and anterior cingulate cortex more broadly (Acevedo, Aron, Fisher, & Brown, 2012; Aron et al., 2005; Bartels & Zeki, 2000, 2004). Relevant to social connection, subjects who show the most middle-insula activity also rate themselves as closer to their romantic partner, and greater activity in the VS is associated with longer relationship length (Acevedo et al., 2012). Together, these findings suggest that the insula, particularly the middle insula, and the VS play important roles in processing both physical and social warmth; however, these studies did not focus on more interactive forms of social connection beyond passively viewing pictures of loved ones.

Following the premise that mechanisms involved in temperature perception have been coopted to detect signs of social connection, we tested two consequences of this potential social-physical warmth overlap. First, we investigated whether experiencing social warmth increases feelings of warmth and experiencing physical warmth increases feelings of social connection. Second, we examined whether physical and social warmth share overlapping neural activity in the insula and VS. To test these questions, we asked participants to hold a warm pack and a ball for the physical-warmth manipulation and read loving and neutral messages from their closest friends and family members for the social-warmth manipulation. Following each manipulation, participants were asked to rate their feelings of warmth and connection in response to each task. In addition, because similarities between neural responses to social and physical warmth could be attributed to the perceived pleasantness of each experience, we included an additional task

involving a soft, pleasant touch to investigate the unique contribution of warmth to the experience of connection.

Method

Participants

Twenty young adults (mean age = 20.2 years, 13 females) who were either University of California, Los Angeles, (UCLA) undergraduates or friends of UCLA undergraduates were determined eligible to participate after identifying at least six close friends and family members (i.e., *close others*) who would be willing to be contacted in regards to the study. All participants were deemed scanner ready (right-handed, not claustrophobic, free of metal, not pregnant if female) during an initial e-mail screening. Of these participants, 55% identified as Asian or Asian American, 40% as Caucasian, and 5% as Latina. Procedures were run in accordance with the guidelines of the UCLA Institutional Review Board.

Procedures

Pre-scan message collection. Prior to the scanning session, participants' close others were contacted via e-mail to help create the social-warmth task. Participants pre-rated how close they were to their close others on a scale from 1, *not at all close*, to 10, *extremely close* (average rating = 8.17, range = 6–10). We sent e-mails to close others explaining that we were conducting a study exploring the brain's response to messages from friends and family members, and we asked that they provide us with 12 brief messages to the participant. Half of the messages were to be about why they loved and appreciated the participant, and the other half were facts. Contacts were asked not to discuss the messages with the participants so that all participants remained unaware of potential study goals.

Imaging procedures. In the scanner, participants completed three tasks: a social-warmth task, a pleasant-touch task, and a physical-warmth task. The social-warmth and pleasant-touch tasks were counterbalanced, and the scan always ended with the physical-warmth task. This was done to ensure that the pleasant-touch runs remained temperature neutral and to avoid carryover effects from the physical-warmth runs.

During the social-warmth task, participants read the messages from their close friends and family members on scanner-compatible goggles. A 2-s cue explaining who the messages were from was followed by two messages (either both positive or both neutral) for 6 s each in a block design. Each block was separated by 7 s of rest. Examples of positive messages from actual close others included "Whenever I am completely lost, you are the person I turn to," and "I love you more than anything in the world." Examples of neutral messages included "You have curly hair," and "I have known you for 10 years." During the pleasant-touch task, a research assistant slowly brushed (approximately one brushstroke per second) the participant's left inner forearm with a soft brush and provided neutral touch with a stationary wooden dowel for 10 s each. Finally, in the physical-warmth task, the participant held a warm pack and a neutral, room-temperature ball for 10 s each.[1] Stimuli were repeated 5 times in each condition. Conditions were counterbalanced, and no condition was presented twice in a row.

Post-scan self-report ratings. After the scan, participants rated the extent to which they felt connected after reading the positive and neutral messages and how warm the packs felt; these ratings served as manipulation checks for the social- and physical-warmth tasks, respectively. Additionally, responses to "how warm [participants felt] after reading these messages" and the extent to which they felt connected during each condition were collected. Finally, participants reported how pleasant each condition was (e.g., "how good did it feel to read the messages," as

an example from the social-warmth task). Ratings were made on a 7-point Likert scale ranging from 1, *not at all*, to 7, *very*.

Image acquisition. Data were acquired on a Siemens Trio 3T MRI scanner with foam padding surrounding the participants' head to restrict movement. For each participant, we acquired a high-resolution structural T2-weighted echo-planar imaging volume—spin-echo, repetition time (TR) = 5,000 ms, echo time (TE) = 34 ms, matrix size = 128 × 128, resolution = 1.6 × 1.6 × 3 mm, field of view (FOV) = 200 mm, 36 slices, 3-mm thick, flip angle = 90°, bandwidth = 1302 Hz/Px—that was coplanar with the functional scans. For the social-warmth task, two functional scans each lasting 7.5 min were acquired—gradient-echo, TR = 2,000 ms, TE = 30 ms, flip angle = 90°, matrix size = 64 × 64, resolution = 3.1 × 3.1 × 4.0 mm, FOV = 200 mm, 33 axial slices, 4-mm thick, flip angle = 90°, bandwidth = 2604 Hz/Px. Additionally, two pleasant-touch scans lasting 3 min and 45 s each, and one physical-warmth scan lasting 5.5 min, were acquired. Signal loss resulting from dropout in ventral frontal and subcortical regions was relatively low, with 62% and 100% signal acquired in these regions, respectively.

fMRI data analysis. Imaging data were analyzed using Statistical Parametric Mapping (SPM) software (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). For preprocessing, images for each subject were realigned to correct for head motion, normalized into a standard stereotactic space, and smoothed with an 8-mm Gaussian kernel, full width at half maximum (FWHM), to increase signal-to-noise ratio. The 12 s during which messages were on the screen for the social-warmth task and the 10-s stimulation period for the pleasant-touch and physical-warmth tasks were modeled as blocks. Rest periods during which participants viewed a fixation cross between blocks served as the implicit baseline. Linear contrasts for each experimental condition relative to its control condition (positive messages

compared with neutral messages, brush compared with dowel, and warm pack compared with ball) were computed for each participant. These individual contrast images were then used in group-level analyses. One participant was removed because of signal dropout, which left a final imaging sample of 19.

Group-level results were examined in two ways. First, activity to each of the three tasks was examined across the whole brain. Then, to examine shared neural activity to social and physical warmth, we tested both tasks (each condition relative to its control condition) against the conjunction null, which identifies neural regions that were active during both tasks. For regions showing overlapping neural activity, we then used the MarsBar Toolbox (Brett, Anton, Valabregue, & Poline, 2002) to extract parameter estimates from that functional region of interest (ROI) for each task separately (for display purposes). We also ran the conjunction between social warmth and pleasant touch and between physical warmth and pleasant touch.

Analyses were corrected for multiple comparisons using the 3DClustSim function in AFNI software (Medical College of Wisconsin, Milwaukee, WI), which uses a Monte Carlo simulation to determine the minimum cluster size necessary to maintain a false-discovery rate (FDR) of .05. Based on the parameters of this study (79 × 95 × 68 dimensions, 3.5 × 3.5 × 5 voxels, smoothing kernel of 8 mm FWHM; 10,000 iterations), results of 3DClustSim indicated a voxel-wise threshold of $p < .001$ combined with a minimum cluster size of 21, which corresponded with a corrected $p < .05$. This threshold ($p < .001$, 21 voxels) was used for all analyses. All coordinates are reported in Montreal Neurological Institute (MNI) format.

Results

Post-scan self-report

Consistent with the task manipulations, results revealed that participants felt more connected after reading the loving messages from close others ($M = 5.93$, $SD = 0.96$) than after reading the neutral messages ($M = 3.92$, $SD = 1.29$), $t(19) = 7.27$, $p < .01$). In addition, participants rated the warm pack as warmer ($M = 5.00$, $SD = 0.94$) than the ball ($M = 3.22$, $SD = 1.48$), $t(9) = 5.51$, $p < .01$.[2]

With regards to the more general measure of perceived pleasantness, the positive messages were experienced as more pleasant ($M = 6.15$, $SD = 0.92$) than the neutral messages ($M = 4.10$, $SD = 1.77$, $t(9) = 3.96$, $p < .01$), the warm pack as more pleasant ($M = 5.74$, $SD = 1.10$) than the ball ($M = 3.79$, $SD = 0.86$, $t(18) = 5.77$, $p < .01$), and the brushing as more pleasant ($M = 5.6$, $SD = 1.10$) than the dowel ($M = 2.89$, $SD = 1.15$, $t(18) = 7.65$, $p < .01$). However, when comparing across tasks (each condition relative to its control), we found that the pleasant-touch task (brushing vs. dowel) was rated the most pleasant ($M = 2.68$ $SD = 1.53$), followed by the social-warmth task (positive vs. neutral messages; $M = 2.05$, $SD = 1.64$) and the physical-warmth task (warm pack vs. the ball; $M = 1.95$, $SD = 1.47$). Indeed, the pleasant-touch task was rated as marginally more pleasant than the physical-warmth task ($t(17) = -1.86$, $p = .08$). There were no other differences in pleasantness across the conditions—social vs. physical warmth: $t(9) = 1.04$, $p = .33$; pleasant touch vs. social warmth: $t(9) = -1.80$, $p = .11$.

In line with the hypothesis that there is an interplay between social and physical warmth, results showed that reading the positive messages from close friends and family members led to increased feelings of warmth ($M = 6.14$, $SD = 0.71$) compared with reading the neutral messages ($M = 3.80$, $SD = 1.52$, $t(9) = 5.44$, $p < .01$, $d = 1.98$). Furthermore, simply holding the warm pack led to increased ratings of connection ($M = 2.42$, $SD = 1.39$) compared with holding the ball ($M = 1.63$, $SD = 1.17$, $t(18) = 3.34$, $p < .01$, $d = 0.78$). Brushing also led to marginal increases in

feelings of connection (M = 2.35, SD = 1.31) compared with the dowel (M = 1.95, SD = 1.31, $t(18) = 1.93$, $p = .07$).

When comparing across tasks (each condition relative to its control), we found that participants reported feeling significantly more "connected" during the social-warmth task (positive vs. neutral messages: M = 2.00, SD = 1.22) compared with the physical-warmth task (warm pack vs. ball: M = 0.79, SD = 1.03, $t(18) = 3.67$, $p < .01$), or the pleasant-touch task (brush vs. dowel: M = 0.47, SD = 1.07, $t(18) = 4.12$, $p < .01$). There were no differences in self-reported feelings of connection during the physical-warmth task compared with the pleasant-touch task ($t(17) = 0.95$, $p = .36$).

Imaging results

Neural activity to physical warmth. First, neural activity during exposure to warm compared with neutral stimuli was examined across the whole brain. Replicating previous work on the brain's response to warm stimuli, we found greater activity in the bilateral VS, left middle insula, and left anterior insula when participants were holding the warm pack compared with when they were holding the ball. There was also increased activity in the right posterior insula as well as in the primary and secondary somatosensory cortices, which is consistent with results of studies that involve cutaneous sensory stimuli, such as warmth (Becerra et al., 1999; Craig, 2003; Davis et al., 1998; Olausson et al., 2005; Rolls et al., 2008; Verhagen et al., 2004; see Table 1 for a full list of activations.)

Neural activity to social warmth. Next, we assessed activity to reading positive, loving messages from friends and family members compared with neutral messages. As expected, participants displayed extensive activity in the VS, the anterior and middle insula, the pACC, and the ventral tegmental area to reading the positive messages (vs. neutral messages). There was

also increased activity in several neural regions previously associated with mentalizing (dorsomedial prefrontal cortex, temporal pole, precuneus) as well as increased activity in septohypothalamic regions previously implicated in affiliative responding (Moll et al., 2012; see Table 2 for a full list of activations).

Neural activity to pleasant touch. Neural activity to pleasant as opposed to neutral touch did not lead to increased activity in the VS. Instead, brushing (vs. the dowel) led to increased activity in the right posterior insula ($x = 38$, $y = -18$, $z = 22$, $t(18) = 5.51$), and primary and secondary somatosensory cortices, a finding that replicated prior work on pleasant touch (Olausson et al., 2002; see Table 3 for a full list of activations).

Shared neural activity across tasks. To assess shared neural regions associated with processing social and physical warmth, we ran a conjunction analysis between neural activity during exposure to positive messages (vs. neutral messages) and neural activity during exposure to warm stimuli (vs. the ball). The conjunction analysis revealed shared neural activity in the left VS ($x = -16$, $y = 0$, $z = -8$, $t(18) = 4.78$, $k = 84$), and left middle insula ($x = -38$, $y = 4$, $z = -16$, $t(18) = 4.58$, $k = 21$), during the social and physical-warmth tasks, in which participants read positive (vs. neutral) messages and held the warm pack (vs. the ball), respectively (Fig. 1). It is important to note that there was no overlapping neural activity during the social-warmth and pleasant-touch tasks, which suggests that the shared neural responses to physical and social warmth may not be solely due to increases in perceived pleasantness. Finally, the conjunction between activity during physical warmth and pleasant touch (brush vs. dowel) revealed activity in the left posterior insula ($x = 42$, $y = -16$, $z = 18$, $t = 4.75$, $k = 216$), extending into the secondary somatosensory cortex ($x = 58$, $y = -18$, $z = 24$, $t = 4.51$).

Discussion

The relationship between social and physical warmth has received increasing empirical attention; however, the neural mechanisms underlying both forms of warmth have not been examined together. The present study adds to previous work from the embodied-cognition literature by showing that self-reported feelings of warmth increased following a social-warmth induction and feelings of connection increased after participants simply held a warm object. Furthermore, in support of the theory that social warmth is built on basic mechanisms involved in temperature perception and regulation, physical and social warmth displayed overlapping neural mechanisms in the middle insula and VS, regions associated with processing warmth and with highly rewarding outcomes. Indeed, these findings are consistent with research showing that physical warmth is processed interoceptively (as opposed to cutaneous touch, which is processed exteroceptively; Craig, 2002), and thus, whereas warmth may seem like a more external, sensory stimulus, it is actually more closely linked with internal motivational and affective states. Together, these results suggest a potential mechanism by which social warmth, the contented subjective experience of feeling loved by and connected to other people, has become such a pleasant experience and lends credence to the description of connection experiences as "heartwarming."

An interesting finding was that social warmth did not show any overlapping activity with a task involving pleasant physical touch. This suggests that the shared activity to social and physical warmth in this study was not solely due to increases in positive affect. In other words, even though the pleasant-touch task (relative to its control task) was rated the most pleasant, only neural activity during physical warmth showed a similar pattern as social warmth. This is not to say that physical touch does not play a role in feelings of social connection. In fact, physical affection in the form of sensual or affiliative touch between close others is likely a major part of

feeling close and connected. Future work exploring neural activity to touch from a close other as opposed to an inanimate object held by an experimenter (as in this study) may further elucidate the role of physical touch in the experience of social connection and add to existing work using interpersonal touch (Coan, Schaefer, & Davidson, 2006; Inagaki & Eisenberger, 2011).

These results may have implications for the beneficial effects of physical warmth on social relationships. Indeed, even small manipulations that increase physical warmth have been shown to bolster social bonds. After holding warm objects, participants reported feeling closer to other people (Ijzerman & Semin, 2009), increased their trusting behavior (Kang et al., 2011), and in the current study, felt more socially connected. Furthermore, participants both inside and outside of the lab appear to seek out physical warmth following social rejection (Bargh & Shalev, 2012; Zhong & Leonardelli, 2008). Given the importance of social connections for general well-being and happiness, the present results may inform larger interventions designed to combat feelings of isolation or loneliness through temperature manipulations.

In the present study, the insula and VS, regions known to have a high density of μ-opioid receptors (Cross, Hille, & Slater, 1987; Jones et al., 1999; Zubieta et al., 2001) were the only regions to show activity to both social and physical warmth. Although not explicitly tested here, μ-opioids may contribute to the shared neural circuitry underlying physical and social warmth (Handler, Geller, & Adler, 1992; Panksepp, 1998). With regard to physical warmth, μ-opioids have been shown to play a role in temperature regulation, such that μ-opioid agonists (e.g., morphine, heroin) can increase body temperature (Clark, Murphy, Lipton, & Clark, 1983) and μ-opioid antagonists can decrease body temperature (Handler et al., 1992; Spencer, Hruby, & Burks, 1988). In addition, animal research has highlighted a role for μ-opioids in the social-bonding processes that may underlie feelings of social warmth. Thus, morphine, a μ-opioid

agonist, can reduce crying to social separation and speed the comfort response, characterized by a relaxing of the body when being held by an experimenter. Conversely, naloxone, an opioid antagonist, increases crying behavior when chicks are in a group and delays the comfort response to being held by an experimenter when separated from the group, which suggests that the chicks are no longer feeling a sense of comfort from their social experiences (Panksepp, Bean, Bishop, Vilberg, & Sahley, 1980). An interesting direction for future studies will be to incorporate pharmacological interventions of the μ-opioid system with self-reports on subjective experiences of social connection to present a clearer picture of how exactly opioids contribute to feelings of social warmth from positive social experiences.

In sum, the current study elucidates a shared neural mechanism by which the brain processes pleasant, warm stimuli and the feelings associated with connecting with close others, or social warmth. Furthermore, these results highlight one way by which social integration is critical to survival and further the study of the feelings associated with social connection.

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Footnotes

1. This task also included a condition in which participants held cold packs. However, in an effort to keep the control conditions similar across tasks, we focused on the neutral condition for the comparison, and thus results from the cold-pack condition are not included here.

2. For some items, data were obtained only from a small subset of the sample (n = 10) because a scale was missing in the first several participants' questionnaire packets. Thus, these behavioral results should be interpreted with caution.

Table 1.

Brain Regions More Active When Participants Held a Warm Pack Compared With a Neutral Object

Anatomical region	Hemisphere	Brodmann's area	MNI coordinates			*t*(18)	*k*
			x	*y*	*z*		
Ventral striatum	Left	—	–16	4	–4	5.81	321
Ventral striatum	Right	—	16	4	–6	4.97	30
Anterior insula	Left	—	–26	24	–8	4.83	53
Middle insula	Left	—	–40	2	–12	4.85	37
Posterior insula	Right	—	40	–16	16	5.83	377
Secondary somatosensory cortex	Right	40	46	–22	22	4.59	—
Primary somatosensory cortex	Right	2	58	–18	24	5.13	—
Primary somatosensory cortex	Right	2	48	–24	56	4.87	186
Inferior parietal lobule	Left	40	–58	–26	28	4.78	33
Dorsomedial prefrontal cortex	Left	8	–8	44	50	4.26	34

Note: All activations were significant at $p < .001$, 21 voxels. Statistics in the *t* column show values at peak coordinates. Cluster voxel extent is represented by *k*; an activation that does not include a *k* value extends from the larger cluster listed above that activation. MNI = Montreal Neurological Institute.

Table 2.

Brain Regions More Active When Participants Read Positive Messages From Loved Ones Compared With Neutral Messages From Loved Ones

Anatomical region	Hemisphere	Brodmann's area	MNI coordinates			*t*(18)	*k*
			x	*y*	*z*		
Brainstem/periaqueductal gray	Left	—	–4	–26	–20	7.24	1,097
Ventral tegmental area	Right	—	8	–12	–20	4.78	—
Ventral tegmental area	Left	—	–8	–16	–18	4.64	—
Substantia nigra	Left	—	–10	–22	–8	3.77	—
Septal area		—	0	4	–2	6.09	—
Hypothalamus	Left	—	–4	–10	0	4.53	—
Ventral striatum	Left	—	–12	2	–4	4.56	—
Ventral striatum	Right	—	4	6	–2	6.04	—
Anterior/middle insula	Left	—	–38	8	–12	5.35	178
Middle temporal gyrus	Right	21	54	0	–10	6.39	346
Anterior/middle insula	Right	—	44	16	–8	4.44	—
Pregenual cingulate cortex	Left	—	–2	40	10	7.41	770
Pregenual cingulate cortex	Right	32	10	30	–4	5.20	59
Dorsomedial prefrontal cortex	Right	10	6	58	20	7.06	—
Corpus callosum	Right	—	14	10	24	6.70	52
Dorsal anterior cingulate cortex	Right	32	8	26	28	5.92	100
Midcingulate cortex	Left	31	–6	–16	46	5.09	21
Temporal pole	Left	38	–52	12	–22	5.58	190
Temporal pole	Right	28	28	6	–20	6.61	145
Superior temporal gyrus	Left	22	–56	–38	8	5.44	103
Precuneus	Left	7	–18	–60	54	4.46	24
Caudate	Left	—	–12	18	14	5.72	63
Cerebellum	Left	—	–2	–50	–36	4.83	119
Cerebellum	Left	—	0	–76	–26	4.29	21
Premotor cortex	Left	6	–48	–2	56	5.48	89
Premotor cortex	Left	6	–18	–4	76	4.36	21
Inferior frontal gyrus	Left	45	–42	28	2	5.46	74
Hippocampus	Right	—	22	–26	–6	4.67	84
Occipital cortex	Left/Right	17/18/19	–24	–96	24	8.28	4,546

Note: All activations were significant at $p < .001$, 21 voxels. Statistics in the *t* column show values at peak coordinates. Cluster voxel extent is represented by *k*; an activation that does not

include a *k* value extends from the larger cluster listed above that activation. MNI = Montreal Neurological Institute.

Table 3.

Brain Regions More Active When Participants Were Brushed Compared With Touched With a Dowel

Anatomical region	Hemisphere	Brodmann's area	MNI coordinates			*t*(18)	*k*
			x	*y*	*z*		
Primary somatosensory cortex	Right	2	30	–38	64	8.37	501
Primary somatosensory cortex	Left	1/2/3	–56	–24	36	7.86	808
Inferior parietal lobule	Right	40	58	–34	24	5.86	662
Secondary somatosensory cortex	Right	40	44	–24	24	5.61	—
Posterior insula	Right	—	38	–18	22	5.51	—
Premotor cortex	Left	6	–62	4	30	5.61	79
Motor cortex	Left	4	–32	–12	56	5.86	662
Motor cortex	Right	4	38	–6	60	4.44	35

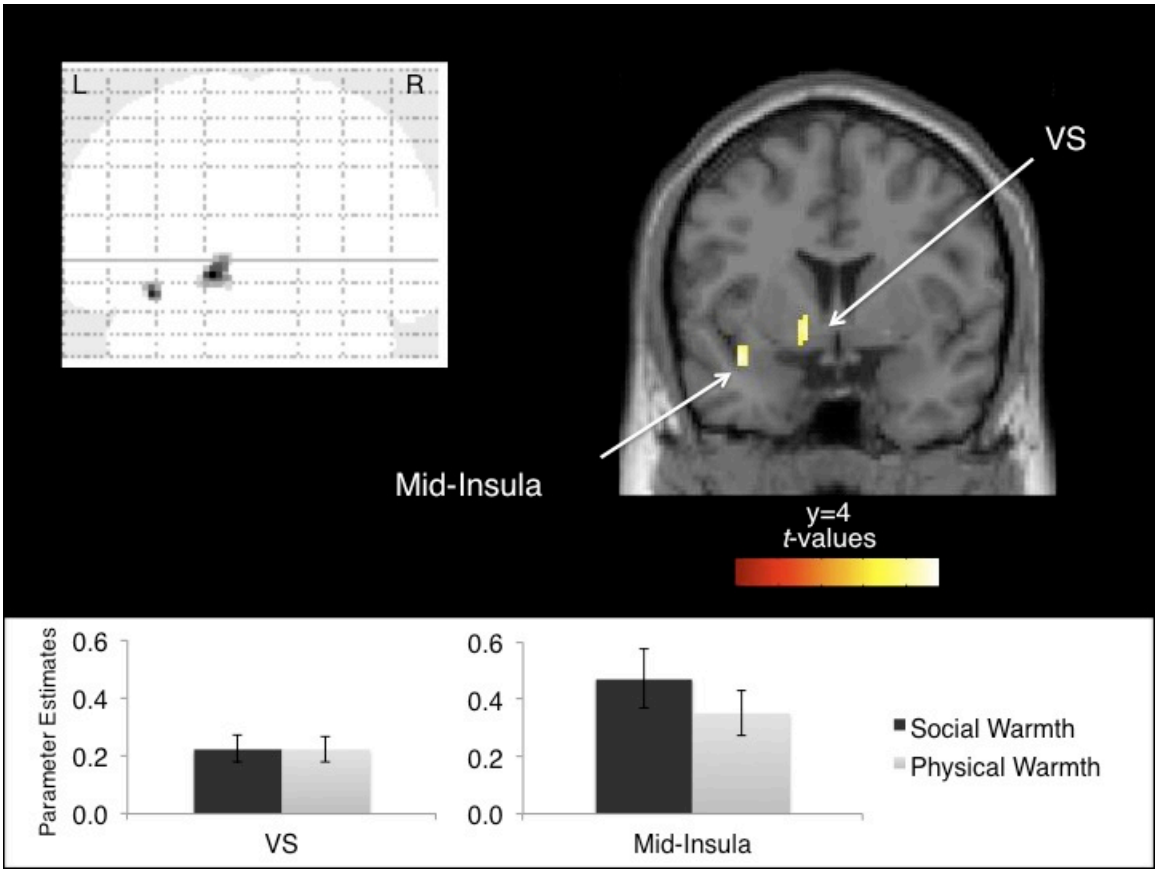
Note: All activations significant at $p < .001$, 21 voxels. Statistics in the *t* column show values at peak coordinates. Cluster voxel extent is represented by *k*. An activation that does not include a *k* value extends from the larger cluster listed above that activation. MNI = Montreal Neurological Institute.

Figure Caption

Figure 1.

Results for the conjunction between social warmth (positive messages as opposed to neutral messages) and physical warmth (warm pack as opposed to ball). The glass brain and coronal slice show activations in the left ventral striatum and left middle insula for this conjunction. The graphs show parameter estimates from these functional regions of interest (ROIs) during the social-warmth and physical-warmth tasks. L = left, R = right.

Figure 1.


L
R
VS
Mid-Insula
y=4
t-values
Parameter Estimates
0.6
0.4
0.2
0.0
VS
Mid-Insula
Social Warmth
Physical Warmth

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Paper 2:

Opioids and social bonding:
The effect of naltrexone on feelings of social connection

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Abstract

Close social bonds are critical to a happy and fulfilled life and yet, little is known about the neurochemical mechanisms that keep individuals feeling close and connected to one another. According to the brain opioid theory of social attachment, opioids may underlie the contented feelings associated with social connection and may be critical to continued bonding. However, the role of opioids in feelings of connection toward close others has not yet been examined in humans. To examine this, 31 volunteers participated in a double-blind placebo controlled crossover study with the opioid antagonist, naltrexone. Participants came to the lab once on naltrexone and once on placebo to complete a task designed to elicit feelings of social connection and also completed daily diary reports while on naltrexone and placebo. In line with hypotheses, and for the first time in humans, naltrexone (vs. placebo) significantly reduced feelings of connection both in the lab and in the real-world. These results highlight the importance of opioids for social bonding with close others, lending support to the brain opioid theory of social attachment.

Having and maintaining close social bonds is so fundamental to health, well-being, and normal functioning that bonding has been referred to as a basic need, much like the need for food and water (Baumeister & Leary, 1995). In fact, being deprived of care and support early in life results in severe cognitive, social, developmental, and health consequences throughout development (Bowlby, 1988; Gunnar, 2001; House, Landis, & Umberson, 1988; Holt-Lundstad, Smith, & Layton, 2010; Tottenham & Sheridan, 2010). However, although humans require close social bonds to survive and thrive (Bowlby, 1988; Taylor, 2010; Uchino, 2004) few have explored the experience of social connection—the positive, contented feelings associated with being close to others—or how individuals come to feel connected to those they love the most. Furthermore, little is known about the neurochemical mechanisms that help support social bonds, especially in humans.

According to the brain opioid theory of social attachment, endogenous opioids, specifically μ-opioids, are thought to mediate the pleasant feelings stemming from social bonding and affiliation (Panksepp, 1998). Opioids are neurochemicals, known for their association with feelings of euphoria and reward and specifically, with the 'liking,' or the contented, satisfied, side of reward as opposed to the 'wanting,' or motivation to approach rewards (Berridge & Kringelbach, 2008; Berridge, Robinson, & Aldridge, 2009; Depue & Morrone-Strupinsky, 2005). In the context of close social bonds, opioids are thought to underlie the pleasurable satisfaction felt from achieving social connection. However, although data from animal studies support the theory that opioids are involved in social bonding, this has not yet been experimentally examined in humans.

In animals, blocking opioid activity via an opioid antagonist leads to increased crying when animals are placed together in a group suggesting that the animals are no longer

experiencing the comfort or pleasure from being in the group (Panksepp, Bean, Bishop, Vilberg, & Sahley, 1980). Conversely, morphine, an opioid agonist, decreases crying after social separation. Here, exogenous opioid administration may be replacing the pleasure of being in a group. In a similar vein, placebo-treated baby lambs show a clear preference for their own mothers (vs. an unknown mother) after birth, whereas naltrexone, an opioid antagonist, eliminates the preference for the mother (Shayit, Nowak, Keller, & Weller, 2003). Finally, μ-opioid receptor knockout mice (vs. controls) show no preference for bedding with their mother's scent, again suggesting that the knockout mice no longer find the mother a source of comfort or derive as much pleasure from cues of her presence (Moles, Kieffer, D'Amato, 2004). Although not tested yet, it is possible that opioids play a similar role in human bonding relationships as in these animal relationships.

In humans, most data relevant to the rewarding effects of opioids come from studies on highly pleasing nonsocial rewards such as drugs, alcohol, and sugary food. Thus, μ-agonists such as heroin and morphine can elicit increases in euphoria, drug liking, pleasant body sensations, and thoughts and feelings of being carefree and sedated in non-addicted, healthy individuals (Becerra, Harter, Gonzalez, & Borsook, 2006; Casey, Svensson, Morrow, Raz, Jones, & Minoshima, 2000; Seecof & Tennant, 1986; Tress & El-Sobky, 1977; Zacny, 2001). Conversely, antagonists such as naltrexone competitively bind to μ-receptors to reduce the pleasure experienced from μ-agonists and other substances of abuse such as alcohol (Gold et al., 1982; Ray & Hutchison, 2007).

Only a handful of studies have explored the effects of opioids on perceptions of social rewards and social attachment experiences in humans. With regard to the effect of opioids on social rewards, morphine (vs. naltrexone) leads to higher attractiveness ratings for the most

attractive faces presented, suggesting that opioids can enhance 'liking' toward certain stimuli (Chelnokova et al., 2014). However, in a different study naloxone, another opioid-antagonist, failed to reduce ratings of pleasure to images of sport scenes and erotica (Kut, Candia, von Overbeck, Pok, Fink, & Folkers, 2011). Interestingly, only one study (reported in Depue & Morrone-Strupinsky, 2005 but not published on its own) has examined the role of opioids in social attachment processes. Here, female participants were administered either naltrexone or placebo and were then asked to rate their feelings of connection in response to watching two separate movie clips: an affiliative movie clip of a couple giving birth to their first child and a neutral film clip of a nature scene (Depue & Morrone-Strupinsky, 2005). As hypothesized, watching the affiliative clip (compared to the neutral clip) led to increases in feelings of connection for those high in trait affiliation (but not for those low in trait affiliation). However, in line with the brain opioid theory of social attachment, naltrexone erased the increases in warm, affectionate feelings to watching the affiliative movie clip for these individuals.

Though not directly manipulating opioids, neuroimaging findings on close social bonds show that opioid-rich neural regions activate to cues of close others. Thus, reading loving messages (vs. neutral messages) from close friends and family members activates the ventral striatum (VS), ventral tegmental area (VTA), pregenual (pACC) and dorsal anterior cingulate cortex (dACC); orbitofrontal cortex (OFC), and insula, all regions known to be high in μ-opioid receptors (Cross, Hille, & Slater, 1987; Inagaki & Eisenberger, 2013; Jones et al., 1999; Panskepp & Bishop, 1981; Vanderschuren, Stein, Wiegant, & Van Ree, 1995; Willoch et al., 1999; Wise & Herkenham, 1982; Zubieta et al., 2001). Similarly, the VS, OFC, and VTA are more active when viewing images of close others (vs. strangers or acquaintances) such as one's

own baby or romantic partner (Acevedo, Aron, Fisher, & Brown, 2012; Bartels & Zeki, 2004; Strathearn, Li, Fonagy, & Montague, 2008).

Together, emerging evidence from humans and animals point to the possibility that μ-opioids contribute to the experience of bonding and connecting with those we love the most, but this has not yet been explored in humans. As such, the current study aimed to test the brain opioid theory of social attachment in a double-blind placebo-controlled crossover study with the opioid-antagonist, naltrexone. We hypothesized that naltrexone, compared to placebo, would lead to reduced feelings of connection both in the laboratory as well as in the real-world.

Method

Participants

After screening 50 potential participants, 37 individuals were enrolled in the study. Out of this sample, 2 participants were removed after being unresponsive to scheduling requests, 1 participant asked to be removed from the study prior to the first session, and 3 participants (all females) reported physical symptoms at a severe level after the first day of the study drug and were removed by the study physician. The final sample to complete the entire experimental protocol included 31 participants (21 females, *M age* = 21.55, *SD* = 3.34) with 38.7% Caucasian, 35.5% Asian, 12.9% Hispanic, 6.5% African American, and 6.5% reporting Mixed Ethnicity. Participants were paid up to $160 as compensation for taking part in the study. The protocol was approved and run in accordance with UCLA's Institutional Review Board.

Screening and Experimental Procedures

Interested volunteers were initially screened via phone and email to assess general physical and mental health, drug and medication use, difficulty taking or swallowing pills, and allergies to medications. Additionally, participants reported on their willingness to provide

contact information for 6-8 close friends and family members (for the social connection task described below).

Following initial screening, participants completed a physical examination at UCLA's Clinical and Translational Science Institute (CTSI). Under the oversight of the study physician, a study nurse obtained vitals signs (heart rate, blood pressure, height and weight) and drew blood to test for liver functioning and pregnancy, if female. Next, the experimenter collected a urine sample to test for drug use (THC, Opiates, Cocaine, AMP, mAMP), and administered the Patient Health Questionnaire (PHQ-9; Spitzer, Kroenke, Williams, 1999) to assess self-reported symptoms of depression.

To be included in the study, participants needed to be in good health, between the ages of 18 and 35, and fluent in English. Exclusion criteria were any major self-reported physical health or psychiatric disorders, medications including opiates, and pregnancy, if female. Additionally, participants who tested positive on the urine drug test, had a BMI greater than 35, showed clinically-relevant abnormalities on the screening blood tests, or reported a PHQ-9 score above 13 were excluded.

Eligible participants were then scheduled for a baseline session followed by two experimental sessions: one while on naltrexone and one while on placebo. During the baseline session, participants received instructions for taking the study drugs and for completing the daily diary component of the study. They then completed demographics and personality measures (not examined here). For all but 1 session for 1 participant (who was run in the morning), experimental sessions were held in the afternoon (between 1:00pm and 4:00pm) to control for natural diurnal variations in cortisol, which has a well-known inverse-relationship with opioids (Naber et al., 1981). Approximately one hour after taking the study drug, when naltrexone shows

peak effects (Lee, Wagner, Tanada, Frost, Bice, & Dannals, 1988; Ray, Chin, & Miotto, 2010*),* participants completed the social connection task in the laboratory.

Study Drug Schedule

Drugs were administered in a double-blind within-subjects crossover design. Based on a previously established titration schedule (Bujarski, MacKillop, & Ray, 2012; Ray, Bujarski, Chin, & Miotto, 2011), participants took 4 doses of naltrexone, titrating the dose up slowly over 4 days (25 mg for days 1 and 2 and 50mg for days 3 and 4) as well as 4 matched placebo pills on a separate 4 days. Relevant to the importance of μ-receptors for social bonding, naltrexone has previously been shown to have a high affinity for μ-receptors (Lee et al.,1988; Weerts et al., 2008) and to reduce the subjective liking of alcohol (McCaul, Wand, Eissenberg, Rohde, & Cheskin, 2000). Each participant began taking their study drugs 3 days prior to the scheduled experimental session and took the fourth pill in the presence of the experimenter during their experimental session. Drug compliance was assessed by packing the study drugs with 50mg of riboflavin. Urine samples were then collected at each experimental session and analyzed for riboflavin content using a UV light. All samples tested positive for riboflavin suggesting that all participants were compliant with the study drug schedule. In between each experimental session there was 10-day washout period.

Naltrexone was provided and dispensed by UCLA's Investigational Drug Section. The trial was registered on the U. S. National Institutes of Health Clinical Trials registry as NCT01672723.

Lab tasks

A description of how the social connection task was constructed has been explained previously (Inagaki & Eisenberger, 2013) but is summarized here. Prior to the experimental

sessions, experimenters emailed 6-8 close friends and family members (parents, grandparents, siblings, significant others, friends) for each participant to request assistance with the social connection task. Friends and family were asked to respond with 12 brief sentences, 6 positive, loving messages and 6 neutral messages or facts. Neutral messages were collected to create a neutral condition to control for any feelings of connection due simply to reading messages from close others. Examples of positive messages received from actual friends and family include "You have enriched my days and given me great joy," "Thank you for loving me at my worst," "You're my number one," "I am so grateful to have you in my life and I completely don't deserve you. You're a gift!" Sample neutral messages were "You have a younger sister," "You play basketball, "You are a female."

Once in the lab, participants then read the positive and neutral messages from friends and family members. Messages were presented in blocks of 6 messages (either all positive or all neutral) beginning with a 2-second cue explaining who the messages were from, followed by the 6 messages, one at a time, for 6-seconds each. After each set of messages, participants rated how connected (connected, touched, and warm, α *placebo positive messages* = .90, α *placebo neutral messages* = .94, α *naltrexone positive messages* = .95, α *naltrexone positive messages* = .95) they felt while reading the messages. Ratings were made on a 1-7 scale anchored by "not at all" and "very." To reduce habituation effects to this social connection task, messages from 3 of the participants' close friends and family members were presented during the first experimental session and the remaining messages from a different 2-3 close others during the second experimental session.

Daily Diary

In addition to the experimental sessions, participants completed a daily diary component of the study in order to assess feelings of connection in the real-world. For 8 days (4 while on placebo, 4 while on naltrexone), participants were asked to think back to the last 24 hours and respond to how disconnected ("I felt out of touch and disconnected from others") they felt. Feelings of disconnection were reverse-coded to measure daily feelings of social connection.

In addition to feelings of social connection, participants reported on the severity of the following physical symptoms (5 point scale ranging from 1-no symptoms to 5-very severe symptoms) for each day they were taking study drugs: headache, dizziness/faintness, shortness of breath, rapid/irregular heartbeat, stomach/abdominal discomfort, nausea, appetite increase/decrease, difficulty urinating, muscle/bone/joint pain, fever, tiredness/fatigue. To further assess the subjective severity of the symptoms overall, participants were asked how distressing they found the reported symptoms on a 0=not at all to 7=very scale.

Statistical Analyses

In order to assess changes in feelings of connection to the lab task, data was submitted to a 2 (drug: placebo vs. naltrexone) x 2 (valence: neutral vs. positive messages from friends and family) x 2 (order: placebo first vs. naltrexone first) x 2 (gender: male vs. female) repeated measures analysis of variance (ANOVA) in SPSS.

Daily diary data was analyzed with a 2 (drug: placebo vs. naltrexone) x 2 (dose: 25mg vs. 50mg) x 2 (order: placebo first vs. naltrexone first) x 2 (gender: male vs. female) repeated measures ANOVA. Dosage was included as an additional variable because previous work has shown that the 50mg dose of naltrexone (compared to baseline without naltrexone) completely blocks μ-opioid receptor binding in the regions previously shown to activate to the social connection task used in the current study (including the VS, ACC, OFC, and insula; Weerts et

al., 2008). However, there is no published data on receptor binding for the 25mg dose and it is possible that μ-opioid receptors are not completely blocked at this lower dose. There were no interactions with order or gender and so these variables were dropped when evaluating real-world feelings of connection.

Results

When evaluating the reliability of the study drug blind, 61% of participants guessed correctly when on placebo and 55% guessed correctly when on naltrexone. These percentages were not significantly greater than chance (50%) for either placebo (χ^2 (1) = .35, p = .55) or naltrexone (χ^2 (1) = .14, p = .71). Physical symptoms reported at the end of each day when on the study medication revealed increases in reported headaches, dizziness/faintness, nausea, and appetite increase/decrease when on naltrexone compared to placebo (p's < .05) with nausea as the most commonly reported symptom. However, there were no differences in how distressing participants found the symptoms when on naltrexone (M = 1.87, SD = 1.07) compared to placebo (M = 1.55, SD = .84, $t(20^1)$ = .88, p = .39) and overall, levels of distress about the symptoms were low (ratings between 1 and 2 on a 1-7 scale).

Replicating our previous study (Inagaki & Eisenberger, 2013) and again validating the ability of the social connection lab task to induce feelings of connection, participants reported greater feelings of connection to the positive (M = 6.47, SD = .53) than the neutral messages (M = 4.57, SD = 1.24, $F(1, 30)$ = 95.84, p < .001).

Effect of naltrexone on feelings of connection in the lab

To assess whether naltrexone altered feelings of connection in the lab, participant ratings to the social connection task were submitted to a 2 (drug) x 2 (valence: neutral vs. positive messages) x 2 (order: placebo first vs. naltrexone first) x 2 (gender) repeated measures ANOVA.

This analysis revealed significant interactions between drug and gender and drug and order and so order was entered as a covariate while keeping gender as a between-subjects variable. There was not an interaction between drug and valence ($F(1, 27) = .36$, $p = .55$), however, dividing the messages to look only at the neutral messages (the control condition) suggested that these messages were not serving as a uniform control condition across both conditions and genders. Hence, there was an interaction between drug and gender ($F(1, 29) = 5.77$, $p = .02$) such that the males reported greater feelings of connection on naltrexone (*M naltrexone* = 5.02, *SD naltrexone* = 1.27) compared to placebo (*M placebo* = 4.19, *SD placebo* = 1.50, $F(1, 9) = 7.76$, $p = .02$) and females showed no difference depending on drug ($F(1, 20) = .42$, $p = .53$). Given that the neutral messages were not consistently acting as a control condition for both the males and the females on both naltrexone and placebo, further analyses focused specifically on feelings of connection to the positive messages on their own (instead of comparing them to a non-uniform control condition).

No interaction with gender was found when evaluating feelings of connection to the positive messages and so this variable was dropped, however there was a drug x order interaction ($F(1, 29) = 9.91$, $p = .004$) and so order was controlled for when examining the effect of naltrexone on feelings of connection to the positive messages.

Confirming the hypothesis that opioids are important to feelings of connection with close others, naltrexone (vs. placebo) reduced feelings of connection to reading the positive messages ($F(1, 29) = 6.90$, $p = .01$, Fig. 1).

Effect of naltrexone on real-world feelings of connection

Turning to real-world feelings of social connection, there was a significant drug x dose interaction ($F(1, 24) = 4.87$, $p = .04$). In support of the main study hypothesis, participants

reported feeling less socially connected on the full 50mg dose of naltrexone ($F(1, 25^2) = 6.56$, $p = .02$, Fig. 2) compared to comparable days of placebo, but no changes in connection for the 25mg dose ($F(1, 29) = .69$, $p = .41$).

Discussion

As humans, we highly value and depend on close social bonds throughout life. Even so, relatively little is known about the neurobiological mechanisms that help support the experience of social connection. In support of the brain opioid theory of social attachment, the opioid antagonist, naltrexone, was found to reduce feelings of social connection in the lab and, for the first time, in the real world suggesting that opioids are a critical component of social bonding. This is the first study to highlight the importance of opioids to social connection with close others in humans.

It is unclear why naltrexone (vs. placebo) led the males in this study to report increased feelings of connection to reading neutral messages from their close others. Given the relatively small sample size of the males in this study (n = 9) we are cautious not to over interpret the significance of gender when it comes to the effect of naltrexone on responses to neutral messages, particularly because naltrexone reduced feelings of connection for both males and females to the positive messages from close others and during the real-world assessments. Interestingly, μ-opioid receptor density appears greater in women than men (including the amygdala and caudate; Zubieta, Dannals, & Frost, 1999). However, as no previous studies have assessed the response of opioid-blockade to social bonding in both males and females in humans (the sample in Depue & Morrone-Strupinsky, 2005 was all female), more research is needed before we can make any strong conclusions about the drug by gender interaction to neutral messages in the current study.

There is emerging evidence that sensitivity to rewarding stimuli such as opiates or other drugs of abuse varies depending on a polymorphism in the μ-opioid receptor gene (OPRM1) (Bond et al., 1998; Dlugos et al., 2011; Drakenberg et al., 2006; Matthes et al., 1996; Ray & Hutchison, 2004). In particular, G allele carriers are more sensitive to β-endorphins (Bond et al., 1998), the rewarding effects of alcohol (Ray & Hutchinson, 2004), and the reward-blunting effects of naltrexone (Ray & Hutchinson, 2007). G allele carriers also appear more sensitive to social situations. For instance, G allele carriers report an increased need for affiliation, as measured by lower levels of avoidant attachment, and increased pleasure in social situations relative to those with the A allele (Troisi et al., 2011). Similarly, carrying the G allele (vs. the A allele) relates to increased rejection sensitivity and increased neural activity to an experience of social pain (Way, Taylor, & Eisenberger, 2009). To the extent that genetic variation confers sensitivity to social reward and pain more generally, allelic variation in OPRM1 may also contribute to the effects of opioid-blockade on feelings of social connection as measured here.

Of note is the relevance of other commonly studied hormones and neurochemicals relevant to social bonding. In particular, dopamine, oxytocin, prolactin, and serotonin all interact with and contribute to the actions of opioids (Bodnar, 2010; Depue & Morrone-Strupinsky, 2005; Keverne, 1988; Panksepp, 1998; Uvnas-Moberg, 1997) and may collectively interact to regulate feelings of social connection and social bonding, but are beyond the scope of the current study.

Naltrexone's ability to reduce feelings of social connection may have implications for the use of this drug in addicted populations. Originally developed and prescribed to help treat opioid dependence and alcoholism (Anton, Moak, Waid, Latham, Malcolm, & Dias, 1999; Martin, Jasinski, & Mansky, 1973), the current results suggest that an unintended side effect of

naltrexone treatment may be reduced feelings of connection with others. Social support is especially important during times of need (Cohen & Wills, 1985; House et al., 1988), such as when struggling with an addiction, and as such, any negative changes to how one perceives their network may introduce unintended barriers to recovery. Reduced feelings of connection may also partially contribute to why long-term compliance with naltrexone is somewhat low (Cramer, Rosenheck, Kirk, Krol, & Krystal, 2003; Ray et al., 2010). Of course, in some cases, problems with social bonding or social connection may precede and follow addiction, however, moving forward it is worth understanding how naltrexone may affect feelings of social connection in addicted populations as well as healthy individuals, as studied here.

Humans have the capacity to form and maintain deeply emotional and meaningful bonds with others. Critical to these bonds are feelings of connection, the positive, contented feelings that come from being close to others, that have previously been hypothesized to involve the endogenous opioid system. In a direct test of this hypothesis, the current study found that naltrexone (vs. a placebo) reduced feelings of connection both in the lab and in the real-world. Results help push the understanding of social bonding and connection forward.

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Footnotes

1. How distressing participants found their daily symptoms was added partway into the study and obtained from the final 21 participants.

2. 6 participants failed to complete daily diary responses for both days when on 25mg of naltrexone (1 participant), both days when on 50mg of naltrexone (3 participants), or comparable days when on placebo (2 participants).

Figure Captions

Figure 1.

Effect of drug on feelings of connection to reading positive messages from friends and family, controlling for order. Naltrexone (vs. placebo) led to reduced feelings of connection to reading the messages. Error bars reflect between-subject standard errors and therefore should not be directly compared to each other because the current study used a within-subjects design.

Figure 2.

Changes in feelings of connection outside of the lab in the real world. Feelings of disconnection were reverse-coded such that higher numbers reflect more feelings of connection and lower numbers reflect less feelings of connection. Naltrexone (vs. placebo) led to reduced feelings of connection when participants were on the 50mg dose. Error bars reflect between-subject standard errors.

Figure 1.

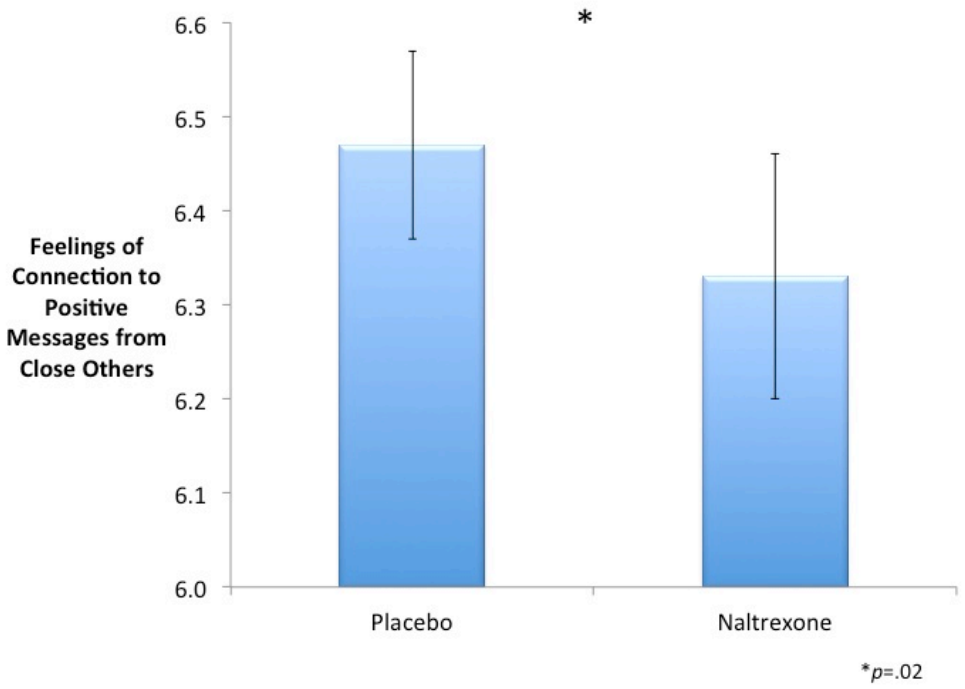
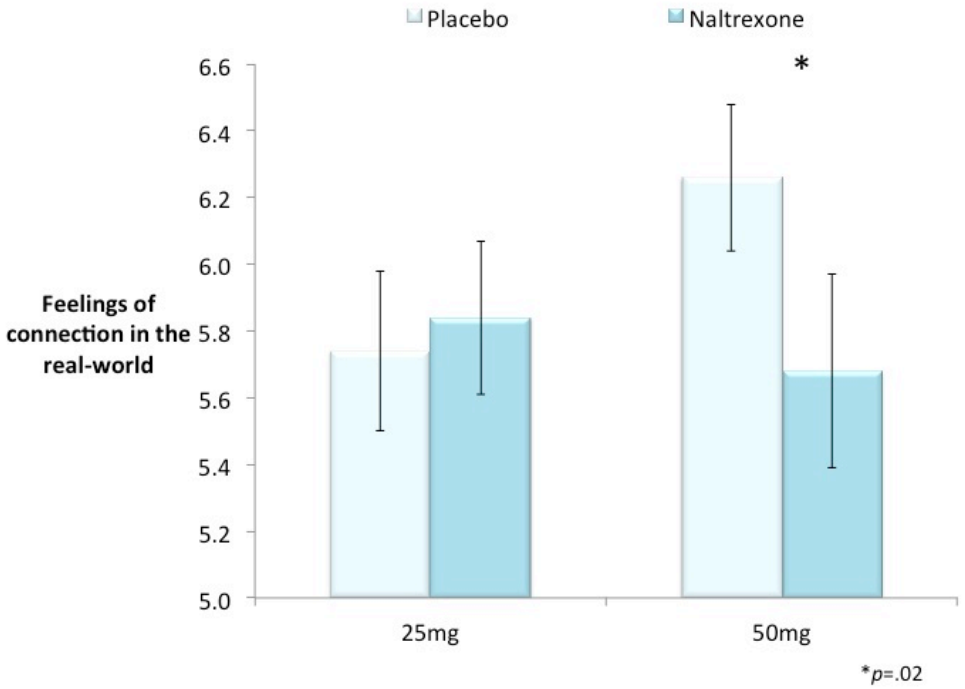


Figure 2.



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Paper 3:

Naltrexone reduces warmth-induced feelings of social connection

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Abstract

"Heartwarming" social experiences, when one feels interpersonally connected to others, have recently been linked with actual physical warmth. According to one theory (Panksepp, 1998), "social warmth" and physical warmth may be closely linked because both experiences are supported by similar neurobiological mechanisms, however, the neurochemical substrates underlying this overlap are unexplored. In this study, an opioid antagonist, naltrexone, was administered in order to examine the role of opioids, previously shown to alter temperature and social bonding, on perceived thermal intensity and feelings of connection from physical warmth. 31 participants took both naltrexone and placebo and completed a temperature manipulation task (held a warm pack, cold pack, and neutral object) while on each drug. Replicating previous work, feelings of connection were significantly increased after participants held a warm (vs. neutral) object. In addition, there was a drug effect on feelings of connection such that feelings of connection to holding a warm pack (vs. a neutral object) were reduced when participants were on naltrexone compared to placebo. No such drug effects were found for ratings of thermal intensity. These results lend further support to the theory that social and physical warmth share neurobiological mechanisms and that social connection is a basic need on its own.

"And it's that reaching, that gesture, that reflex we have to pull what's warm-whether it's something or someone-toward us, that feeling we get when we do that, that feeling of being safe in the world. . .that's happiness"

Design Flaws of the Human Condition by Paul Schmidtberger

What does it feel like to connect with someone else? In many cultures, the language used to describe experiences of social connection, such as 'heartwarming' or 'warm' moments, reference physical warmth (Alberts & Decsy, 1990). Beyond mere metaphor, a small body of research now suggests that changes to actual physical warmth can also affect perceptions of "social warmth," feeling loved by and connected to others. After holding warm objects, participants rate another person as interpersonally warmer (Williams & Bargh, 2008), report feeling closer to other people (Ijzerman & Semin, 2009), increase their trusting behavior (Kang, Williams, Clark, Gray, & Bargh, 2011), and feel more socially connected (Inagaki & Eisenberger, 2013). While these results suggest an overlap between experiences of social and physical warmth, the mechanisms, particularly the neurochemical mechanisms, linking these two concepts are unknown.

From a neurobiological perspective, social and physical warmth may be so closely linked because they share some of the same neurocircuitry (Panksepp, 1998; Panksepp, Nelson, & Bekkedal, 1997). Given the importance of social relationships early in life (Bowlby, 1988; Harlow, 1958), social warmth may have piggybacked onto other basic functions in the body, such as thermoregulatory mechanisms, which then help the individual monitor and reinforce social connections. As part of the thermoregulatory system, endogenous opioids, widely studied neurochemicals also known for their role in reward and analgesia, mediate changes in body temperature (Adler, Geller, Roscow, & Cochin, 1988). Thus, administering μ-opioid agonists, such as morphine, leads to increases in body temperature (Clark, Murphy, Lipton, & Clark,

1983) and μ-opioid antagonists, such as naloxone, decrease body temperature (Handler, Geller, & Adler, 1992; Spencer, Hruby, & Burks, 1988). Relevant to social warmth, pharmacological manipulations of the opioid system subsequently affect social experiences with μ-agonists increasing behavioral displays of social pleasure and μ-antagonists blocking this pleasure (Panksepp, Bean, Bishop, Vilberg, & Sahley, 1980). Together, results from animal work point to the possibility that opioids may also contribute to the overlap between experiences of social and physical warmth. However, the contribution of μ-opioids to feelings of social connection that come from physical warmth have not been examined.

In humans, opioid-rich neural regions, such as the insula and ventral striatum, show increased activity to innocuous physical warmth. For instance, participants asked to hold warm (vs. neutral) stimuli show increased activity in the insula (Becerra et al., 1999; Davis, Kwan, Crawley, & Mikulis, 1998; Olausson, Charron, Marchand, Villemure, Strigo, & Bushnell, 2005; Rolls, Grabenhorst, & Parris, 2008; Verhagen, Kadohisa, & Rolls, 2004) and increases in self-reported pleasure to holding a warm stimulus is associated with increased ventral striatum (VS) activity (Rolls et al., 2008). In regards to social warmth, viewing images of a loved one activates a number of opioid-rich regions, including the VS and mid-insula (Acevedo, Aron, Fisher, & Brown, 2012; Aron, Fisher, Mashek, Strong, Li, & Brown, 2005; Bartels & Zeki, 2000, 2004). Finally, in the first neuroimaging study to examine physical and social warmth together, the VS and mid-insula were the only two regions to show overlapping neural activity between the two tasks (Inagaki & Eisenberger, 2013). To the extent that physical and social warmth truly do overlap, not just psychologically, but neurobiologically, opioids may also be involved in the feelings of connection that come from physical warmth.

To examine the role of μ-opioids on feelings of connection that come from physical warmth, participants were given naltrexone, an opioid receptor antagonist with a high affinity for μ-receptors (Weerts et al., 2008), and placebo prior to completing a temperature manipulation task (holding and evaluating a warm pack, a cold pack, and a neutral object) in the laboratory. Following the theory that social and physical warmth share similar neurocircuitry (Panksepp, 1998; Panksepp, et al., 1997), we have two predictions. First, we expect holding a warm (vs. neutral) object to lead to increases in feelings of social connection and second, that naltrexone (vs. placebo) will reduce these reported feelings of connection. No effects of naltrexone on thermal intensity (i.e. how warm or cold the items felt) are expected.

Methods

Participants

Thirty-one volunteers (21 females, *M age* = 21.55, *SD* = 3.34) participated as part of a larger research study on the effects of naltrexone on social connection. The sample was ethnically diverse with 38.7% Caucasian, 35.5% Asian, 12.9% Hispanic, 6.5% African American, and 6.5% reporting mixed ethnicity. For completing the entire study, participants were paid up to $160. The following procedures were run in compliance with UCLA's Institutional Review Board under the oversight of the Office for Protection of Research Subjects.

Screening and Experimental Procedures

Interested participants were scheduled for a physical examination at UCLA's Clinical and Translational Science Institute (CTSI) where a study nurse drew blood to test for liver functioning and pregnancy, if female, and assess vital signs (heart rate, blood pressure, height and weight). The experimenter then measured depression levels by administering the Patient

Health Questionnaire (PHQ-9; Spitzer, Kroenke, Williams, 1999) and ran a urine drug test (for THC, Opiates, Cocaine, AMP, and mAMP).

Inclusion criteria required participants to be in good health, between the ages of 18 and 35, and fluent in English. Participants were excluded if they reported any major physical health or psychiatric disorders (including a PHQ-9 score above a 13), medication use, tested positive on the urine drug test, had a BMI greater than 35, or showed any clinically-relevant abnormalities (e.g., liver function tests) or pregnancy (if female) on the blood test.

Following screening, eligible participants were scheduled for a baseline session where they received instructions for taking the study drugs (see *Study Drug Schedule* below). They then came in for two separate experimental sessions, one on each study drug, separated by a 10-day washout period during which time no study drugs were taken.

Study Drug Schedule

The opioid antagonist used in this study was oral naltrexone, an FDA-approved drug used to help manage alcoholism and opioid addiction. Study drugs were dispensed by UCLA's Investigational Drug Section in a double-blind within-subjects crossover design such that each participant took both naltrexone and placebo. Based on a previously established titration schedule (Bujarski, MacKillop, & Ray, 2012; Ray, Bujarski, Chin, & Miotto, 2011), participants took 4 doses of naltrexone over 4 days (25 mg for days 1 and 2 and 50mg for days 3 and 4) as well as 4 matched placebo pills. The fourth pill of each condition was taken in the presence of the experimenter in the lab prior to beginning the temperature manipulation. To ensure drug compliance, drugs were packed with 50mg of riboflavin. Urine samples were then evaluated at the beginning of each experimental session under a UV light for riboflavin content. The study

was registered on the U. S. National Institutes of Health Clinical Trials registry as NCT01672723.

Temperature manipulation

Approximately one hour after taking the study drug, when naltrexone reaches its peak effect (Lee, Wagner, Tanada, Frost, Bice, & Dannals, 1988), participants held and evaluated a warm pack, a cold pack, and as an additional control for physically holding an object, a neutral room temperature object (a squeeze ball) under the cover story that the experimenters were interested in their "ratings to some commonly used products." Participants were cued to pick up the warm pack, the cold pack, and the neutral object and then simply hold each item for 30 seconds each. After holding each item, participants made ratings on thermal intensity (how warm and cool the item felt) as well as their feelings of connection ("how connected did you feel when holding this item?").

Statistical Analyses

For ease of interpretation, difference scores were calculated, subtracting mean ratings in the neutral object control condition from mean ratings in each of the other temperature conditions (warm pack and cold pack). To assess the effect of our pharmacological manipulation on feelings of connection and thermal intensity, a 2 (condition: placebo vs. naltrexone) x 2 (order: placebo first vs. naltrexone first) x 2 (gender: male vs. female) x 2 (type of object: warm pack vs. cold pack) repeated measures analysis of variance (ANOVA) was initially run in SPSS. As expected, no interactions with order or gender were found and thus both variables were dropped from further analyses.

Results

Manipulation check

In regard to the study drug, all urine samples tested positive for riboflavin indicating 100% compliance with the study drug schedule.

When looking at the effect of the temperature manipulation on thermal intensity, there was a main effect of type of object on how warm ($F(1, 30) = 887.55$, $p < .001$) and how cool the items were rated ($F(1,30) = 727.42$, $p < .001$). Validating the temperature manipulation, the warm pack was rated as warmer ($M = 2.61$, $SD = 1.28$) than the cold pack ($M = -1.94$, $SD = 1.12$). Similarly, the cold pack was rated as cooler ($M = 4.19$, $SD = 1.60$) than the warm pack ($M = -1.23$, $SD = 1.50$).

In addition, there was a main effect of type of object on self-reported feelings of connection ($F(1,30) = 16.53$, $p < .001$). Replicating previous work and confirming our first hypothesis, participants reported more feelings of connection after holding the warm pack ($M = 1.10$, $SD = 1.66$) compared to holding the cold pack ($M = -.74$, $SD = 1.53$).

Effect of naltrexone on self-reports to temperature manipulation

To evaluate the effect of naltrexone on feelings of connection in response to the temperature manipulation, a 2 (condition: placebo vs. naltrexone) x 2 (type of object: warm pack vs. cold pack) repeated measures ANOVA was run. There was a significant interaction between drug condition and type of object on feelings of connection ($F(1, 30) = 5.03$, $p = .03$). The interaction was then further evaluated for the effect of our pharmacological manipulation on feelings of connection toward each type of object separately.

Confirming the second hypothesis, naltrexone (compared to placebo) reduced feelings of connection to holding the warm pack ($F(1,30) = 4.58$, $p = .04$, Fig. 1). There was no effect of naltrexone on feelings of connection to holding the cold pack ($F(1, 30) = .01$, $p = .93$), suggesting that the reductions in feelings of connection were specific to physical warmth.

As expected, no interactions between drug condition and type of object were found for ratings of thermal intensity for how warm the objects were rated ($F(1, 30) = .13$, $p = .72$) or how cool the objects were rated ($F(1, 30) = .22$, $p = .65$). That is, naltrexone did not alter perceptions of how physically warm or cool the objects were.

Discussion

Social and physical warmth are linked, not just by metaphorical language, but also by neurobiological mechanisms. In the first study to assess the role of the opioid system on feelings of connection following physical warmth, naltrexone (vs. placebo) was shown to reduce feelings of social connection to holding a warm object (vs. a cold pack), but not to affect ratings of thermal intensity. We have already shown that experiences of social warmth and physical warmth share overlapping neural circuitry (Inagaki & Eisenberger, 2013) and that naltrexone (vs. placebo) can reduce feelings of connection both in the lab and in the real-world (Inagaki, Ray, Irwin, Way, & Eisenberger, in prep). These results further extend an understanding of the basic neurobiological mechanisms that underlie social connection and lend further support to the theory that social and physical warmth share similar neurobiological mechanisms (Panksepp, 1998).

Why might social and physical warmth overlap? An integral part of human experience is connecting with others. Even from birth, we rely on and need others as much as we rely on and need warmth, food, and water in order to survive. For example, prematurely born infants survive longer if placed in relatively warmer incubators (Silverman, Fertig, & Berger, 1958). However, due to our altricial nature at birth, the only way to obtain warmth, food, and water after birth is via other human beings, our caregivers. Thus, our basic need for warmth may have been fulfilled concurrently with the presence of a caregiver and so the systems that help regulate

temperature may have then been coopted to also help "regulate" social experience with warmth signaling connection and cold signaling the loss of connection. While the importance of physical warmth from social interaction has long been suggested by previous work in animals (Blumberg, Efimova, & Alberts, 1992; Harlow, 1958; Stone, Bonnet, & Hofer, 1976), only recently have we begun to understand the extent of the overlap in humans.

The current results add to the existing literature that suggests there is a specific effect of naltrexone on subjective, but not necessarily objective experience. In other words, objective evaluations of a stimulus, such as intensity or valence, do not appear to be opioid-mediated, whereas subjective experience may be. For example, naltrexone (vs. placebo) has no effect on the perceived sweetness of sugary drinks, but does reduce the pleasantness of consuming the drinks (Bertino, Beauchamp, & Engelman, 1991). Similarly, naltrexone, particularly at high doses (100mg), reduce how much participants report liking an alcoholic beverage, but do not effect more objective indicators of drunkenness such as how "high" or intoxicated they feel (McCaul, Wand, Eissenberg, Rohde, & Cheskin, 2000). In regard to temperature perception, morphine has been shown to reduce how unpleasant noxious thermal stimuli feel, but do not alter how warm or cold the same stimuli are rated (Morin, Duncan, Lavigne, Boily, & Bushnell, 1999). Collectively, these results suggest that endogenous opioid activity may be more tightly linked with valenced subjective experience.

Though not tested here, there is a potential role of early life experience on the social and physical warmth overlap. Early relationships, particularly with caregivers, have long been theorized to be critical to development (Ainsworth, Blehar, Waters, & Wall, 1978; Bowlby, 1988). As more recent examples, higher maternal warmth (defined as supportive, affectionate behavior with a child) is associated with better social skills later in life (Steelman, Assel, Swank,

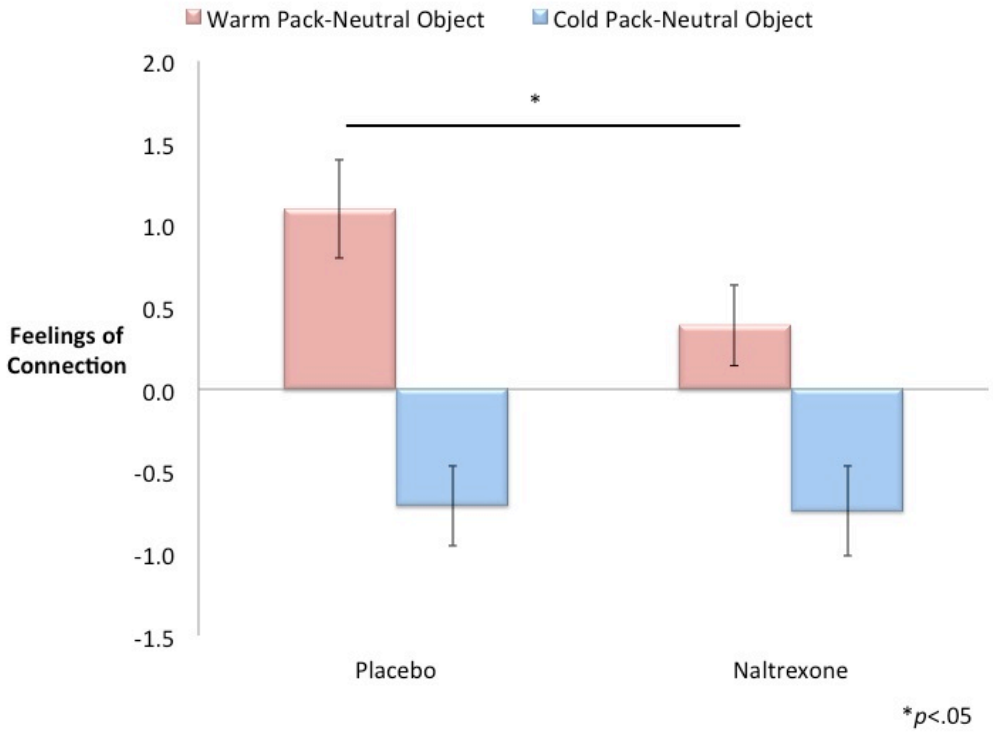
Smith, & Landry, 2002) and in a separate sample, with the downregulation of inflammatory genes, a potential mediator in the link between social experience and health (Chen, Miller, Kobor, & Cole, 2011). Yet to be tested is whether greater exposure to physical and social warmth early in life, perhaps via affiliative contact, is also associated with better health or better social functioning in adulthood. Future work integrating the contribution of early social experience, particularly with one's caregivers, may help clarify the strength of the association between social and physical warmth for certain individuals later in life.

In conclusion, physical warmth has emerged as an important contributor to social warmth, feeling loved by and connected to others. Furthering the importance of μ-opioids for social bonding more generally, the current study reveals the importance of opioids to feelings of connection that also stem from experiences of physical warmth and help uncover another mechanism through which we remain socially bonded.

Figure 1.

Reduced feelings of connection to holding a warm pack (vs. neutral object) on naltrexone compared to placebo. No such effect was found for holding a cold pack.

Figure 1.


Warm Pack-Neutral Object
Cold Pack-Neutral Object
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Feelings of Connection
*
Placebo
Naltrexone
*p<.05

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CONCLUSION

Those around us can enrich our lives, particularly those individuals with whom we share the deepest, closest relationships. The three papers in this dissertation took a multi-method approach in order to examine the neurobiological mechanisms underlying experiences of social connection, experiences that are integral to maintaining our closest bonds, in the service of helping us understand why connecting would have such profound effects on our well-being, happiness (Diener & Seligman, 2002; Czikszentmihalyi & Hunter, 2003), and health (Holt-Lundstad et al., 2010; House, et al., 1988; Taylor, 2007). By separately utilizing neuroimaging, pharmacological, and daily diary techniques, this work helped to provide a richer understanding of social experience with close others. Below, I summarize the contribution of each paper and what new knowledge has been gained from this research as a whole.

Paper 1 began with the basic question of what it feels like to connect with another person by assessing the contribution of psychological and physical warmth to social connection. Hypotheses were built on the theory that social attachments rely on other regulatory controls in the body, such as thermoregulatory controls, which regulate our warm internal body temperature (Panksepp, 1998). This study achieved two main goals. First, we established the validity of a new paradigm designed to elicit feelings of social connection by presenting loving messages written by the friends and family of each of our participants. Second, this study highlighted a link between physical and social warmth by showing that feelings of connection could be increased simply by holding a warm (vs. neutral) object, that feelings of warmth could be increased by an experience of social connection, and importantly, that physical and social warmth share overlapping neural mechanisms. Specifically, overlapping activity was found in the ventral striatum and middle insula, but no such overlapping activity was found between

social warmth and another pleasant task, physical touch, suggesting that the shared activity was not solely due to increases in positive affect. Collectively, these results contributed to our understanding of feelings of connection and suggest that physical warmth, on its own, may confer benefits to social bonding.

Paper 1 showed that an experience of social connection leads to increased activity in many neural regions known to be high in μ-opioid receptors. These results dovetail nicely with the brain opioid theory of social attachment that suggests that the pleasant feelings that come from social bonding are opioid-mediated. Therefore paper 2 directly manipulated endogenous opioid activity with the opioid-antagonist, naltrexone, in a sample of 31 healthy human volunteers to assess the role of opioids in feelings of connection to our previously established social connection task (messages from friends and family). Furthermore, this study examined the effect of opioid-blockade in the real world when participants were engaged in more naturalistic social interactions. In line with study hypotheses, and for the first time in humans, the findings from paper 2 confirmed the long theorized importance of opioids for feelings of connection by showing that naltrexone (vs. placebo) can reduce feelings of connection to reading positive, loving messages from one's own friends and family and can reduce feelings of connection toward others in the real-world. The findings from this paper help uncover one of the basic neurochemical mechanisms that keep us socially connected to our loved ones and contribute to a greater understanding of a larger neurobiological model of social attachment.

Finally, paper 3 returned to the theory from paper 1 suggesting that social attachments are supported by some of the same systems that underlie thermoregulation by exploring the role of opioids in the social and physical warmth overlap. To assess the role of opioids in warmth-induced feelings of connection, participants took naltrexone, before holding a warm pack, cold

pack, and neutral object and then rated their feelings of connection to holding each item. Lending further support to the neurobiological overlap between social and physical warmth, naltrexone (vs. placebo) was shown to reduce feelings of connection from holding a warm pack. Interestingly, ratings of thermal intensity (how warm the object felt) were not altered by naltrexone, suggesting that opioids may be more important for valenced subjective experience. As a whole, the findings from this study further implicate opioids as important neurochemical contributors to social connection.

Together, the findings from this dissertation push scientific understanding of the neural and neurochemical mechanisms underlying what it feels like to connect with others and why social connection may be considered a basic, central need all on its own. However, much more work is left to be done. It is my hope that the processes illuminated here help serve as the foundation for future work on how relationships contribute to health and ultimately help those who are having trouble feeling connected.

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