

Opioids and Social Connection

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Abstract

Social connection, the pleasurable, subjective experience of feeling close to and bonded with other people, is critical for well-being and continued social bonding. Despite the importance of social connection for many important outcomes, few researchers have experimentally examined how humans connect with those to whom they feel close. The strongest insights into the biological bases of social connection come from animal research, which shows that social bonds rely on the same neurochemicals that support general motivation. One class of neurochemicals, opioids, has received increased attention in recent years with the rise of pharmacological methods to manipulate opioids in humans. This article reviews emerging findings to show that opioids affect social feelings, behaviors, and perceptions in both positive and negative social experiences and concludes with the implications of such findings. Future work should consider the subjective feelings of social connection felt during interactions with close social contacts in order to further the understanding of social connection.

Keywords

social affiliation, social bonding, attachment, social reward, endogenous opioids

Research on animals and humans from almost every subfield of psychology, psychiatry, anthropology, sociology, and public health converge to highlight the importance of having and maintaining nurturing, affiliative bonds for normal functioning, overall health, happiness, and longevity. Understanding how humans bond with and feel socially connected to one another is, therefore, of utmost importance. However, relative to the theorized importance of social connection for well-being, less research has focused on the underlying neurobiological mechanisms supporting social bonding in close relationships. In particular, little is known about how humans feel socially connected to their closest friends and family members and about the neurochemical contributors to this psychological experience. One class of neurochemicals long-theorized to be important for social connection is opioids. With new findings from human subjects emerging in recent years, we can revisit the contribution of opioids to social connection and evaluate whether the brain opioid theory of social attachment, originally developed in animals, applies to humans.

The brain opioid theory of social attachment posits that opioids, specifically μ -opioids, underlie the pleasurable satisfaction felt from achieving social connection, particularly with people with whom a social bond exists

(Panksepp, Herman, Conner, Bishop, & Scott, 1978). Furthermore, experiences of social loss or separation lead to reduced opioid activity and increased reactivity to social stressors. Why might opioids contribute to social connection? Human survival depends on our ability to connect and bond with one another, especially during the beginning of life when we are particularly vulnerable. Like our response to other life-sustaining stimuli (e.g., food), we may have evolved to find close social bonds particularly valuable. By extension, breaking such bonds would be experienced as especially aversive (Eisenberger, 2015). Opioids therefore join other neurochemicals in the body—oxytocin (Bartz, 2016) and dopamine (Feldman, 2017)—that reinforce the value of social bonds and contribute to feelings of social connection and affiliative behavior. However, until recently, opioids have remained underexplored.

Extensive data from animals (for recent reviews, see Loseth, Ellingsen, & Leknes, 2014; Machin & Dunbar, 2011) suggest that opioids are released during affiliative

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		Opioid Activity	
		Internally Release/Externally Stimulate (e.g., with morphine)	Internally Inhibit/Externally Block (e.g., with naltrexone)
Social Experience	Positive (e.g., sharing a warm moment with a loved one)	Increase feelings of social connection or Decrease feelings of social disconnection	Decrease feelings of social connection or Increase feelings of social disconnection
	Negative (e.g., separation from a loved one)	Increase feelings of social connection or Decrease feelings of social disconnection	Decrease feelings of social connection or Increase feelings of social disconnection

Fig. 1. Hypothesized relation between opioids and social connection. In positive social experiences, administering drugs to stimulate opioid activity mimics the natural release of opioids in the body and increases feelings of social connection. Conversely, blocking opioids decreases feelings of social connection. In negative social experiences, releasing or stimulating opioids decreases feelings of social disconnection, and inhibiting or blocking opioids increases feelings of social disconnection. The green boxes indicate optimal responding for continued social bonding, and the red boxes indicate disruptions to social bonding.

behavior and increase feelings of social connection, whereas inhibiting opioids (resulting in low opioid tone) motivates social contact and increases feelings of social disconnection. Externally altering opioid activity with opiate drugs leads to similar effects on social behavior and feelings of social connection (Fig. 1). Extending the theory's hypotheses to human experience, we can infer that sharing the day with a friend or relaxing on the couch with a romantic partner would release opioids, whereas the distress from being socially isolated could be alleviated by hanging out with a friend or stimulating opioids via external means.

Although the brain opioid theory of social attachment suggests that opioids are involved in feelings of social connection, researchers cannot ask animals how they feel in social situations and, instead, must infer feelings from their behavior. Therefore, it remains unclear whether animal social behavior (e.g., huddling) translates to the highly subjective human experience of feeling socially connected to others.

In the last 3 years, the number of published studies in which drugs were used to manipulate opioid activity in response to social experiences in humans increased from one (Depue & Morrone-Strupinsky, 2005) to nearly a dozen. The strength and promise of using pharmacology methods is that we can understand the causal link between the body's opioid system and subjective feelings. For instance, administering morphine mimics the

release of opioids in the body and stimulates opioid activity, whereas administering a drug such as naltrexone blocks opioid activity. Thus, I will review placebo-controlled pharmacology studies conducted in humans in an effort to organize and guide research in this burgeoning area. Findings are organized on the basis of the valence of the social experience, and I will separately consider effects seen in positive social experiences relevant to feelings of social connection and effects seen in negative social experiences relevant to feelings of social disconnection. I will then return to the brain opioid theory of social attachment to provide suggestions for future research and conclude with the implications of the current review for clinical outcomes.

Opioids and Positive Social Experiences

Affiliating with other people, especially those we are close to, feels pleasurable, and feelings of social connection that arise from affiliating with others ensure continued bonding. If opioids contribute to feelings of social connection, then blocking opioids (vs. placebo conditions that do not alter opioids) should decrease the positive feelings usually experienced when bonding with close social contacts. Consistent with this notion, the first demonstration of opioids and social connection in humans found that blocking opioids with naltrexone reduced both feelings of warmth and affection to an

affiliative film clip and tolerance to painful heat following the film clip, but only in women with high levels of trait affiliation (Depue & Morrone-Strupinsky, 2005). Since then, opioids and *subjective feelings* to a positive social experience have been pharmacologically explored in only three studies. Schweiger, Stemmler, Burgdorf, and Wacker (2014) showed that naltrexone reduced pleasant feelings (e.g., coziness, being liked) in women after a trust game. Next, in an extension of the possibility that physical warmth contributes to social bonding (Inagaki & Eisenberger, 2013; Inagaki, Irwin, Moieni, Jevtic, & Eisenberger, 2016), we showed that naltrexone reduced feelings of social connection typically induced by holding a warm object (Inagaki, Irwin, & Eisenberger, 2015). Finally, in the only study in which feelings of social connection in response to close social contacts were examined, we showed that naltrexone reduced feelings of social connection from reading loving messages from close friends and family members (Inagaki, Ray, Irwin, Way, & Eisenberger, 2016). Furthermore, we demonstrated that naltrexone reduced daily feelings of social connection, which suggests that opioids may support continued social bonding. Taken together, studies that manipulate opioid activity in response to positive social experiences suggest that opioids do indeed contribute to feelings of social connection by showing that blocking opioids reduces the pleasurable effects that typically arise from these social experiences.

Opiates also affect affiliation-related behavior and perceptions of social cues, though results are more mixed. In men, morphine (vs. naltrexone) increased the decision to continue viewing pictures of attractive strangers, the attractiveness ratings of the most attractive pictures (Chelnokova et al., 2014), and eye gaze toward the eye region of the face (Chelnokova et al., 2016). Buprenorphine, a drug used similarly to morphine, led to greater memory for the location of happy faces but not fearful or angry faces (Syal et al., 2015), and stimulating opioids with a different drug (remifentanyl) led men to rate neutral social and nonsocial pictures as more pleasant (Gospic et al., 2008). In the other direction, blocking instead of stimulating opioids (naltrexone vs. a placebo) decreased positive facial mimicry to smiling strangers (Meier et al., 2016) and decreased the amount of money invested during an economic trust game in women (Schweiger et al., 2014). However, another study found that naltrexone did not alter ratings of social and nonsocial pictures nor did naltrexone alter facial mimicry (Wardle, Bershad, & de Wit, 2016). In sum, manipulating opioid activity in positive social experiences alters social behavior and social perceptions in a pattern that is somewhat consistent with the original theory. However, no researchers have

examined social behavior or perceptions to people with whom one feels close.

Opioids and Negative Social Experiences

In negative social experiences, stimulating opioids should decrease feelings of social disconnection, and blocking opioids should increase feelings of social disconnection. In recent years, a handful of new studies have explored opioids and negative social experiences, though support for the theory has been mixed (e.g., Burgdorf, Rinn, & Stemmler, 2016). Consistent with theorizing, results have shown that buprenorphine, which stimulates opioids, increased satisfaction with performance to a social stressor (giving a speech; Bershad, Jaffe, Childs, & de Wit, 2015) and reduced sensitivity to recognizing negative facial expressions (e.g., fear; Ipser et al., 2013). However, other findings are inconsistent. For instance, although one would hypothesize that feelings of anxiety to a social stressor should be decreased by an opiate, buprenorphine did not alter feelings of anxiety (Bershad et al., 2015). More puzzling, some findings support the opposite pattern. Naltrexone increased attention to negative facial expressions (anger, fear, sadness), which is consistent with how naltrexone is theorized to affect social perceptions (Wardle et al., 2016). However, in a departure from the hypothesized pattern, naltrexone also increased attention to positive facial expressions (happiness) and reduced sensitivity (reaction time) to recognizing negative facial expressions (fear and sadness; Wardle et al., 2016).

In sum, results regarding opioids and negative social experience are largely mixed, with some findings consistent with the hypotheses from the original theory, some null findings, and some findings in the opposite direction. However, much more work is needed on opioids and responses to negative social experiences. Recommendations for rectifying inconsistencies in this literature are offered in the next section.

Returning to the Brain Opioid Theory of Social Attachment

The brain opioid theory of social attachment is supported by a deep and long-standing animal literature. Relative to the animal findings, the human literature is still in its infancy. With the resurgence of social-pharmacology methods to understand how opioids affect social processing, it is time to return to this literature's theoretical roots. Two critical pieces of the original theory should be highlighted when conducting future work and considering results from the existing literature.

First, the current understanding of opioids and social bonding from the animal literature comes from opioid manipulations to affiliative behavior in existing relationships (e.g., mother-infant pairs, animals in social housing). On the basis of these animal studies, one would expect opioids to release in humans during affiliative interactions with close social contacts, such as when sharing a comforting moment with a parent or a warm embrace with an old friend. However, most of the studies reviewed assessed responses to socially distant strangers whom one will never interact with or see again, which is a fundamentally different experience than interacting with people one knows well. The current theoretical perspective suggests that opioids are most likely to contribute to social feelings in response to bonding with people in established relationships. Responses to newly formed dating partners or thrilling new experiences may not rely on opioids but on other neurochemicals theorized to contribute to human sociality—dopamine (Depue & Morrone-Strupinsky (2005) and oxytocin (Machin & Dunbar, 2011). Considering both the stage of the social relationship (strangers, newly formed relationships, established relationships) and the types of behaviors within those relationships will be important when interpreting the effects of opioid manipulations in response to social cues. Furthermore, although the findings reviewed here appear mixed in their support of the original theory, no single study has assessed the effect of manipulations to both social experience (positive and negative) and opioids (agonist and antagonist) on social connection. Such an undertaking will be important to fully test the predictions put forth in Figure 1.

Second, although social behavior and perceptions of other people are informative and important to measure, it is the subjective feelings within relationships that were originally proposed to be opioid-mediated. In particular, it is important for future work to measure the contented, satisfied feelings within close relationships as opposed to the higher-arousal, approach-oriented or desirous feelings that characterize new relationship formation, for example (Depue & Morrone-Strupinsky, 2005), if a complete understanding of social bonding is to be pushed forward. Relatedly, an implicit assumption about opioids and social bonding is that opioid activity contributes not only to feelings of social connection during a single affiliative interaction, but also to continued bonding (Machin & Dunbar, 2011). Assessing longer-term effects of opioid manipulations on feelings of social connection and social affiliation will have the largest implications for social bonding over time and for clinical outcomes.

Finally, it should be acknowledged that although the original theory is about central effects on the μ receptors (i.e., opioid activity in the brain), opioid receptors exist

throughout the body. One caveat to using social-pharmacology methods is that most drugs used to manipulate the opioid system affect all of the body's opioid receptors and are therefore imperfect for precisely testing the theory without using more invasive neuroimaging techniques (e.g., positron-emission tomography; see Hsu et al., 2013, for a relevant example).

Relevance for Clinical Populations

Social-pharmacological methods are a useful tool for understanding how social psychology (a) affects and is affected by the body's neurochemistry, (b) is affected by therapeutic drugs, and (c) contributes to long-term health. Therefore, results from social-pharmacology studies, such as those reviewed here, have implications for a range of clinical outcomes marked by social withdrawal, feelings of social disconnection, and other social deficits (e.g., depression; Panksepp, Wright, Döbrössy, Schlaepfer, & Coenen, 2014). Social factors are also emerging as key contributors to the entire trajectory of disease diagnosis and treatment, including identifying individuals at risk (e.g., Slavich & Irwin, 2014), estimating the progression of disease (e.g., Lutgendorf & Sood, 2011), and predicting recovery (e.g., Heilig, Epstein, Nader, & Shaham, 2016). Opioids should be considered among other health-related pathways in the body (e.g., inflammation; Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2017) to better understand how social interactions affect health outcomes.

As one example of the clinical implications of the current results, opioid medications are often prescribed to aid recovery in addicted populations. The current review suggests that an unrecognized side effect of blocking opioids is decreased feelings of social connection and heightened responses to social stress, which may introduce additional barriers to recovery. Therefore, examining the effects of opioids on social processing will inform more effective options for people seeking treatment from addiction. Indeed, relapse is most commonly triggered by social stressors (Heilig et al., 2016), and social support for abstinence has a significant influence on treatment success (Havassy, Hall, & Wasserman, 1991). If treatment-seeking individuals are already socially vulnerable, treatment options will need to address ways to maintain feelings of social connection that are altered by the medications themselves.

Conclusions

In summary, pharmacological opioid manipulations in social experiences have begun to bridge the rich animal literature on social connection and evidence for the role of opioids in human social relationships. However, more work is needed before firm conclusions can be made

regarding the contribution of opioids to human social bonding. In particular, future work should measure subjective feelings in response to close social relationships. With the human literature exploring opioids and social connection experiencing a resurgence, we can better understand the important experience of social connection and elucidate new paths by which social experience affects health.

Recommended Reading

- Depue, R. A., & Morrone-Strupinsky, J. V. (2005). (See References). A comprehensive review of the neurobiological mechanisms that contribute to social affiliation and bonding.
- Inagaki, T. K., Ray, L. A., Irwin, M. R., Way, B. M., & Eisenberger, N. I. (2016). (See References). A representative pharmacology study in humans that examines opioids and feelings of social connection to close social contacts during a positive social experience.
- Loseth, G. E., Ellingsen, D.-M., & Leknes, S. (2014). (See References). A recent review of the animal literature supporting the brain opioid theory of social attachment that presents a new model to reconcile opposing findings in that literature.
- Machin, A. J., & Dunbar, R. (2011). (See References). A recent review of the brain opioid theory of social attachment that provides more in-depth information about interactions between the opioid system and other neurochemical systems theorized to be important for social connection (e.g., oxytocin).
- Nelson, E. E., & Panksepp, J. (1998). Brain substrates of infant-mother attachment: Contributions of opioids, oxytocin, and norepinephrine. *Neuroscience and Biobehavioral Reviews*, *22*, 437–452. A classic overview of the brain opioid theory of social attachment.

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Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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