Study Protocol with SAP

Official Title: An fMRI Study of Opioid-related Changes in Neural Activity

ClinicalTrials.gov ID (NCT number): NCT02818036

Protocol Date: 8/13/15

Scientific Background

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). More specifically, opioids have been proposed to underlie the affiliative, interpersonal feelings (e.g. warmth, affection) that come from social connection (Depue and Morrone-Strupinsky, 2005; Panksepp, 1998). Furthermore, the theory states that experiences of social loss or separation lead to reduced opioid activity thus leading to feelings of disconnection and separation distress. Although few studies have examined the role of opioids in human attachment relationships, data from animal models support the theory that opioids are involved in social bonding (e.g., Burkett et al, 2011; Kalin et al, 1988; Kalin et al, 1995; Keverne et al, 1989; Moles et al., 2004; Panksepp et al., 1980; Shayit et al., 2003; Schino & Troisi, 1992; Trezza et al, 2011).

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). One early study (described in Depue and Morrone-Strupinsky, 2005 but not published on its own), examined the role of opioids in social attachment processes. Here, female participants were administered naltrexone (25mg) and placebo (separated by a 4-day period) and were 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. In line with the brain opioid theory of social attachment, naltrexone (vs. placebo) reduced the increases in warm, affectionate feelings to watching the affiliative clip (compared to the neutral clip) among those high in trait affiliation. Similarly, Schweiger and colleagues (2014) have recently shown that a 25mg dose of naltrexone (vs. placebo) reduced affiliative feelings (cozy, comforting, liked, secure) after an economic trust game. Furthermore, we have recently shown that naltrexone (vs. placebo) reduces feelings of connection both in the lab and out in the real world (Inagaki, Ray, Irwin, Way, & Eisenberger, 2016). Together, these results suggest that opioids may subserve feelings of connection.

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 (Inagaki & Eisenberger, 2013), all regions known to be high in μ-opioid receptors (Cross, Hille, & Slater, 1987; 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). Though not tested yet, it is possible that opioid antagonism may reduce activity in these affiliation-related neural regions.

Together, emerging evidence from humans and animals point to the possibility that μ-opioids contribute to the experience of bonding and connecting with others, but few have explored the role of opioids in social bonding in humans. As such, the current study aims to test the brain opioid theory of social attachment to better understand the role of opioids in maintaining close social bonds.

References cited:

Acevedo, B. P., Aron, A., Fisher, H. E., & Brown, L. L. (2012). Neural correlates of long-term intense romantic love. Social Cognitive Affective Neuroscience, 7, 145-159.
Bartels, A. & Zeki, S. (2004). The neural correlates of maternal and romantic love. Neuroimage, 21, 1155-1166.
Baumeister RF, Leary MR (1995). The need to belong: desire for interpersonal attachments as a fundamental human motivation. Psychol Bull 117: 497-529.
Bowlby, J. (1988). A Secure Base: Parent-Child Attachment and Healthy Human Development, Basic Books, USA.
Burkett, J. P., Spiegel, L. L., Inoue, K., Murphy, A. Z., & Young, L. J. (2011). Activation of mu-opioid receptors in the dorsal striatum in necessary for adult social attachment in monogamous prairie voles. Neuropsychopharmacology, 36, 2200-2210.
Chelnokova O, Laeng B, Eikemo M, Riegels J, Løseth G, Maurud H et al (2014). Rewards of Beauty: The Opioid System Mediates Social Motivation in Humans. Mol Psychiatr 19: 746-747.
Cross A. J., Hille, C., & Slater, P. (1967). Subtraction autoradiography of opiate receptor subtypes in human brain. Brain Research, 18, 343-8.
Depue RA, Morrone-Strupinsky JV (2005). A neurobehavioral model of affiliative bonding: implications for conceptualizing a human trait of affiliation. Behav and Brain Sci 28: 350-395.
Dunbar, R. I. M. (2010). The social role of touch in humans and primates: behavioural function and neurobiological mechanisms. Neuroscience and Biobehavioral Reviews, 34, 260-268.
Fabre-Nys, C., Meller, R. E., & Keverne, E. B. (1982). Opiate antagonists stimulate affiliative behaviour in monkeys. Pharmacology Biochemistry & Behavior, 16, 653-659.
Gunnar MR (2001). Effects of early deprivation. In: Nelson CA, Luciana M (eds). Handbook of Developmental Cognitive Neuroscience. Cambridge: Massachusetts, pp 617-629.
Holt-Lundstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: a meta-analytic review. PLoS Medicine, 7, e1000316.
House JS, Landis KR, Umberson D (1988). Social relationships and health. Science, 241, 540-5.
Inagaki TK, Eisenberger NI (2013). Shared neural mechanisms underlying "social warmth" and physical warmth. Psychol Sci 24: 2272-2280.

Inagaki, T. K., Ray, L. A., Irwin, M. R., Way, B. M., & Eisenberger, N. I. (2016). Opioids and social bonding: Naltrexone reduces feelings of social connection. Social Cognitive and Affective Neuroscience, 11, 728-35.
Jones, A. K. P., Kitchen, N. D., Watabe, H., Cunninghman, V. J., Jones, T., Luthra, S. K., & Thomas, G. T. (1999). Measurement of changes in opioid receptor binding in vivo during trigeminal neuralgic pain using [11C]Diprenorphine and Positron Emission Tomography. Journal of Cerebral Blood Flow and Metabolism, 19, 803-808.
Kalin NH, Shelton SE, Barksdale CM (1988). Opiate modulation of separation-induced distress in non-human primates. Brain Res 440: 285-292.
Kalin NH, Shelton SE, Lynn DE (1995). Opiate systems in mother and infant primates coordinate intimate contact during reunion. Psychoneuroendocrinology 20: 735-742.
Keverne EB, Martensz ND, Tuite B (1989). Beta-endorphin concentrations in cerebrospinal fluid of monkeys are influenced by grooming relationships. Psychoneuroendocrinology 14: 155-161.
Martel, F. L., Nevison, C. M., Rayment, F. D., Simpson, M. J. A., & Keverne, E. B. (1993). Opioid receptor blockade reduces maternal affect and social grooming in rhesus monkeys. Psychoneuroendocrinology, 18, 307-321.
Meller, R. E., Keverne, E. B., & Herbert, J. (1980). Behavioural and endocrine effects of naltrexone in male talapoin monkeys. Pharmacology Biochemistry & Behavior, 13, 663-672.
Moles A, Kieffer BL, D'Amato FR (2004). Deficit in attachment behavior in mice lacking the mu-opioid receptor gene. Science 304: 1983-1986.
Nelson, E. E., & Panksepp, J. (1998). Brain substrates of infant-mother attachment: contributions of opioids, oxytocin, and norepinephrine. Neuroscience & Biobehavioral Reviews, 22, 437-52.
Panksepp J (1998). Affective Neuroscience. Oxford University Press: New York, NY.
Panksepp J, Bean NJ, Bishop P, Vilberg T, Sahley TL (1980). Opioid blockade and social comfort in chicks. Pharmacol Biochem Be 13: 673-683.
Panksepp, J., Bean, N. J., Bishop, P., Vilberg, T., & Sahley, T. L. (1980). Opioid blockade and social comfort in chicks. Pharmacology Biochemistry and Behavior, 13, 673-683.
Schino, G. & Troisi, A. (1992). Opiate receptor blockade in juvenile macaques: effect on affiliative interactions with their mothers and group companions. Brain Research, 576, 125-130.
Schweiger, D., Stemmler, G., Burgdorf, C., & Wacker, J. (2014). Opioid receptor blockade and warmth-liking: effects on interpersonal trust and frontal asymmetry. Social Cognitive and Affective Neuroscience, 9, 1608-1615. Shayit M, Nowak R, Keller M, Weller A (2003). Establishment of a preference by the newborn lamb for its mother: the role of opioids. Behav Neurosci 117: 446-454.
Strathearn, L., Li, J., Fonagy, P., & Montague, P. R. (2008). What's in a smile? Maternal brain responses to infant facial cues. Pediatrics, 122, 40-51.
Taylor SE (2010). Mechanisms linking early life stress to adult health outcomes. Proc Natl Acad Sci U S A 107: 8507-8512.
Taylor, S. E. (2010). Mechanisms linking early life stress to adult health outcomes. Proceedings of the National Academy of Sciences, 107, 8507-8512.
Tottenham, N., & Sheridan, M. A. (2010). A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. Frontiers in Human Neuroscience, 3, 1-18.
Trezza V, Damsteegt R, Marijke Achterberg EJ, Vanderschuren LJMJ (2011). Nucleus accumbens μ-opioid receptors mediate social reward. J Neurosci 31: 6362-6370.
Uchino BN (2004). Social support and physical health: Understanding the health consequences

of our relationships. Yale University Press: New Haven, CT.
Vanderschuren, L. J. M. J, Stein, E. A., Wiegant, V. M., & Van Ree, J. M. (1995). Social play alters regional brain opioid receptor binding in juvenile rats. Brain Research, 680, 148-156.
Willoch, F., Tolle, R., Wester, J., Munz, F., Petzold, A., Schwaiger, M., Conrad, B., et al. (1999). Central pain after pontine infarction is associated with changes in opioid receptor binding: a PET study with 11C-Diprenorphine. American Journal of Neuroradiology, 20, 686-690.
Wise, S. P., & Herkenham, M. (1982). Opiate receptor distribution in the cerebral cortex of the rhesus monkey. Science, 218, 387-389.
Zubieta, J., Smith, Y. R., Bueller, J. A., Xu, Y., Kilbourn, M. R., Jewett, D. M., Meyer, C. R., Koeppe, R. A., & Stohler, C. S. (2001). Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science, 239, 311-315.

Study Objectives

This study will examine the role of opioids on social connection processes and more specifically, will explore the effect of blocking opioids on feelings of social connection and connection-related neural activity.

Study Design & Methods

Overview: To assess the role of opioids in the experience of connecting with others, an opioid antagonist, naltrexone, will be administered in a randomized, double-blinded, placebo controlled design. Participants will attend a baseline session where they will complete trait measures in order to obtain baseline measures in feelings of connection. Participants will then be scheduled for an fMRI scan where they will be randomly assigned to a drug condition (naltrexone or placebo). During the scan, participants will complete a number of tasks designed to elicit feelings of social connection. After the scan, participants will complete self-report measures in order to assess the effect of opioid antagonism on perceptions of their social relationships.

Timeline and anticipated duration of study procedures:
1. Telephone Screening (15 minutes)
2. In-person visit #1 (Sennott Square): review and sign consent form, baseline questionnaires (60 minutes)
3. In-person visit #2 (Neuroscience Imaging Center): Experimental Session at fMRI scanner (3 hours)

3a. Assignment to study drug, wait for peak effects (60 minutes)
3b. fMRI scan (60 minutes)
3c. post scan assessments and video recording (60 minutes)

Total time: 4 hours

IN-PERSON BASELINE VISIT #1:
Participants will review the consent form and be allowed to ask clarifications before giving consent to participate. Participants will then answer questions about their perceptions of their

social relationships, feelings over the past 24 hours, general health and health-related behaviors, and demographics. In addition, participants will be asked to complete a number of personality measures to establish a baseline for social interactions and feelings about relationships.

IN-PERSON VISIT #2:
On the day of the study, participants will arrive at the Magnetic Resonance Research Center (MRRC) where they will complete a urine drug test to test for the presence of opiates and other drugs, a urine pregnancy test (if female) and complete a baseline physical symptoms checklist. A positive urine test for either drugs or pregnancy will result in the withdrawal of the participant from the study.

To ensure safety for an MRI scan, participants will undergo a two-step safety screening procedure with the MRI technician. First, a written screening form is completed during a face-to-face interview with the participant and the technologist. Once the participant has passed the written screening, then visual screening is performed by the technologist to identify and eliminate any contraindicated objects on the participant's body or clothing. Participants will then be randomly assigned to receive either 50mg of oral naltrexone or placebo.

Details on drug randomization and study drug blind methods: (1) Randomization: An individual unassociated with the main study will randomly assign participants to drug A or drug B on the day of the scheduled scanning session by using a block randomization method. This will ensure that there are equal numbers of men and women assigned to each drug condition. This individual will not have access to any of the data or any information about the participant except for their gender and age. It will be necessary for the person in charge of randomization to know the gender and age of the participant so that they may keep the two conditions balanced. (2) Study Drug Blind: The PI (Tristen Inagaki), study coordinator, any trained research assistant's, and the participants will all be blinded during the study, thereby maintaining the double-blind. Only the study physician, Dr. Carmen Andreescu, and the individual who performs the randomization will be unblinded. The PI will be told which drug is A and which is B at the end of data collection. Finally, the drug and placebo will be packaged into identical capsules so that the pills look identical to the experimenters.

fMRI SCAN:
Approximately 60 minutes after taking the study drug, when naltrexone is known to show peak effects (Lee et al, 1988), participants will complete an fMRI scan. During this time they will be asked to either lie still inside the bore of the magnet while brain scans are acquired or be asked to perform the following tasks inside the MRI machine:

Messages task: Participants will read a variety of messages from friends and family members, and from strangers. Messages will be presented in a block design with 3 messages presented per block, separated by 6-second rest periods. Participants will read both positive and neutral messages from close others and as further control conditions, positive and neutral messages from strangers.

Picture task: Prior to attending their experimental session, participants will provide the study coordinator with 2 images of 2 different people with whom they feel close. Once in the scanner,

participants will view images of their close others as well as gender, race, and age-matched strangers as a control condition. In between blocks of pictures, participants will complete mental arithmetic.

POST SCAN ASSESSMENTS:
Outside of the scanner, participants will rate their feelings of connection (e.g. "How connected did reading the messages make you feel?", "How warm did reading the messages make you feel?", "How touched did reading the messages make you feel?") to reading each set of messages. They will also complete the same physical symptoms checklist that they completed prior to taking the study drug and their perceptions of their close other from the picture task.

Eligibility Criteria

Inclusion criteria require participants to be in good health, between the ages of 18 and 35, fluent in English, be willing to provide digital photographs of their close others (for the picture scanner task) and identify 6-8 friends and family members who might be willing to be contacted in regards to the current research study (for the messages scanner task). In addition, participants must be right-handed and free of metal (for the fMRI scan).

Participants will be excluded for the following:
Self-reported current or past diagnoses of physical or mental illness.
Score on the Patient Health Questionnaire (depressive symptoms) above a 9
Positive urine drug test (for THC, Opiates, Cocaine, AMP, and mAMP)
Positive urine pregnancy test
Use of any prescription medication, except for birth control
Use of any over-the-counter medications on the day of the fMRI session and 24 hours after the fMRI session
Self-reported problems with liver functioning, including hepatitis or liver failure
Difficulty swallowing or taking pills

fMRI specific exclusions:
BMI greater than 35 or weight greater than 400 lbs (the weight limit of the fMRI scanner)
Claustrophia
Nonremovable metal in the body

Statistical Considerations

Primary outcomes: Neural activity and self-reported feelings of connection in response to the messages task and the picture-viewing task.

Neuroimaging outcome: The imaging data will be analyzed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Images for each participant will be realigned to correct for head motion, normalized into a standard stereotactic space, and smoothed with an 8mm Gaussian kernel, full width at half maximum, to increase signal-to-noise ratio. The imaging tasks are all block designs and therefore we will use a boxcar function convolved with a canonical hemodynamic response function. For each participant, each block

type will be modeled separately (e.g. viewing images of a close other will be modeled separately from viewing images of a stranger). After the task is modeled for each participant, planned comparisons will be computed as linear contrasts to investigate neural activity separately during each of the conditions compared to baseline (fixation crosshairs) and each condition compared to its respective control condition (e.g. images of close other vs. images of stranger). Random effects analyses of the group will be computed using the contrast images generated for each participant.

To assess between-group differences in the effect of naltrexone vs. placebo on neural responses to the different tasks, we will conduct two kinds of analyses for each task. First, based on a priori hypotheses regarding the effect of naltrexone on affiliation-related neural responses, we will conduct region-of-interest (ROI) analyses, using structurally-defined ROIs, to examine between-group differences in neural activity in these pre-specified neural regions ($p<.05$, corrected). For the task where participants read messages from their loved ones, ROIs of the VS and mid-insula, have been created (with the PickAtlas toolbox) using the automated anatomical atlas (AAL; Tzourio-Mazoyer et al., 2002), and will be examined to see if average neural activity in these regions differs between naltrexone and placebo participants in response to the messages. Similarly, for the picture-viewing task, ROIs of the left and right VS will be analyzed in the same way (these have also been structurally defined previously; Inagaki et al., 2015). Second, to more fully investigate the specific neural regions that are differentially activated as a function of naltrexone (beyond the predicted ROIs), we will conduct whole-brain between-group analyses to see which neural regions differ in activity among participants exposed to naltrexone vs. placebo ($p<.001$, 10 voxels).

Feelings of social connection: To assess between-group differences in the effect of naltrexone vs. placebo on self-reported feelings of connection in response to the scanner tasks, we will conduct independent samples t-tests.

Results for primary outcomes

Effect of Naltrexone on Neural Activity to Messages task: To examine the effect of naltrexone on neural activity to the social warmth task, analyses were constrained to the a-priori defined VS and MI mask. VS and MI activity was greater to messages from close others than strangers (*left* $t(76)=6.138$, $p<.001$; *right* $t(76)=4.493$, $p<.001$). Naltrexone, however, reduced VS and MI activity to the social warmth task as compared to placebo (*left* $t(75)=1.859$, $p=.034$; *right* $t(75)=2.198$, $p=.016$).

Effect of Naltrexone on Feelings of Social Connection to Messages task: The effect of drug on feelings of social connection to the messages task was in the expected direction, but did not reach statistical significance ($p>.10$).