Social Relationships and Public Health:

A Social Neuroscience Perspective focusing on the Opioid System

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Abstract

Social relationships are one of the most important influences upon both our physical and mental health. Yet, the mechanisms by which social interactions impact health have been difficult to identify through strictly psychological approaches. Integrating psychological and neuroscience approaches is likely to provide new insights into these mechanisms. The working hypothesis presented in this chapter is that spending time with close others leads to a shift in the neurochemical milieu, particularly the endogenous opioids, that fosters a physiological state promoting relaxation, growth, and healing. More specifically, these socially triggered alterations in neurotransmission acting on the μ-opioid receptor are hypothesized to lead to decreases in sympathetic nervous system activity, hypothalamic-pituitary-adrenal axis output, and chronic inflammation, which ultimately lead to a better physical health profile. It is hoped that melding biological and psychological approaches can improve understanding of social effects and thereby lead to interventions and social environments that improve public health. (150 words)

Highlights

- Social interactions are the most potent behavioral influence on health
- In spite of extensive research, the psychological mediators of these effects are unclear.
- The quality of ones social connections impact concentrations of the endogenous opiods, which are neurotransmitters that affect the functioning of peripheral physiological systems that influence health such as the sympathetic nervous system, hypothalamic-pituitary-adrenal stress axis, and the immune system.
- Understanding the interaction between opioid neurochemistry and psychological state are likely to be critical for a mechanistic understanding of social influences on health

Whether it be dinner with a spouse or working on a proposal with a co-worker, our daily lives are filled with social interactions. Over the last forty years, a robust body of evidence has emerged indicating that the frequency and quality of these interactions impacts not only psychological well-being, but also physical health. A recent meta-analysis of studies examining the effects of social relationships on mortality compellingly demonstrates the robustness of this effect. Based primarily on prospective studies, impoverished social relationships have an effect on mortality comparable in magnitude to that of cigarette smoking. This effect is greater than that of regular exercise, obesity, and even pharmacological treatment for hypertension (Holt-Lunstad, Smith, & Layton, 2010). Thus, it appears that a doctor's best health advice to a patient is: "Go see a friend."

With such profound influences on health, it is imperative to understand the mechanisms by which social relationships impact health. If these pathways are better understood, perhaps environments or interventions that foster more positive social interactions can be created and thereby improve public health. Although identifying these mechanisms has been a goal since the first studies establishing a link between social relationships and health in the 1970's, progress on this front has been slow (Thoits, 2011). Much of this research has focused on identifying the psychological mechanisms for this effect and it is proposed here that supplementing this research with neuroscientific, and particularly neurochemical data, may foster advances in understanding of the mechanisms by which social interactions affect health. To provide a background for this approach the proposed psychological mechanisms for social influences on health will be discussed in the next section before turning to hypotheses concerning the neurochemical mechanisms underlying social relationships.

Psychological Mechanisms for Social Effects on Health

The web of interactions each human has with others are obviously intricately complex. Nevertheless, these interactions have generally been reduced to several gross measures that are commonly used in health research. The structure of social interactions is often measured by the degree of social integration, which refers to the social ties that an individual has with others whether they be members of primary groups such as the family or secondary groups such as someone who attends the same church. Often the frequency and regularity of these interactions is also recorded. Another common measure is perceived social support, which refers to the degree to which one feels that one has readily available sources of emotional, informational, and instrumental support (House, Kahn, McLeod, & Williams, 1985). Received support refers to the actual exchange of these resources (Dunkel-Schetter & Bennett, 1990).

These particular measures are delineated here because they are thought to effect health via different mechanisms. For example, perceived social support has been argued to be particularly important in the face of stress, serving as a buffer against the adverse consequences of stress (S. Cohen & Wills, 1985). Social integration, on the other hand, has been argued to be less important in the face of stress, but rather have primarily main effects on health (S. Cohen, 2004). Studies of received support have revealed inconsistent effects on health, with many studies actually reporting links between received social support and higher mortality (e.g. (Krause, 1997). Hypotheses to explain these counterintuitive effects of received support are beyond the scope of this chapter (for a further discussion, see (Uchino, 2009), but suffice it to say that there is much still to be learned about the mechanisms by which social support operates.

For the sake of discussion here, main effects of social interactions, encompassing both social integration and perceived social support, will be focused upon (Lakey & Orehek, 2011).

Multiple psychological pathways for social support and social integration have been proposed. For example, higher social support has been linked to greater self-esteem (Symister & Friend, 2003), greater positive affect (Diener & Seligman, 2002), and lower depression (Russell & Cutrona, 1991). It would seem natural that these would be viable mediating pathways by which social interactions influence health. However, the mediating role for such psychological processes upon physical health outcomes has been exceedingly difficult to document for either measures of social support or social integration (Thoits, 2011). This lack of reliable psychological mediators is not limited to epidemiological studies, but is also seen in laboratory stress studies. Studies that manipulate social support prior to or during a stressor often show robust effects of the manipulation on reducing physiological measures of stress (e.g. cardiovascular reactivity), but rarely document mediating effects of self-reported affect or stress. Uchino, Bowen, Carlisle, & Birmingham (2012) succinctly summarize both epidemiological and laboratory studies of social support by stating "In general, the available recent literature provides no evidence that the influence of perceived or received social support on cardiovascular, neuroendocrine, and/or immunity is statistically mediated by anxiety, life stress, subjective stress, or depression." ((Uchino, Bowen, Carlisle, & Birmingham, 2012), p. 951).

This is a rather disheartening conclusion and forces a return to the drawing board and, in particular, the aforementioned epidemiological studies as they may provide a clue to the potential mechanisms responsible for this relationship. Although there are few measures in health psychology and social neuroscience that can be as reliably measured as mortality, there are many different routes to this end-point. A natural question is whether or not social relationships

contribute equally to these outcomes or whether there are particular diseases that are most influenced by social relationships and are the main contributors to the demonstrated effects of social relationships on mortality. Although the number of studies upon which to draw is smaller, there do not appear to be major differences across diseases. In other words, having richer social relationships appears to reduce the risk of dying from diseases as diverse as cardiovascular disease (Barth, Schneider, & von Kanel, 2010), infectious disease (Lee & Rotheram-Borus, 2001), and cancer (Pinquart & Duberstein, 2010). Because these diseases have very different etiologies, it suggests that physiological systems that affect multiple biological targets are likely to be involved. Examples of such systems would be the autonomic nervous system, hypothalamic-pituitary-adrenal (HPA) stress axis, and the immune system. The question then becomes, do social interactions impact these pathways directly. In other words, do social interactions directly trigger activation or deactivation of these systems by pathways that are automatic or not fully accessible to the explicit recollection that forms the foundations for the self-reported experiences that are recorded with psychological measures.

Social Interactions and Health-Relevant Peripheral Physiological Pathways

The clearest data for social interaction effects on peripheral physiology comes from studies of ambulatory blood pressure, which is a good predictor of mortality as well as hypertension and other adverse cardiovascular outcomes (Boggia et al., 2011). In an experience sampling study assessing social interactions of adults, interacting with one's partner, relative to strangers or being alone, was associated with reduced systolic (SBP) and diastolic blood pressure (Gump, Polk, Kamarck, & Shiffman, 2001). Not surprisingly, measures of arousal, intimacy, and emotional support were significantly higher when interacting with one's partner. However, these did not mediate the effects of the social situation upon blood pressure. Similar results were seen

in a another study of healthy adults (Holt-Lunstad, Uchino, Smith, Olson-Cerny, & Nealey-Moore, 2003), where being in the presence of family members or a spouse was associated with lower systolic and diastolic blood pressure than being around nonfamily members. Again, even though these social relationships were associated with differences in affect, intimacy, and disclosure these psychological variables did not mediate the effect. In the work environment, traffic agents interacting with a coworker had lower SBP and lower negative affect than when interacting with a stranger (Brondolo, Karlin, Alexander, Bobrow, & Schwartz, 1999). However, affective state did not mediate the effects of the social situation on blood pressure. Thus, being with close others seems to have a positive effect on cardiovascular function by mechanisms that may not necessarily be accessible to conscious awareness.

With respect to cortisol as a measure of HPA axis output, there is evidence for social influences on cortisol reactivity throughout the lifespan. For example, in infants, sensitive parenting can blunt the cortisol response to separation stress (Gunnar & Donzella, 2002). This has also been seen in adolescents where an experience sampling study showed that when adolescents were alone, they had 14% higher cortisol levels than when they were with others, controlling for time of day effects (Adam, 2006). Just like with the previously described cardiovascular studies the effect of social interactions on this physiological marker controlled for self-reported emotional experience, which indicates that feeling distressed is not necessary for activation of physiological systems with health-relevance. Similar results were found in an experience sampling study with college students, where solitude was associated with higher cortisol (Matias, Nicolson, & Freire, 2011). Again, this effect was not mediated by negative affect or positive affect. In adults, there is evidence that social networks (Lai et al., 2012), social support (Heaney, Phillips, & Carroll, 2010), and loneliness (Adam, Hawkley, Kudielka, &

Cacioppo, 2006) can affect diurnal patterns in cortisol activity. At the same time, there is also evidence that negative affective states are associated with momentary cortisol levels as well (e.g. (Smyth et al., 1998). However, there has not been much evidence for a mediating role of affective state between social interactions and HPA axis activity. Taken together, these studies suggest that social interactions can impact HPA axis activity, but that it is not necessary that these social effects impact psychological state.

In addition to these studies in humans, there is corroborative evidence from nonhuman primates where social behavior can be more accurately quantified due to the ability to systematically observe their social interactions in a way that is not possible in human studies. The nonhuman primate model is highly applicable to social influences on health, as social bonds are related to longevity in nonhuman primates as well. For example, female baboons that have greater social integration, as measured by the time spent in proximity with others and grooming others, live longer. The effects of stable relationships of this type on longevity are independent from and stronger than the effects of dominance status (Silk et al., 2010).

Although the link between HPA axis activity and longevity hasn't been directly made, it is a likely candidate for being a contributing mediator of such effects. Across nonhuman primates, species socially organized such that subordinates have good social support have lower cortisol levels than those species where subordinates do not have access to such support (Abbott et al., 2003). In wild male yellow baboons (Sapolsky, Alberts, & Altmann, 1997) as well as wild male olive baboons (Ray & Sapolsky, 1992) males who spend more time grooming and in the proximity of others have lower levels of cortisol. Similarly, in captive female rhesus monkeys, animals that are higher on sociability have lower cortisol levels throughout most of the year (Gust, Gordon, Hambright, & Wilson, 1993). Interestingly, more recent work using social

network analysis in both female rhesus monkeys (Brent, Semple, Dubuc, Heistermann, & Maclarnon, 2011) as well as female baboons (Wittig et al., 2008) in the wild shows that it is particularly focused social relationships that tend to be associated with lower glucocorticoid levels (as measured in fecal matter), which are presumed to reflect HPA axis output. In other words, having a few reliable relationships appears to reduce HPA axis activity more than having a broader social network that has less reliability. This will be an important issue to address in future research in human social epidemiology studies.

One system highly influenced by cortisol is the immune system. This system has a better documented impact on health outcomes than the HPA axis, as it directly affects disease processes such as atherosclerosis or viral infection. Just like in the HPA axis, there are robust effects of sociality on the immune system. However, whether the effects of social interactions upon immune parameters are mediated by HPA axis activation or not is less clear and likely to vary depending on the measure and the experience of the individual or animal. In captive long-tailed macaques, natural killer cell activity is highest among those who are more social (Kaplan et al., 1991). In rhesus macaques, differences in levels of social interaction were associated with the degree of sympathetic nervous system fibers innervating the lymph nodes (Sloan, Capitanio, Tarara, & Cole, 2008), indicating that differences in sociability are linked to structural differences in the sympathetic nervous system. Although correlational, these data are suggestive that it is the greater stress associated with lower levels of sociality that lead to these structural changes, as stress can lead to increases in sympathetic innervation (Sloan et al., 2007). These low sociable animals also had poorer antibody response to vaccination, which would be consistent with placing them at greater risk for viral infection.

Overall, these nonhuman primate studies indicate that frequent social interactions with other members of the species reduce activity in peripheral physiological systems relevant to health. Although the subjective correlates of these effects are obviously open to interpretation, they provide compelling support for a direct effects pathway by which social interactions can influence potential downstream physiological processes and thereby contribute to disease progression and onset.

If we return to the central question concerning the mechanisms by which social interactions affect mortality, it seems that social interactions trigger peripheral physiological pathways that can affect disease. However, this still begs the question as to how one category of stimulus, social interactions, trigger these multiple pathways. Do social interactions stimulate each of these peripheral physiological systems separately? Or, do different components of social interactions stimulate a particular system? Do social interactions stimulate one upstream system that then triggers each of these peripheral physiological systems in common? The working hypothesis here is that social relationships act on a common pathway in the brain to trigger these downstream pathways. Thus, social interactions activate a minimal number of systems in the brain which then trigger these multiple downstream pathways. Admittedly, this is a bold claim. After all, if a drug company salesman advertised that he had a drug that could help reduce risk of all-cause mortality, he would naturally be ridiculed as a peddler of snake-oil, because a drug should only affect one specific biochemical pathway involved in a particular disease. Yet, social relationships seem to be a "drug" that have effects across a variety of diseases. How they might have such a common effect is the subject of the next section.

Neural and Neurochemical Processing of Social Interactions

Where in the brain are social interactions processed? There are many areas, but one of particular relevance here are the reward pathways. Converging evidence from both pharmacological and neuroimaging studies suggest that there is tremendous overlap between the processing of social stimlui that are rewarding and general rewarding stimuli such as money (Knutson, Westdorp, Kaiser, & Hommer, 2000) or food (McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007). For example, anticipation of social approval in the form of friendly faces (Spreckelmeyer et al., 2009) activates overlapping ventral striatal circuits with that of the anticipation of money. Similar overlapping activation was seen when acquiring a favorable social reputation or acquiring financial reward (Izuma, Saito, & Sadato, 2008). Although there is tremendous overlap between social and nonsocial rewards, this is not to say the two are identical, as particularly in the consummatory phase of reward there is greater delineation between them (Rademacher et al., 2010).

This neural activity in the reward centers of the brain while processing social stimuli is of relevance for health measures, most notably pain. Viewing pictures of a romantic partner reduces the aversiveness of experimental pain stimuli, relative to viewing pictures of a stranger (Eisenberger et al., 2011; Master et al., 2009; Younger, Aron, Parke, Chatterjee, & Mackey, 2010). The activity in the ventral striatum (Younger, Aron, Parke, Chatterjee, & Mackey, 2010) and the VMPFC (Eisenberger et al., 2011) correlates with the degree of pain reduction, suggesting that the greater degree to which seeing a romantic partner activates these areas the greater reduction in pain.

Although these neuroimaging studies don't identify the neurochemical system involved, one system that could be involved in both social reward as well as social analgesia is the opioid system. In particular, the μ-opioid receptor is probably best known for being the site of action

for both morphine, the prototypical pain-killer, and heroin, the prototypical euphorogenic drug of abuse. Both the rewarding and pain suppressing effects of stimulation of the μ-opioid receptor are likely to be of relevance for understanding the mechanisms by which social interactions impact health outcomes. In the normal individual, the μ-opioid receptor is acted upon by several opioid neurotransmitters, most particularly β -endorphin and the enkephalins (S. H. Snyder & Pasternak, 2003), which will be referred to here as the endogenous opioids.

This notion of opioid involvement in social bonds was first recognized by Jaak Panksepp in the 1970's and has received recent theoretical elaboration. For example, Depue and Morrone-Strupinksy (2005) relied heavily upon the opioid system in their neurobehavioral theory of affiliative bonding as did Machin and Dunbar (Machin & Dunbar, 2011) in their Brain Opioid Theory of Social Attachment (BOTSA). The basic underlying premise of these theories is that social interactions trigger opioid release, which then acts on the μ-opioid receptor to form and maintain social bonds.

A social bond is loosely defined here as an enduring, interdependent social relationship that is characterized by a felt sense of belonging as well as a set of behaviors indicative of closeness such as frequency of interaction, degree of influence on each other, and willingness to engage in altruistic behaviors for the well-being of the other (A. Aron, Aron, & Smollan, 1992; Berscheid, Snyder, & Omoto, 1989). Although these certainly apply to romantic relationships this definition also includes familial relationships and friendships. Even more broadly, there is no reason to postulate that this type of bond does not extend to pets, which can reduce stress (Allen, Blascovich, & Mendes, 2002). Furthermore, parasocial relationships, such as those encountered in television shows or fictional works can also provide an experience of belonging (Derrick,

Gabriel, & Hugenberg, 2009), serving as social surrogates much like cloth surrogates in Harlow's (Harlow, 1958) classic studies on infant monkeys separated from their mothers.

There is evidence indicating that opioids are involved in both the formation of social bonds as well as their maintenance. This has been most clearly established in the bond between the mother and the infant. In sheep, blockade of opioid signaling in the lamb within the first few hours after birth prevents it from forming a preference for the mother (Shayit, Nowak, Keller, & Weller, 2003). This has been corroborated via genetic means as well. μ-opioid receptor knockout mice have deficits in selective approach of their mothers, indicating that they haven't formed a bond with them (Moles, Kieffer, & D'Amato, 2004). This early formation of the bond may be important for the proper formation of later social relationships, as mice given naltrexone during development to block the formation of their bond with the mother seek out less social interaction and find it less rewarding when they are adolescents (Cinque et al., 2012). This suggests that the early attachment bond is important for later relationships as well. In other words, the mechanisms underlying attachment to the mother extend to other relationships (Broad, Curley, & Keverne, 2006). Consistent with this, in adult prairie voles which normally form a pair-bond after mating, antagonism of the μ-opioid receptor prevents the formation of this bond (Burkett, Spiegel, Inoue, Murphy, & Young, 2011).

Opioids may also be involved in the maintenance of social bonds between peers. In primates, grooming fosters social cohesion and elicits release of endogenous opioids (Keverne, Martensz, & Tuite, 1989) and also reduces sympathetic activation (Aureli, Preston, & de Waal, Frans B. M., 1999). Similarly in adolescent rodents, endogenous opioids are released during play (Vanderschuren, Niesink, Spruijt, & Van Ree, 1995). Unfortunately, there is minimal human data upon which to verify these findings, but based on the social changes in heroin addicts

(Rosenbaum, 1981) it would appear that the opioids operate similarly in humans. In such individuals, the drug substitutes for social bonds and they find maintaining their social relationships less rewarding.

Such observations of heroin addicts is what led Panksepp and colleagues (Panksepp, Herman, Vilberg, Bishop, & DeEskinazi, 1980) to form their initial hypothesis. In particular, he noted that the behavioral manifestations of social separation (e.g. romantic breakup) and heroin withdrawal were similar. Both share an increase in sleeplessness, irritability, the stress hormone cortisol, depressive feelings, and loss of appetite. This made him wonder if a fall in endogenous opioids were contributing to the behaviors associated with social separations such as the death of a loved one or a romantic breakup. To test this hypothesis, he and others administered low doses of morphine to infants of various species (monkeys: (Kalin, Shelton, & Barksdale, 1988); dogs: (Panksepp, Herman, Conner, Bishop, & Scott, 1978), guinea pigs: (B. H. Herman & Panksepp, 1978); rats: (Carden, Barr, & Hofer, 1991), and chickens: (Warnick, McCurdy, & Sufka, 2005) and found that it reduced the behavioral manifestations of distress upon separation from the mother. This data suggests that the stimulation of the μ-opioid receptor by morphine is remedying a fall in endogenous opioid signaling due to removal of the mother.

A natural question is whether this occurs in humans, and of particular relevance to the topic here, does it extend beyond the maternal-infant bond to bonds between adults. Based on Positron Emission Tomography (PET) scanning of μ-opioid receptor mediated transmission in women, it appears that a decrease in social connection might be associated with reduced endogenous signaling at the μ-opioid receptor (Zubieta et al., 2003). When participants recalled the death of a loved one or the break-up of a romantic relationship, there was a decrease in endogenous opioid release. The technical challenges of this type of study though, limit the

interpretation as the participants need to recall this event for 30 minutes to obtain a reliable measure of μ-opioid mediated neurotransmission and naturally the narrow bore of the scanner precludes actual social interaction.

Further corroborative evidence comes from a study of genetic variation in the μ-opioid receptor gene (*OPRM1*). Within exon 1 of this gene, there is a polymorphism (A118G) that leads to reduced expression of the μ-opioid receptor (PET and mouse studies). An association study of the relationship between this polymorphism and social rejection, indicated that the *OPRM1* G allele is associated with greater self-reported dispositional concern and worry about social rejection (Way, Taylor, & Eisenberger, 2009). These dispositional concerns over being excluded by others are also manifest in the neural response to an actual experience of social exclusion. Carriers of the G allele exhibited greater activity within the dACC and anterior insula when being excluded from an online ball-tossing game (Cyberball).

Although it is difficult to draw inferences concerning the efficacy of μ-opioid mediated signaling from genetic association studies like this, these data do suggest that the opioid system is involved in the response to separation from other individuals. Most importantly, the other individuals in this experiment were not attachment figures, so this study also suggests that the opioid system is involved in multiple types of relationships. It will be an important question for future research to identify the degree to which shifts in μ-opioid mediated neurotransmission are affected by different types of relationships. In sum, human studies corroborate animal studies and indicate that social separation leads to a decrease in opioid mediated neurotransmission.

Effects of Endogenous Opioids on Peripheral Physiology

In addition to instantiating social bonds at the neurochemical level, the opioids may also be critical mediators of peripheral pathways that can elicit the physiological effects that

exacerbate disease. This is an important component to the notion that endogenous opioids might be involved in mediating the effects of social relationships upon health.

The effects of the central opioid system on peripheral physiological has been most clearly demonstrated for the HPA axis. The μ-opioid receptor is localized in the paraventricular nucleus of the hypothalamus (Zheng, Bosch, & Ronnekleiv, 2005), which is the location of the Corticotrophin Releasing Hormone (CRH) cells that initiate the hypothalamic-pituitary-adrenal stress axis response that culminates in the release of cortisol into the bloodstream. Studies of the firing properties of cells in this region indicate that stimulation of the μ-opioid receptor has an inhibitory effect (Wuarin & Dudek, 1996). This is consistent with studies showing that morphine administration inhibits cortisol release (Zis, Haskett, Albala, & Carroll, 1984) and that withdrawal from morphine leads to robust cortisol release (Drolet et al., 2001) – a critical component of the aversiveness of withdrawal from this drug. Thus, based on the fall in levels of opioids seen when separated from a valuable social contact it is reasonable to postulate this as a mechanism mediating the stress response seen with the loss of social support.

The effects of a fall in opioids is not limited to the HPA axis. There is also evidence that the loss in μ-opioid receptor stimulation can lead to large increases in sympathetic output and loss of parasympathetic tone, which can drive a pro-inflammatory state (Kienbaum et al., 2002). Thus, the opioid system is potentially a critical link in transducing the positive effects of social interactions into peripheral physiological effects.

Towards a Model of Opioid Involvement in Social Effects on Health

Based on the discussion thus far, the working model is that social interactions increase the levels of neurotransmitters that signal through the μ-opioid receptor, which lead to better physiological regulation and health. Therefore, it would seem that the path forward for the field

is to assess how different forms of social interactions impact μ-opioid mediated neurotransmission and subsequent peripheral physiological measures. This would go a long ways towards establishing the opioid system as a critical mediator of the effects of social interactions on health.

One could gain the impression from this review that psychological factors are irrelevant for understanding the mechanisms by which social interactions impact health. However, just because psychological processes don't appear to mediate the social effects on health doesn't mean they don't moderate them. In fact, assessment of neurochemical measures at the exclusion of psychological ones is unlikely to lead to significant advancements in understanding the mechanisms by which social influences affect health. Social stimuli are likely to differentially activate the opioid system as a function of multiple psychological variables such as family history and personality. Inattention to these factors may occlude real effects.

The few studies that have looked at the interaction of psychological factors with opioid signaling indicate that the actual relationship between social interactions and the opioid system is likely to be far more complex than has been presented up to this point. For example, in a study of emotional responses to a film clip of a married couple bonding before the birth of their first child, blockade of the μ-opioid receptor with naltrexone prevented feelings of warmth and affiliation, but only in participants who reported high levels of social closeness (a subscale of the MPQ; (Depue & Morrone-Strupinsky, 2005). This study preselected participants high and low on this scale which assesses sociability and the degree to which one values close interpersonal relationships. This film not only increased feelings of warmth and affiliation among those high in dispositional social closeness, but also increased their pain tolerance much like the previously mentioned studies that found viewing pictures of ones romantic partner had pain suppressing

effects. These pain suppressing effects of watching the film clip were blocked by naltrexone, but only in individuals high in social closeness. This suggest the opioid system functions differentially in those at opposite ends of this personality scale and that those who are lower in social closeness are less able to activate their opioid system. This finding certainly supports the model proposed previously, but if one did not pay attention to these personality effects one could potentially not see an effect of the opioid manipulation.

Another psychological moderator that might be important to attend to in studies of opioid mediated social effects is anger regulation style (Bruehl, Burns, Chung, & Chont, 2009). In particular, those who dispositionally tend to outwardly express their anger, as assessed by the Spielberger State-Trait Anger Expression Inventory (sample items: When angry or furious "I do things like slam doors", "I say nasty things", or "I strike out at whatever is infuriating"), appear to have lower levels of endogenous μ-opioid mediated neurotransmission. When the μ-opioid receptor is blocked by naltrexone, individuals high in anger expressivity show little difference in pain response from placebo, while those who are lower on this scale show marked differences (Bruehl, Burns, Chung, Ward, & Johnson, 2002). Follow-up analyses showed that the hyper-response to pain in those high in anger expressivity is partially mediated by this opioid dysfunction (Bruehl, Chung, Burns, & Biridepalli, 2003). This impaired opioid function in high anger expression individuals is consistent with their heightened cardiovascular reactivity during anger provocation (Burns, Bruehl, & Caceres, 2004). Of relevance for epidemiologists and public health researchers, the genetic variant affecting levels of the μ-opioid receptor described earlier (A118G) also moderates the effects of trait anger out on acute pain sensitivity (Bruehl, Chung, & Burns, 2008).

In a different strain of research, similar results have been found with a repressive stress coping style. Individuals who are low on this dispositional measure, and presumably high in emotional expressivity, tend to have reduced endogenous opioid signaling as they are more responsive to opioid blockade (Jamner & Leigh, 1999). Thus, it appears that those who tend to express their anger and other emotions outwardly may lack sufficient endogenous opioid signaling to inhibit both pain and anger expression, which leads to greater peripheral physiological activation and correlated health consequences. Such individuals may show reduced salubrious effects of social relationships because social interactions may be less able to activate their opioid system. Or, conversely, because of their low levels of endogenous opioids social relationships may be even more important for individuals who have high anger expressivity. These are naturally questions for future research, but these studies indicate that for a complete understanding of how social relationships impact health both psychological and neurochemical measurements will be necessary.

In summary, opioid mediated neurotransmission is modulated by social variables and, in turn, differences in opioidergic function affect psychology and sociality. This bidirectional influence between the neurochemical and psychosocial realms indicates that neuroscientists, public health researchers, and psychologists have much to gain by talking to each other. It also suggests that improved understanding of how individual differences in both neurochemical and psychological function interact can lead to social and environmental interventions that can alter neurochemical signaling in a manner that promotes better health.

Biography of Author

Dr. Way was trained as a neuropharmacologist in the nonhuman primate laboratory of Dr. William P. Melega at the University of California at Los Angeles before doing his post-doctoral research in Health Psychology with Drs. Naomi I. Eisenberger, Matthew D. Lieberman, and Shelley E. Taylor also at UCLA. Dr. Way's research focuses on the bidirectional relationships between the social and neurochemical worlds.

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