

RUNNING HEAD: Opioids and social connection to close others

Opioids and social bonding: Effect of naltrexone on feelings of social connection and
ventral striatum activity to close others

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Abstract

Close social bonds are critical to immediate and long-term well-being. However, the neurochemical mechanisms by which we remain connected to our closest loved ones are not well understood. Opioids have long been theorized to contribute to social bonding via their actions on the brain. But feelings of social connection toward one's own close others and direct comparisons of ventral striatum (VS) activity in response to close others and strangers, a neural correlate of social bonding, have not been explored. Therefore, the current clinical trial examined whether opioids causally affect neural and experiential signatures of social bonding. Eighty participants were administered naltrexone ($n=40$), an opioid antagonist that blocks natural opioid processing, or placebo ($n=40$) before completing an fMRI scan where they viewed images of their close others and individuals they had not seen before (i.e., strangers). Feelings of social connection to the close others and physical symptoms commonly experienced when taking naltrexone were also collected. In support of hypotheses, naltrexone (vs. placebo) reduced feelings of social connection toward the close others (e.g., family, friends, romantic partners). Furthermore, naltrexone (vs. placebo) reduced left VS activity in response to images of the same close others, but did not alter left VS activity to strangers. Finally, the positive correlation between feelings of connection and VS activity to close others present in the placebo condition was erased by naltrexone. Effects remained after adjusting for physical symptoms. Together, results lend support to theories suggesting that opioids contribute to social bonding, especially with our closest loved ones.

Keywords: brain opioid theory; mu-opioid antagonist; emotion; social reward; social attachments

Feeling socially connected to others, the affectively pleasant experience of being close to and bonded with others, is vital to physical and mental health and emotional and social well-being (Bowlby, 1988; Cacioppo & Cacioppo, 2018; Durkheim, 1897/1951; Holt-Lunstad, Smith, & Layton, 2010; Robles, Slatcher, Trombello, & McGinn, 2014; Stanton, Selcuk, Farrell, Slatcher, & Ong, 2019). Further, humans highly value feelings of social connection within relationships (Baumeister & Leary, 1995) and feelings of connection predict relationship stability, suggesting they are critical for maintaining social relationships over time (Attridge, Berscheid, & Simpson, 1995; Canevello & Crocker, 2010; Van Horn et al., 1997). However, relative to the theorized importance of social connection for health and well-being and for continued social bonding, understanding of the neural and neurochemical mechanisms by which we feel connected to our close others remains poor. The current study, therefore, begins to fill three previously unexplored gaps in understanding about the neurobiological mechanisms underlying social connection by: (1) testing a long-standing animal model of social connection in humans; (2) investigating the causal contribution of opioids to social connection toward close others and strangers within the same study; and (3) linking brain activity in response to close others with feelings of social connection to the same individuals.

Brain Opioid Theory of Social Attachment

The brain opioid theory of social attachment (BOTSA), first outlined in the 1970's, proposes that endogenous opioids are released by experiences of social connection and mediate the feelings stemming from such experiences (Panksepp, Herman, Conner, Bishop, & Scott, 1978; Panksepp, Herman, Vilberg, Bishop, & DeEsquinazi,

1980). Specifically, actions on brain μ -opioid receptors underlie feelings of social connection, especially those toward close others, and may be important in the maintenance of social relationships over time (Eisenberger, 2012; Inagaki, 2018a; Machin & Dunbar, 2011). By extension, blocking opioids, via pharmacological intervention as one example, during an attempt at social connection would subsequently alter the experience of social connection by reducing activity in neural regions rich in opioid receptors and subsequent feelings of social connection.

In the animal literature, a plethora of studies using pharmacological manipulations of the opioid system have shown that opioids causally affect social connection behavior (reviewed in Loseth, Ellingsen, & Leknes, 2014; Machin & Dunbar, 2011). As a few representative examples from the extensive animal literature, naloxone, an opioid antagonist that blocks natural opioid processing, (vs. placebo) increased distress vocalizations during social interaction, suggesting the animals were no longer experiencing comfort from the social group (Panksepp, Bean, Bishop, Vilberg, & Sahley, 1980). Similarly, in lambs, preference for the mother over an alien mother was eliminated by naltrexone, another opioid antagonist (Shayit, Nowak, Keller, & Weller, 2003). Though not a pharmacological manipulation, μ -opioid receptor knockout mice (vs. controls) showed a reduced preference for bedding with their mother's scent, again suggesting that the knockout mice no longer found the mother a source of comfort or derived as much pleasure from cues of her presence (Moles, Kieffer, & D'Amato, 2004). Other studies, largely in primates, have shown that opioid antagonism changes social behavior in the opposite direction; increasing connection behavior and contact seeking

(e.g., Fabre-Nys, Meller, & Keverne, 1982; Martel, Nevison, Simpson, & Keverne, 1995; Schino & Troisi, 1992).

Although the subjective experience of non-human animal participants cannot be known from behavior alone, collectively, the animal literature suggests that any experience of connection that might occur during social interaction with close others are altered following opioid antagonism. Indeed, BOTSA is a well-characterized, and longstanding theory in the animal literature, but has not been systematically tested in humans. For instance, much less is known about how opioids might impact the subjective experience of feelings of social connection and even less is known about neural activity to existing social bonds because no previous studies have examined both outcomes in response to close others in the same study. Therefore, it remains unclear whether or how opioids contribute to the experience of social connection with one's own close others in humans.

Extending BOTSA to humans

Renewed interest in extending the findings on opioids and animal social behavior to the affective experience of social connection in humans has surfaced in recent years (Inagaki, 2018a). In the first study in humans to examine opioids and feelings of social connection to affiliative stimuli with a pharmacological manipulation (which was published in a theoretical review paper, but not on its own), naltrexone (vs. placebo) reduced feelings of social connection induced by watching a video of a couple giving birth, but only in those high in trait affiliation (Depue & Morrone-Strupinsky, 2005). Similarly, affiliative feelings after a trust game with strangers were reduced by

naltrexone (25mg, Schweiger, Stemmler, Burgdorf, & Wacker, 2013; cf. Tarr, Launay, Benson, & Dunbar, 2017).

Although previous studies in humans have assessed feelings of social connection to strangers, original theorizing regarding opioids and social bonding suggests opioids may be particularly relevant for connecting with close others. Nearly the entire animal literature has assessed the effect of pharmacological manipulation of opioids on social connection behavior toward known, close others (e.g., mother, offspring, group members), but much less toward unknown strangers. Humans similarly experience social connection most frequently and deeply with close others—family, friends, romantic partners—and these are the bonds that humans maintain over time. Therefore, a striking omission from the current human literature are responses toward one’s own close others. Measuring these more personal responses are important for understanding whether and how opioids influence social bonding.

In the first study to examine the effect of opioid antagonism on responses to close others in humans, naltrexone (vs. placebo) reduced feelings of social connection to loving messages from participants’ close friends and family and general feelings of social connection outside of the lab, but left general pleasant feelings unaltered (Inagaki, Ray, Irwin, Way, & Eisenberger, 2016). Thus, while opioids are known to play a general role in positive responding, naltrexone was shown to have a specific effect on feelings of social connection.

Neural signatures of social connection

Prior work in humans using naltrexone furthered understanding of whether opioids influence social feelings, but the brain opioid theory of social attachment posits

that central opioidergic action, in particular, on μ -receptors, affect social bonding. That is, BOTSA proposes that the pathway by which opioids affect feelings of social connection is through opioid receptors located in the brain. Indeed, the key neural regions known to relate to social bonding with close others, including the ventral striatum (VS), anterior cingulate cortex (ACC), and middle-insula (Inagaki & Eisenberger, 2013), are also among the highest in μ -receptors (Cross, Hille, & Slater, 1987; Jones et al., 1999). However, previous studies on naltrexone and feelings of social connection have not integrated measures of the brain (Depue & Morrone-Strupinsky, 2005; Inagaki et al., 2016; Schweiger et al., 2013; Tarr et al., 2017). μ -opioid receptors exist throughout the body – in the brain, but also in the periphery and gastrointestinal tract. Therefore, it is imperative to measure the brain itself during an in vivo experience of social connection. Absent the measurement of the brain following naltrexone administration, the extent to which opioid action on the brain (as opposed to the digestive system, for example) contributes to feelings of social connection would not be known.

Of particular interest in the current investigation is the nucleus accumbens (NAcc) and surrounding VS, a key node of the basic reward circuit (Haber & Knutson, 2010) that consistently and reliably activates to cues of close others (Inagaki & Eisenberger, 2013, Acevedo, Aron, Fisher, & Brown, 2012, Bartels & Zeki, 2000; Inagaki, Muscatell et al., 2016, Inagaki, Muscatell et al., 2015). The VS has also previously been associated with feelings of connection (Inagaki & Eisenberger, 2012). In animals, the NAcc causally affects social connection behavior (Hansen, 1994; Hansen, Harthorn, & Wallin, 1991; Lee, Clancy & Fleming, 1999; Trezza, Damsteegt,

Achterberg, & Vanderschuren, 2011). And in humans, previous investigations in clinical samples show that naltrexone (vs. placebo) reduces VS activity to rewarding non-social stimuli such as images of alcoholic (vs. nonalcoholic) beverages (Myrick, Anton, Li, Henderson, Randall, & Voronin, 2008; Schacht, Randall, Latham, Voronin, Book, Myrick, & Anton, 2017). Thus, the VS is a key neural region involved in social connection and, separately, naltrexone has been shown to causally reduce VS activity to non-social stimuli as compared to placebo conditions when opioids are not blocked.

More direct evidence for the action of VS opioids on social bonding in humans comes from Positron Emission Tomography (PET) imaging studies that assess μ -receptor binding in vivo. In males, greater laughter with friends is associated with μ -opioid receptor binding in the VS following a social laughter manipulation (vs. baseline; Manninen et al., 2017). Likewise, increased desire for social interaction is associated with μ -receptor binding in the left, but not right, VS in response to feedback from potential romantic partners (Hsu et al., 2013). Taken together, findings from PET imaging align with the existing animal and human literature to suggest central opioid involvement in social connection. However, to date, no studies have pharmacologically manipulated the opioid system to examine the VS's response to one's own close others and strangers in the same study. The use of magnetic resonance imaging (MRI) scanning is well suited to these purposes. MRI is a noninvasive measure of brain activity that, when combined with pharmacological methods, allows any changes in brain activity to be causally attributed to the drug manipulation.

The current study

As such, the current study examined the causal contribution of opioids to social connection with one's own close others and brain activity to the same individuals. Feelings of social connection toward two self-identified close others was assessed following the oral administration of 50mg of naltrexone or placebo. As no studies have previously explored the effect of naltrexone on brain activity to both close others and strangers, brain activity to both social targets was also assessed. The primary focus was on activity in the VS due to a priori hypotheses regarding the potential causal contribution of this region to social connection behavior in animals (e.g., Trezza et al., 2011) and our previous work in humans showing VS activity in response to cues of close others (Inagaki & Eisenberger, 2012; Inagaki & Eisenberger, 2013; Inagaki, Muscatell et al., 2015; Inagaki, Byrne Haltom et al., 2016; Inagaki, Muscatell et al., 2016). Relative to placebo, feelings of social connection toward two of one's own close others and VS activity to the same individuals were expected to decrease following naltrexone administration. No effect of naltrexone on VS activity to strangers was expected.

Method

Participants and Screening

Eighty-two participants were randomly assigned to 50mg of naltrexone or placebo (Figure 1). Block randomization with blocks of 4 was determined by a computer generated random number list. Two participants did not complete the study (one for symptoms at a severe level, one did not fit in the scanner bore) leaving a final sample of 80 participants (M age = 22.39, SD = 3.362, range = 18-31). The target sample size was determined based on a balance between the desire to detect a condition difference and

issues of per participant protocol costs. Effect sizes from prior research on the effect of naltrexone on self-reported feelings of social connection (Inagaki, Ray et al., 2016) and the effect of another pharmacological challenge on VS activity to close others (Inagaki, Muscatell et al., 2015) suggested that condition differences would be medium to large (Cohen's $d = .489 - .740$). Thus, a target sample size of $n = 35$ per group would be needed to replicate the effects with 80% power at an α of .05. Data collection concluded once 80 participants had completed the entire fMRI scanning session to guard against data loss due to symptoms, or excessive movement during the scan.

Recruitment took place via flyers and the University of Pittsburgh's Pitt + Me Research Registry, a voluntary database of individuals interested in research studies. Participants were screened using a two-step process starting with a telephone interview and then an in-person screening visit with the study physician (CA). To be included in the study, participants needed to be in good health, between the ages of 18 and 35, fluent in English, right-handed, and willing to provide digital photographs of their close others (for the Neuroimaging Measure, see below). Participants were excluded for contraindications for naltrexone (hepatic illness or current use of opiates) and MRI scanning (non-removable metal in the body, claustrophobia) as well as general health: major self-reported physical or mental illness, depressive symptoms above a 9 on the Patient Health Questionnaire (PHQ-9; Spitzer, Kroenke, & Williams, 1999), excessive alcohol use (for women: ≥ 4 drinks on an occasion or 8 drinks/week; for men: ≥ 5 drinks on an occasion or 15 drinks/week), medication use aside from birth control, a positive urine drug test (Opiates, Tetrahydrocannabinol (THC), Cocaine, Amphetamines (AMP),

Methamphetamines (mAMP)), a BMI greater than 35, a positive urine pregnancy test. The study physician provided final evaluation and approval of all participants.

The study was registered on the U.S. National Institutes of Health Clinical Trials registry as NCT02818036 (An fMRI study of opioid-related changes in neural activity) and all procedures were performed (between September 2016 and June 2018) in accordance with the University of Pittsburgh's Human Research Protection Office. All participants provided written consent prior to participating. Participants were compensated \$90 for taking part in the study.

Overview of Experimental Design

Details regarding the study procedures are also reported in a paper that reports results from different tasks that asks a theoretically separate question about the contribution of physical warmth to feelings of social connection (Inagaki, Hazlett, & Andreescu, 2019). The paper contributes to a separate line of work (Inagaki & Eisenberger, 2013; Inagaki, Irwin, & Eisenberger, 2015; Inagaki & Human, 2019). For greatest clarity and readability, results are reported separately. However, none of the data or tasks reported here have previously been reported.

On the day of the experimental session, participants completed baseline measures reporting physical symptoms (time 1) and were then randomly assigned to naltrexone or placebo by an individual unassociated with the main study. Approximately sixty minutes after drug administration, when naltrexone shows peak effects (Lee et al., 1988), participants completed an fMRI scan. Finally, post-scan questionnaires were collected (time 2). The University of Pittsburgh's Investigational Drug Service compounded naltrexone and matched placebo tablets and the PI's (TKI) lab dispensed

the drugs in a double-blind manner. On the day of the fMRI scan, only the study physician and individual performing randomization were unblinded, thus maintaining the double-blind and ensuring that neither participant nor experimenter expectations were driving the current effects.

Oral naltrexone, and the standard 50mg dose, is an FDA-approved drug used to manage addiction (Ray, Chin, & Miotto, 2010), but is also used off-label for research purposes. Naltrexone is not habit forming nor a drug of abuse, does not cause dependence, and is well tolerated in long-term administration studies (Kleber, Kosten, Gaspari, & Topazian, 1985). Given the known pharmacokinetics of oral naltrexone (4 hour half-life, rapid and nearly complete absorption from the gastrointestinal tract, peak plasma levels one hour after dosing), a single dose of 50mg produces concentrations in the clinical range (Ray et al., 2010; Wall, Brine, & Perez-Reyes, 1981). Naltrexone is also ideal for testing the current hypotheses that opioids causally impact feelings of social connection and VS activity toward close others because the 50mg dose crosses the blood-brain-barrier to show near complete inhibition of μ -receptor binding in the VS (Weerts et al., 2008), the receptors and neural region hypothesized to affect the experience of social connection.

Self-report Measures

Physical Symptoms

Changes in feelings of social connection may be attributed to feeling unwell from taking a drug. Therefore, physical symptoms commonly experienced when taking naltrexone (Ray et al., 2010; Rounsaville, O'Malley, & O'Connor, 1995) were assessed at time 1 and 2 using a previously developed symptoms scale (Inagaki, Ray et al., 2016)

to evaluate as a covariate. Participants were asked to “rate how you are feeling right now” for headaches, dizziness/faintness, stomach discomfort, nausea, and tiredness/fatigue using the following scale: 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms), 3 (severe symptoms), 4 (very severe symptoms). The average of physical symptoms at each time point was computed to evaluate changes in physical symptoms, but individual symptoms were also evaluated for exploratory purposes. To assess the subjective experience of the physical symptoms, participants were also asked, “overall, how distressing do you find these symptoms?” on a 1 (not distressing at all) to 7 (very distressing) scale.

Feelings of Social Connection

Feelings of social connection toward each of the two close others that participants saw in the scanner (see Neuroimaging Measure) were assessed at time 2 only (i.e., approximately 150 minutes post drug administration). Feelings of social connection toward strangers were not collected. Participants were asked “how connected do you feel to this person?”; “how close do you feel to this person?”; “how comforted do you feel by this person?”; and “how much does this person understand the way you feel about things?” Items were obtained from previous research aiming to measure the same construct (Inagaki & Eisenberger, 2012; Inagaki & Eisenberger, 2013; Inagaki, Ray et al., 2016; Inagaki, Muscatell et al., 2016). Responses to the four items were averaged to create a measure of feelings of social connection ($\alpha=.819$). Ratings were made on a 1-7 scale with 1 indicating ‘not at all’ and 7 indicating ‘a great deal.’

Neuroimaging Measure

To assess VS activity to close others, we used a standard imaging task commonly used in studies on the neural correlates of close social relationships (Acevedo et al., 2012, Aron et al., 2005, Inagaki, Muscatell et al., 2016, Inagaki, Muscatell et al., 2015). The task reliably increases VS activity relative to control conditions. Participants were asked to send two pictures of two different people that ‘they could go to for help or for comfort such as a family member, a close friend or significant other.’ In addition, at time 1, participants were asked “how close are you to this person?” on a 1 (not at all) to 10 (extremely) scale. As expected, close others were rated as close ($M = 9.051$, $SD = .868$) indicating that participants could identify and send images of close others. Closeness ratings were missing from one participant in the placebo condition, but there were no differences in ratings of closeness between drug condition at time 1 ($t(77) = .380$, $p = .353$).

In the scanner, participants viewed images of their close others and images of two different gender, race and age-matched strangers during separate blocks. Images were resized to fit the same standard space for presentation. Emotional expression of the close other and stranger images were not explicitly controlled for, but a majority of the close other images and 100% of the stranger images were smiling. Participants were told that they would see pictures of people they know and some pictures of people they do not know. They were instructed to simply view the pictures. As an additional comparison condition, participants also performed easy mental serial subtraction in order to reduce carryover effects from viewing a close other (i.e., reduce continued thoughts about the close other or feelings that might arise from viewing images of them) as is standard in this task (Acevedo et al., 2012, Aron et al., 2005, Inagaki, Muscatell et

al., 2016, Inagaki, Muscatell et al., 2015). Thus, participants saw a cue such as “count back by 7’s from 1753” on the screen during the serial subtraction blocks.

Eight 16-s blocks (4 close other, 4 stranger) separated by a 1-s fixation crosshair, interleaved with 12-s blocks of serial subtraction were presented via E-Prime 3.0 software (Psychology Software Tools, Pittsburgh, PA). In the current study, participants sent images of friends (43%), family members including parents, siblings, children, and grandparents (39%), and romantic partners (18%). During the fMRI scan, participants also completed a messages task and a temperature perception task, both of which are reported in a separate paper.

fMRI Data Acquisition

Participants were scanned at the MR Research Center at the University of Pittsburgh on a Siemens 3T MAGNETOM Prisma MRI Scanner. A Magnetization Prepared Rapid Gradient Echo scan (MPRAGE; TR/TE=5000/2.97 ms, flip angle=4°, 256 × 256 matrix, 177 sagittal slices, FOV=258; 1 mm thick) was acquired prior to functional scans to aid in data registration. Participants then completed one run of the task (4 mins, 23 secs, T_2^* weighted gradient-echo covering 60 axial slices, TR/TE=1000/28 ms; flip angle=55°; 112 × 112 matrix; FOV=220mm; 2mm thick).

Statistical Analyses

Self-report Data

Changes in physical symptoms as a function of the pharmacological manipulation were assessed with 2 (drug: placebo vs. naltrexone) × 2 (time: 1 vs. 2) repeated measures analyses of variance (ANOVA) in SPSS v.25. Significant interactions were further interrogated with independent samples t-tests to examine

between drug effects at each time point. In addition, paired samples t-tests were run to evaluate changes across time (from time 1 to time 2) within each drug condition.

To assess the effect of naltrexone on feelings of social connection to close others, which was taken at time 2 only, an independent samples t-test with drug as the between-subjects factor was run. It is possible that changes in feelings of social connection are driven by physical symptoms or the distress experienced from the symptoms. Therefore, analyses were also run adjusting for mean-centered physical symptoms and distress of symptoms at time 2.

There was a marginal interaction between drug condition and sex for feelings of social connection ($F(1, 76) = 2.429, p = .062$; M females in placebo condition = 6.524, $SD = .416$, M females in naltrexone condition = 6.403, $SD = .425$; M males in placebo condition = 6.322, $SD = .596$; M males in naltrexone condition = 5.856, $SD = .492$). Critically, no interaction emerged between drug condition and sex for VS activity to images of close others (versus strangers) suggesting that naltrexone did not interact with sex to change the underlying neurobiological process of social connection (p 's > .400). Given the lack of significant interactions, analyses collapsed across sex.

Feelings of social connection and symptoms were non-normally distributed. Therefore, non-parametric analyses were also conducted. Statistical trends were similar for both parametric and non-parametric analyses.

Neuroimaging Data

Imaging data were preprocessed in SPM8 (Wellcome Department of Imaging Neuroscience, London) using the DARTEL procedure. Images were motion corrected and realigned, normalized to the MPRAGE, and warped into MNI space before

smoothing with a 5mm Gaussian kernel FWHM. Linear contrasts for each participant for the main comparisons of interest (close other versus stranger, close other versus serial subtraction, stranger versus serial subtraction) were computed prior to group level analyses. Three participants were removed from final analyses ($n=1$ for poor registration during preprocessing; $n=1$ for a technical error with task presentation; $n=1$ for signal dropout in the VS) leaving an imaging sample of 77 (placebo $n=37$, naltrexone $n=40$).

Region-of-Interest (ROI) analyses

Given our previous research on the role of the VS on social bonding with close others, a primary aim of the current study was to assess the effect of naltrexone on VS activity to close others. Thus, VS regions-of-interest (ROIs) were structurally defined by combining the caudate and putamen from the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and constraining the ROIs at $-10 < x < 10$, $4 < y < 18$, and $-12 < z < 0$ (Inagaki, Muscatell et al., 2016; Inagaki, Muscatell et al., 2015).

Mean parameter estimates from the VS ROI were extracted using Marsbar (<http://marsbar.sourceforge.net>). Based on a previous finding from the PET imaging literature that subjective social experience correlates with left, but not right, VS, parameter estimates were extracted separately for the left and right VS (Hsu et al., 2013).

The effect of drug on VS activity to the fMRI task was assessed with 2 (drug: placebo vs. naltrexone) \times 2 (social target: close others versus strangers) repeated measures ANOVAs. Interactions were further assessed with independent samples t-tests to evaluate the effect of drug (naltrexone versus placebo) on VS activity to each social target. Results are also reported when adjusting for mean-centered physical

symptoms and distress of symptoms at time 2. Correlations between feelings of social connection and mean parameter estimates from the left and right VS activity to close others (vs. strangers) were also run in SPSS in each drug condition separately. Due to directional hypotheses and convention, results are reported as one-tailed. Raw data and syntax can be found on the Open Science Framework:

https://osf.io/evcft/?view_only=29dceb8baddb40dc860c4be278c46b1f

Whole-brain analyses

Three supplementary whole-brain analyses were run to better characterize the effect of naltrexone on neural activity beyond the VS ROI. First, the interaction between drug condition and social target (close others vs. strangers) was assessed across the whole brain. BOLD activity in response to pictures of close others > strangers were also examined in each drug condition separately. Finally, whole-brain regression analyses were run to examine whether feelings of social connection correlate with BOLD signal when viewing images of close others relative to images of strangers.¹ All whole brain results were thresholded at a False Discovery Rate (FDR) of 0.05, 50 voxels.

Results

Drug Blind and Physical Symptoms

Groups were not significantly different on the demographic variables displayed in Table 1 (p 's > .1). Of the entire sample, 57.5% of participants correctly guessed their drug condition. 72.5% correctly guessed placebo and 42.5% correctly guessed naltrexone. Percentages were not different from chance (50%) for placebo ($X^2(1) = 2.489, p = .115$) or naltrexone ($X^2(1) = 1.766, p = .184$) suggesting participants were not able to accurately guess their drug condition assignment.

When evaluating physical symptoms, there was a drug \times time interaction ($F(1,78) = 9.601, p = .002$) that revealed no differences in physical symptoms at time 1 ($M_{\text{placebo}} = .165, SD = .230, M_{\text{naltrexone}} = .166, SD = .181, t(78) = .027, p = .490$). However, as expected, physical symptoms were greater for those in the naltrexone ($M = .425, SD = .357$) than placebo condition ($M = .210, SD = .293, t(78) = 2.942, p = .002$, Cohen's $d = .658$) at time 2. In addition, when looking within drug condition at changes in physical symptoms across time, no changes were found for the placebo group ($t(39) = 1.221, p = .115$), but symptoms increased for the naltrexone group ($t(39) = 4.437, p < .001$). However, out of the 0 – 4 scale, no symptom was reported above a 2 and the only two symptoms to show significant differences between drug condition at time 2 were tiredness/fatigue (50% of placebo participants, 67.5% of naltrexone participants, $t(78) = 2.393, p = .010$) and dizziness/faintness (10% of placebo participants, 32.5% of naltrexone participants, $t(78) = 2.720, p = .004$).

Similarly, there was a drug \times time interaction for distress of the symptoms ($F(1,78) = 2.786, p = .050$) with no differences between drug at time 1 ($t(78) = .728, p = .235$), but greater distress in the naltrexone condition (vs. placebo) at time 2 ($t(78) = 2.014, p = .024$, Cohen's $d = .450$). Changes in distress across time revealed an increase in distress from time 1 to time 2 in the naltrexone ($t(39) = 2.082, p = .022$), but not in the placebo group ($t(39) = .000, p = .500$). As with reported physical symptoms, mean levels of distress in the naltrexone condition at time 2 were relatively low ($M = 1.75, SD = 1.235$). Thus, symptoms in response to drug administration were few and experienced as mild.

Effect of Naltrexone on Feelings of Social Connection

Feelings of social connection toward the two close others were evaluated at time 2. Consistent with the current hypothesis that opioids causally contribute to social connection, naltrexone reduced feelings of social connection toward the two close others ($M = 6.225$, $SD = .512$) as compared to placebo ($M = 6.428$, $SD = .513$, $t(78) = 1.773$, $p = .040$, Cohen's $d = .396$, BCa 90% CI [.010, .385]). Even though symptoms and distress from the symptoms were not related to feelings of social connection in the naltrexone group (physical symptoms $r = .151$, $p = .177$, symptom distress $r = .010$, $p = .475$), results were run again with symptoms and distress from the symptoms each entered as covariates separately. The effect of naltrexone (vs. placebo) on feelings of connection remained even after adjusting for physical symptoms ($F(1,77) = 3.346$, $p = .036$) and distress of the symptoms ($F(1, 77) = 3.348$, $p = .036$). That is, after a single administration of naltrexone, people reported feeling less connected to two of their own close others.

Effect of Naltrexone on Ventral Striatum Activity to Close Others

The effect of naltrexone on VS activity to close others was evaluated with drug \times social target (close others, strangers) interactions using the ROI approach first. Analyses revealed a main effect of social target for both the left ($F(1,75) = 21.505$, $p < .001$) and right VS ($F(1,75) = 14.066$, $p < .001$) such that VS activity was greater to close others than strangers. Importantly, there was also an interaction for the left VS ($F(1, 75) = 3.156$, $p = .040$, Figure 2). The interaction for the right VS was in the same direction, but was not significant ($F(1, 75) = 1.756$, $p = .095$). Assessing the direction of the effects for the left VS revealed no effect of naltrexone on neural activity to strangers (vs. serial subtraction; $t(75) = .181$, $p = .429$, BCa 90% CI [-.073, .088]), but a significant

effect to close others ($t(75)=2.000$, $p = .025$, Cohen's $d = .453$, BCa 90% CI [.016, .165]). Thus, naltrexone reduced left VS activity to close others as compared to placebo. Naltrexone (vs. placebo) did not, however, alter left VS activity to strangers. Results once again held after adjusting for physical symptoms ($F(1,74) = 9.207$, $p = .002$) and distress of the symptoms ($F(1, 74) = 3.582$, $p = .031$) at time 2.

As confirmation of the pattern of results from analyses at ROI correction and to better characterize the effect of naltrexone beyond the VS, the interaction between drug condition and social target (close others vs. strangers) was assessed across the whole brain. No regions showed greater activity to placebo vs. naltrexone at whole brain correction. However, due to the patterns present from the ROI results, neural activity to images of close others vs. strangers were also examined in each drug condition separately. As expected, images of close others > strangers produced robust activity in the VS in the placebo group as well as regions previously implicated in social connection (middle insula, dorsal anterior cingulate cortex, medial prefrontal cortex) and in thinking about the self and others (temporal pole, precuneus; see Table 2 for a full list of activations). In contrast, no peaks in the VS survived whole brain correction in the naltrexone group. Rather, images of close others (vs. strangers) lead to a large activation encompassing the anterior cingulate cortex, medial and lateral prefrontal cortex, and precuneus.

Association Between Feelings of Social Connection and Neural Responses to Close Others

To examine associations between feelings of social connection and neural responses to close others (vs. strangers), whole-brain regression analyses were

conducted in each drug condition separately. In the placebo group, there was a positive correlation between feelings of social connection and BOLD signal in the left VS and right globus pallidus extending into the VS such that those who reported greater feelings of social connection toward their close others showed greater VS activity in response to images of the same individuals (see Figure 3 and Table 3 for a complete list of activations).

In contrast to the correlational pattern present in the placebo group, feelings of social connection were not positively related to VS activity in those who had taken naltrexone. Instead, greater feelings of connection were related to higher BOLD signal in the middle anterior (mACC) and posterior cingulate cortex (PCC), anterior insula (AI), dorsal lateral prefrontal cortex (dACC), and precuneus in response to images of close others (vs. strangers). No activity was negatively correlated with feelings of social connection in either drug condition at whole brain correction.

To evaluate the difference in the correlational pattern between the two drug conditions, parameter estimates from the peak activation for the left VS (from the main effect analysis comparing images of close others to strangers) were entered into a regression analysis in SPSS with drug condition, mean-centered feelings of social connection (at time 2), and the interaction between drug condition and feelings of social connection entered as predictors. Results of this analysis revealed an interaction between drug condition and feelings of connection ($B = .173$, $t = 2.300$, $p = .012$, 90% CI = [.048, .299]), suggesting the association between subjective experience and VS activity depends on drug condition.

Correlations with VS activity averaged across the structural ROI were also evaluated. In the placebo group, feelings of connection were not related to VS activity to close others (vs. strangers; right $r = -.185$, $p = .136$, Bca 90% CI = [-.461, .177]; left $r = -.240$, $p = .076$, Bca 90% CI = [-.489, .043]). For the naltrexone group however, feelings of connection were negatively correlated with right VS activity, such that greater feelings of connection were related to lower right VS activity to images of close others (right $r = -.300$, $p = .030$, Bca 90% CI [-.542, -.010]; left $r = -.248$, $p = .062$, Bca 90% CI = [-.500, .021]). The interaction between condition and feelings of social connection was not significant for VS activity at ROI correction ($p = .302$).

Discussion

Close relationships and feelings of social connection within them are critical for normal development, immediate and long-term health, and the maintenance of relationships over time (Baumeister & Leary, 1995; Bowlby, 1988; Canevello & Crocker, 2010; Holt-Lunstad et al., 2010; Durkheim, 1897/1951), yet feelings of social disconnection are on the rise (Cacioppo & Cacioppo, 2018). As a result, understanding the mechanisms by which humans experience and maintain their close social connections remains important. The current findings build on and extend a longstanding animal literature (Loeth et al., 2014; Machin & Dunbar, 2011) and an emerging body of work in humans (Inagaki, 2018a) to show that opioids causally affect subjective affective social experience, ventral striatum activity to one's own close others, and the relationship between feelings of social connection and ventral striatum activity to the same close others. Results are consistent with perspectives that suggest that opioids

are important for maintaining long-term social bonds (Machin & Dunbar, 2011) and the consummatory phase of affiliation (Depue & Morrone-Strupinsky, 2005).

Investigating responses to those one feels close to and shares a relationship with is less common in the human neuroscience literature. However, in the current study, a single dose of naltrexone altered left VS activity to one's own close others (e.g., children, romantic partner, parents, and friends), but not to strangers. That is, naltrexone reduced left VS activity to close others as compared to placebo, but naltrexone did not alter the same neural activity to strangers. This pattern suggests that the contribution of opioids to social bonding may depend on the strength, importance, or saliency of the social bond (Inagaki, 2018a). Others have shown that opioids affect behavioral responses to images of strangers, but only for those strangers rated as the most attractive (Chelnokova et al., 2014). In addition, results from PET imaging reveal correlations between social behavior (Manninen et al., 2017, Nummenmaa et al., 2016) and μ -receptor binding to social interactions with friends and romantic partners, both of which are highly salient social targets. Thus, the emerging picture regarding opioids and social stimuli suggests that opioids do not merely alter responses to all social stimuli equally, but rather depend on the salience of the social target.

The current findings that naltrexone (vs. placebo) reduce feelings of social connection toward close others are consistent with previous findings in animals and humans (e.g., Inagaki et al., 2016; Panksepp et al., 1980), but may seem to depart from other findings on opioid antagonism and social connection. For example, recent investigations in humans showed no effect of 50mg or 100mg of naltrexone (vs. placebo) on feelings of social connection and closeness among a group of strangers

participating in a silent disco (Tarr et al., 2017). It is possible that this unique social experience, where participants wore headphones while in a group and danced with one another, masked any drug effects, which are often subtle.

Turning to the animal literature, opioid antagonism (vs. placebo) often results in increases, rather than decreases, in social connection behavior (Fabre-Nys et al., 1982; Martel, Nevison, Simpson, & Keverne, 1995; Schino & Troisi, 1992). Though seemingly paradoxical, opioid antagonism may have context-specific effects on social behavior such that antagonism decreases or increases social connection behavior depending on the motivational state of the animal (Loseth et al., 2014). Consistent with this notion, naloxone *decreased* social contact behavior during normal social interaction (Martel et al., 1993), whereas naltrexone *increased* social contact seeking following social separation or isolation (Kalin, Shelton, & Barksdale, 1988). It is also possible that increases in social behavior as seen in animals, such as contact seeking or grooming, represent a decrease in the subjective experience of social connection. That is, one may feel less socially connected as a result of opioid antagonism and may therefore increase social behavior in order to regain the previously felt connection. Although the possibility of compensatory social behavior cannot be examined in animals (i.e., self-reported subjective experience cannot be measured in animals), future research in humans could test whether reductions in feelings of connection as a result of naltrexone predict increases or decreases in social behavior toward close others.

Results from the present study are the first to show that naltrexone alters the association between feelings of social connection toward close others and VS activity to cues of the same individuals. In the placebo group, greater feelings of social connection

were associated with greater VS activity to images of close others (vs. strangers), suggesting activity in the VS is indeed relevant to the subjective experience of social connection with close others. The same correlation between feelings of connection and VS activity was absent in the naltrexone group and further, there was an interaction between drug condition and feelings of connection for the left VS. The interaction suggests that the coupling of subjective experience and brain activity in the VS depends on drug condition and therefore, potentially on the binding of endogenous brain opioids in this region.

Of note, although feelings of connection were not related to VS activity in those who had been administered naltrexone, feelings of connection were related to large clusters of activation in both drug conditions that included peaks in the posterior cingulate cortex (PCC), precuneus, insula, and dorsal lateral prefrontal cortex (dLPFC). The PCC, insula and dLPFC are widely observed in fMRI studies measuring general affective responding (Lindquist, Wager, Kober, Bliss-Moreau, & Feldman Barrett, 2015). The precuneus is also part of a network of regions involved in thinking about the self and others (mentalizing) and in vivid mental imagery (Cavanna & Trimble, 2006). Naltrexone may therefore be disrupting specific aspects of affective responding to close others (i.e., the reward or motivational relevance of cues of close others) while leaving other broader processes, such as mentalizing, intact. That is, even though the VS tends to co-activate with the neural regions listed above, the processes can be dissociated.

Although there was a positive correlation between feelings of connection and VS activity at whole brain correction in the placebo group, the same correlation was not present when assessing VS activity at ROI correction. That is, when averaging across

the structural ROI of the VS, there was no association with feelings of social connection. Likewise, but in a reverse pattern, feelings of connection were negatively correlated with VS activity at ROI correction in the naltrexone group, but the same correlation was not present when assessing brain activity at whole brain correction. There are at least two possibilities that explain these differences. In the placebo group, the location of peak activity in the VS at whole brain correction was just outside of the structural VS ROI and therefore, would not have been captured by the ROI analysis. More generally, the ROI analyses used in the present study averaged signal across all of the voxels within a predefined space (the VS). This averaging may have masked differences between viewing images of close others and strangers if the signal variation was not uniform across the entire ROI. Thus, the part of the region showing significant correlations with feelings would have been averaged out. Finally, the interaction between drug condition and feelings of connection was significant for the brain results at whole brain correction, but not for the result at ROI correction. Given these analysis differences and the lack of an interaction, we are less confident in the correlational patterns using the VS ROI in the current study.

Clinical Relevance

The current results may have clinical implications which could be directly tested in future research. As one example, opioid use disorders in the U.S. are at epidemic levels (Rudd, Aleshire, Zibbell, & Gladden, 2016), necessitating an urgent need to improve the efficacy of current treatment options. Social support for abstinence has a significant influence on treatment success across various drugs of abuse (Havassy, Hall, & Wasserman, 1991) whereas stressors that are social in nature are among the

most common triggers for relapse (Heilig, Epstein, Nader, & Shaham, 2016). Further, many of the FDA-approved medication-assisted treatments for addiction, including naltrexone, act on the endogenous opioid system (principally the μ receptors). The current results suggest that an unrecognized effect of such medications could be altered feelings of connection with close others at a time when support from these individuals may mean the difference between relapse and recovery (Havassy et al., 1991). Future work that directly compares feelings of social connection in groups attempting to maintain abstinence before and after the assistance of opioid antagonists may reveal new avenues to improve the efficacy of medication-assisted treatment. Additionally, longitudinal studies in which naltrexone is administered over longer periods of time (i.e., more than a single dose, as in the current study) will clarify the long-term effect of naltrexone on feelings of social connection in both clinical and non-clinical populations.

Beyond addiction, feelings of social disconnection often precede and are then heightened in a number of clinical disorders (Beeney et al., 2019; Girard et al., 2017). The current findings begin to clarify the causal link between opioids and VS activity to close others which may help us understand who might be vulnerable to the onset of such disorders. Further, results highlight a contributing pathway by which feelings of disconnection persist in those suffering from mental and physical disorder (e.g., Lutgendorf & Sood, 2011). Ultimately, understanding how meaningful, close social relationships can be maintained is not only relevant to healthy populations, but critical to understanding ways to help those struggling with disease.

Limitations and Future Directions

The current study has limitations that could be addressed with additional research. First, the effects of naltrexone on feelings of social connection and VS activity to close others were statistically significant, but modest (Cohen's d around .400). These patterns suggest that opioids are not *necessary* for social bonding, but rather contribute to social bonding. Indeed, other neurochemicals (dopamine (Feldman, 2017); oxytocin (Bartz, 2016)) are also known to contribute to different aspects of social bonding with close others. Interactions among the neurochemicals known to alter social processing could reveal new avenues that contribute to the experience of social connection. Second, previous research suggests women may respond differently to naltrexone than men, potentially due to interactions between gonadal hormones that fluctuate across the menstrual cycle and endogenous opioid activity (Roche & King, 2015). There were no significant interactions with self-reported sex in the current study, but the present study was not designed to investigate sex differences. Future studies with larger samples and assessment during different phases of the menstrual cycle are needed to assess the moderating role of sex on the current results. Third, one of the standard comparison conditions included in the current scanner task is serial subtraction (Aron et al., 2005), however serial subtraction is not well matched to passive image viewing. Future presentation of the current task should include alternative comparison conditions that are better matched to passively viewing images of close others.

Naltrexone is also known to alter the pleasantness with which non-social stimuli are experienced (e.g., McCaul, Wand, Stauffer, Lee, & Rohde, 2001; Yeomans & Gray, 1996) and therefore it is not known, based on the current results alone, whether naltrexone reduces all pleasant responses or whether there is a specific effect on

feelings of social connection. Previous research has shown that naltrexone can reduce feelings of connection to close others while also leaving general positive feelings unaltered (Inagaki, Ray et al., 2016). However, additional research is needed to further clarify whether and when naltrexone specifically alters feelings of connection. In a related vein, further psychometric development of the current self-report measure of feelings of social connection and future investigations that extend the effect of opioids to other measures of subjective experiences within relationships, such as loneliness, social support, attachment security, or responsiveness, are important future directions for understanding the contribution of opioids to social bonding.

The current results are based on the administration of a single dose of naltrexone. However, previous theorizing suggests opioids contribute to the maintenance of existing social bonds over time (Eisenberger, 2012; Inagaki, 2018; Machin & Dunbar, 2011). Although the current results are consistent with this possibility in that naltrexone affected responses to established relationship partners, but not new sources of social interaction, this hypothesis requires longitudinal studies in which naltrexone is administered over longer periods of time as feelings of connection toward a variety of social targets are monitored. Longitudinal assessment will help clarify which relationships opioids affect and would make for an informative future direction for understanding opioids and social bonding.

Finally, although the brain opioid theory of social attachment highlights the μ receptor as the most relevant to social bonding, naltrexone partially inhibits the δ (though only ~25% (SD = 14.49%) inhibition; Weerts et al., 2008) and κ receptors as well (~87% (SD=19.0%) inhibition; Vijay et al., 2017). Therefore, the contribution of μ

receptors to the current findings cannot be isolated from the action of opioids on these other receptors. Although no studies have been conducted in humans on the contribution of κ receptors to social bonding, there is a growing appreciation for κ receptors in social behavior, especially to stress-related and antisocial behavior (e.g., selective aggression, social defeat; Lutz & Kieffer, 2013; Resendez, Kuhnmuensch, Krzywosinski, & Aragona, 2012). An interesting future direction for understanding opioids and social connection may be to administer buprenorphine, which is a full κ antagonist and partial μ agonist, with a similar paradigm as used in the present study and compare results to those reported presently. Should κ receptors be shown to contribute to social connection in humans, this would make for an important update to the brain opioid theory of social attachment.

Conclusion

In conclusion, we show, for the first time, a specific, causal effect of naltrexone on neural and subjective experiential responses to one's own close others such that naltrexone (vs. placebo) reduced left VS activity to close others, but not to strangers, and subsequent feelings of social connection toward the same close others. Furthermore, the positive correlation between feelings of social connection and VS activity present in the placebo group was not present in those administered naltrexone, suggesting the coupling of subjective experience and brain activity depends on an endogenous opioid release. The results lend support to the brain opioid theory of social attachment and further understanding of the neurochemical underpinnings of bonding with our closest loved ones.

Context of the Research

Our research is guided by a theoretical perspective in which brain and body responses are understood to guide the mind and provide the foundation for psychological experience (James, 1884; Schachter & Singer, 1962; Panksepp, 2004). This perspective is especially useful for furthering understanding of why and how social connection has become a basic need for humans (Baumeister & Leary, 1995) and for how social relationships with close others ultimately influence health (Holt-Lunstad et al., 2010). Specifically, the current results show that opioids – whose numerous physiological functions include pain and immune system modulation, thermoregulation, cardiovascular and respiratory control – also causally influence social connection with close others. The present research, therefore, continues our research on the biological mechanisms supporting social connection (Inagaki, Jennings, Eisenberger, & Gianaros, 2018; Inagaki, 2018a; Inagaki, 2018b; Inagaki, Muscatell et al., 2015) and highlights the value of pharmacological fMRI (phfMRI) methods for understanding the causal contribution of the body to the mind.

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Conflict of Interest/Disclosures

Dr. Inagaki declares no competing financial interests. Dr. Andreescu declares no competing financial interests. Ms. Hazlett declares no competing financial interests.

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Footnote

¹. There were no sex differences in the relationship between feelings of social connection and BOLD signal in the VS to images of close others vs. strangers in either drug condition (p 's > .700).

Fig. 1

CONSORT Flow Diagram

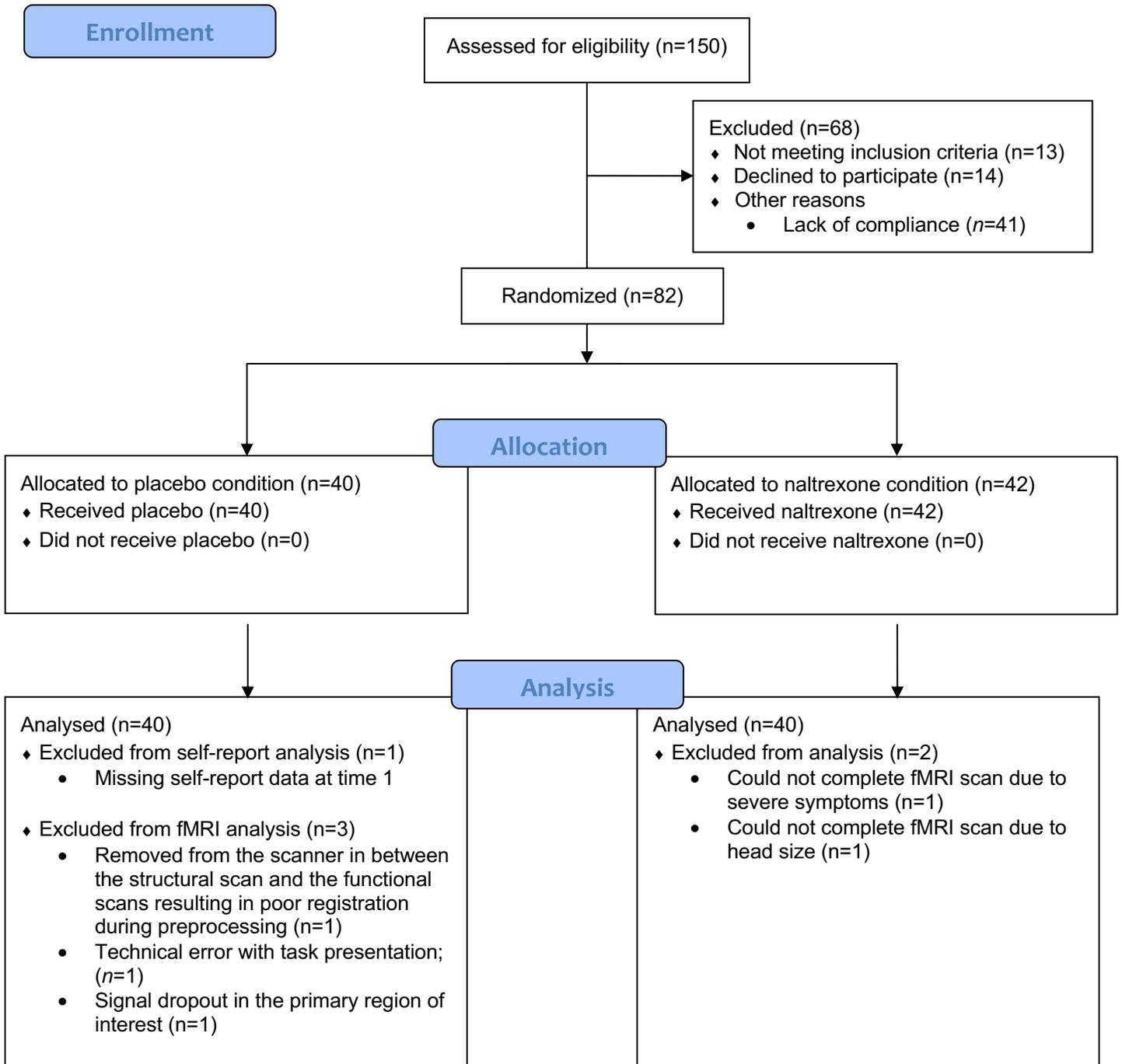


Figure 1. CONSORT Flow Diagram with details regarding participant progress through the study.

Fig. 2

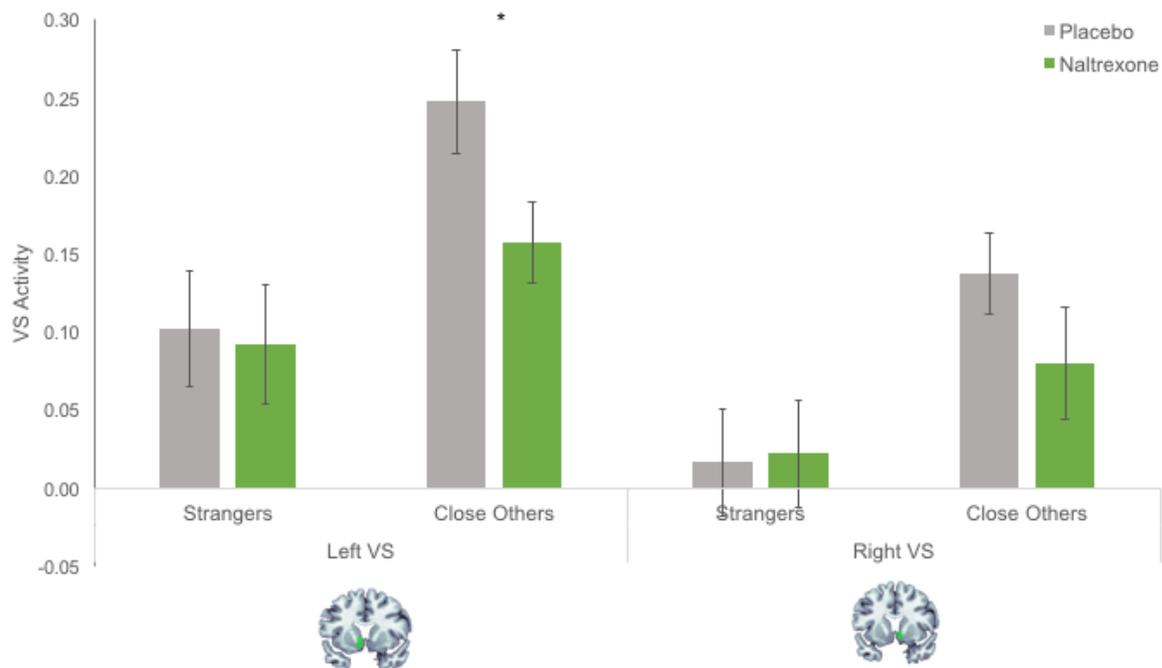


Figure 2. Neural activity (mean parameter estimates) for the left and right ventral striatum (VS) regions of interest in response to close others and strangers for participants in the placebo (grey) and naltrexone (green) conditions. A drug by social target interaction revealed that naltrexone (vs. placebo) lead to less left VS activity to images of one's own close others, but did not affect left VS activity to strangers. The interaction between drug and social target was in the same direction as the pattern for the left VS, but was not significant for the right VS. Results hold when controlling for physical symptoms and distress of symptoms. Error bars represent standard errors.

Fig. 3

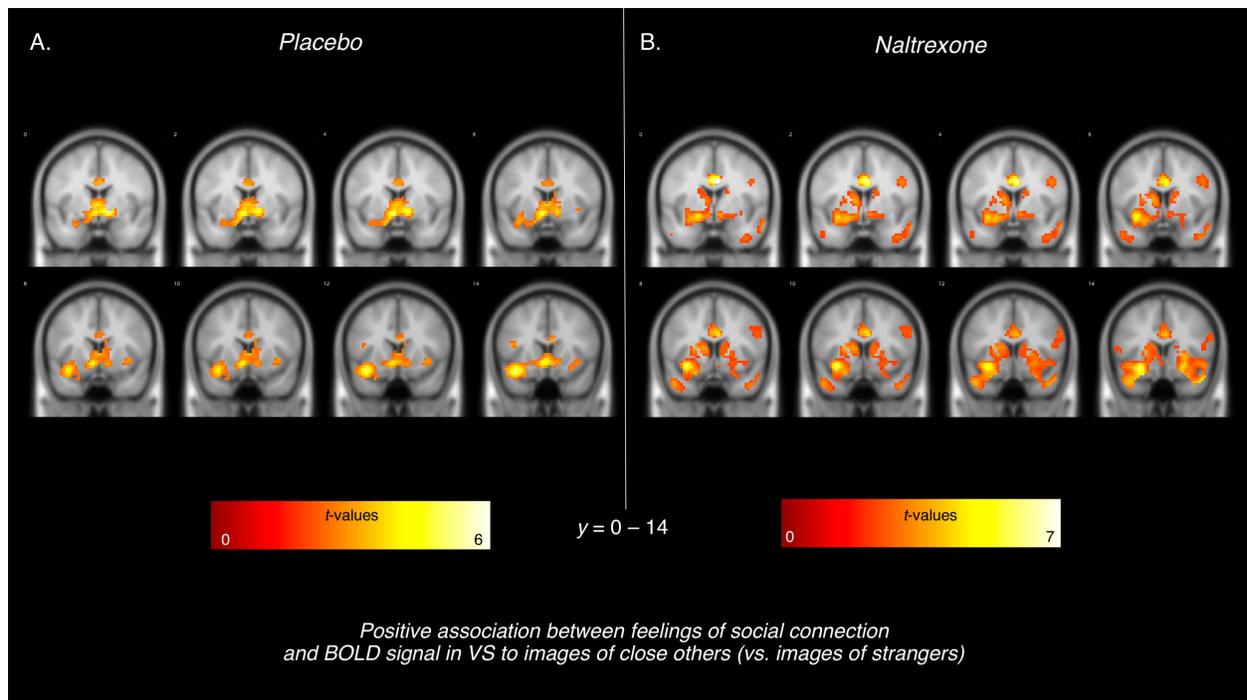


Figure 3. Whole brain regression results displaying extent of activation in the left VS that was positively correlated with feelings of social connection. In the placebo group, greater feelings of social connection collected after the scan was related to greater VS activity in response to images of close others versus strangers. The same association was not present in those who had taken naltrexone. There was also an interaction between drug condition and feelings of social connection for the left VS suggesting the association between feelings of social connection and VS activity depends on endogenous brain opioids. Results corrected for multiple comparisons at a false discovery rate (FDR) of .05.

Table 1. *Sample Characteristics*

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

Table 2. Brain regions more active when viewing images of close others compared to viewing images of strangers

<i>Placebo</i>						
Anatomical Region	BA	x	y	z	t	k
R Occipital Lobe		45	-57	-9	6.34	1299
L Temporal Pole		-39	15	-18	5.55	
L Inferior Temporal Gyrus		-48	-63	-6	5.16	4028
L Ventral Striatum		-3	3	-6	4.68	
L Medial Prefrontal Cortex	10	-3	57	0	4.51	937
R Dorsal Anterior Cingulate Cortex	24	6	0	30	3.13	
R Ventrolateral Prefrontal Cortex	11	24	33	-9	4.61	195
R Dorsolateral Prefrontal Cortex	45	48	33	6	3.75	
R Middle Insula		36	12	-6	3.16	
R Cerebellum		12	-51	-42	4.06	119
R Cerebellum		21	-81	-36	3.68	63
R Precuneus	7	24	-60	60	3.49	73
<i>Naltrexone</i>						
R Middle Anterior Cingulate Cortex	24	3	-3	33	7.84	9079
Dorsal Anterior Cingulate Cortex		0	33	24	4.42	
L Posterior Cingulate Cortex	23	-9	-54	24	6.59	
L Medial Prefrontal Cortex	10	-3	60	3	6.47	

R Ventrolateral Prefrontal Cortex	47	30	27	-18	5.98	
	11	-30	36	-15	5.99	
R Supramarginal Gyrus	2	63	-27	45	4.06	64
L Dorsolateral Prefrontal Cortex	45	-48	36	21	3.62	58
R Precuneus	7	30	-51	51	3.19	83

Note: Activations significant at FDR .05, 50 voxels. L/R=left and right hemispheres; BA=Brodmann's Area; x, y, and z=Montreal Neurological Institute (MNI) coordinates; t = t statistic value at peak coordinates; k =cluster voxel extent; Activations that do not include a k -value extend from the larger cluster listed above those activations. At whole-brain correction, the interaction between drug condition and social target did not result in any significant peaks.

Table 3. *Neural regions in response to images of close others (versus strangers) showing significant positive associations with feelings of social connection*

<i>Placebo</i>						
Anatomical Region	BA	x	y	z	t	k
R Occipital Lobe	37	45	-57	-9	6.05	1387
L Inferior Temporal Gyrus	37	-39	-45	-12	6.44	5696
L Posterior Cingulate Cortex	30	-6	-51	21	5.97	
R Globus Pallidus		12	0	-6	5.65	
L Ventral Striatum		-6	3	-9	5.28	
R Ventrolateral Prefrontal Cortex	11	24	33	-9	5.18	233
R Dorsolateral Prefrontal Cortex	45	48	33	6	3.63	
R Middle Insula		36	12	-6	3.23	
R Cerebellum		12	-51	-42	4.35	141
L Cerebellum		21	-81	-36	4.22	81
R Precuneus	7	27	-57	57	3.29	56
<i>Naltrexone</i>						
R Middle Anterior Cingulate Cortex	24	3	-3	33	7.85	9180
L Posterior Cingulate Cortex	23	-9	-54	24	6.89	

L Anterior Insula	47	-27	18	-15	6.86	
R Supramarginal Gyrus		63	-27	45	4.12	70
L Dorsolateral Prefrontal Cortex	45	-48	36	21	3.64	58
R Precuneus	7	30	-51	51	3.16	81

Note: Activations significant at FDR .05, 50 voxels. L and R refer to left and right hemispheres. BA=Brodmann's Area; x, y, and z=Montreal Neurological Institute (MNI) coordinates; *t*=t statistic value at peak coordinates; *k*=cluster voxel extent; Activations that do not include a *k*-value extend from the larger cluster listed above those activations. At whole brain correction, no regions were negatively associated with feelings of social connection in either drug condition.