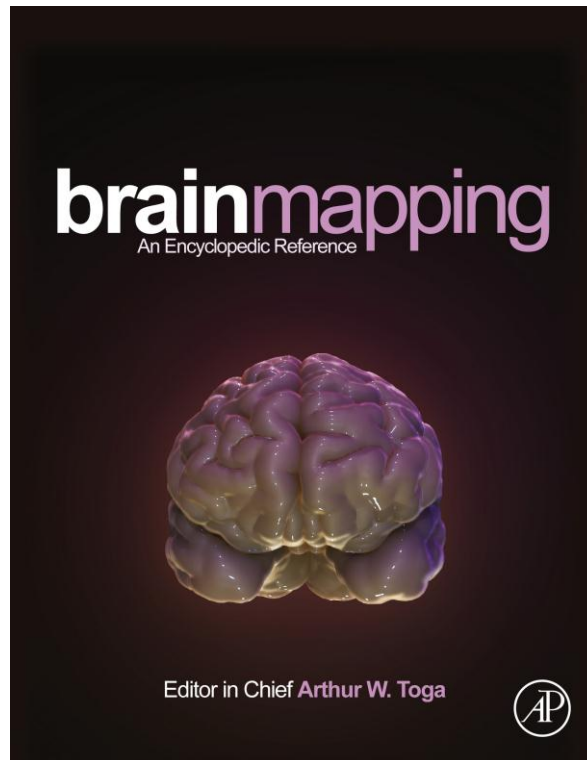


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Tchalova K., and Eisenberger N.I. (2015) How the Brain Feels the Hurt of Heartbreak: Examining the Neurobiological Overlap Between Social and Physical Pain. In: Arthur W. Toga, editor. *Brain Mapping: An Encyclopedic Reference*, vol. 3, pp. 15-20. Academic Press: Elsevier.

How the Brain Feels the Hurt of Heartbreak: Examining the Neurobiological Overlap Between Social and Physical Pain

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Glossary

Allele One of two or more alternative forms of a gene at a specific location in the genetic sequence.

Analgesia The absence of the sense of pain.

Antagonist A chemical compound that binds to a receptor and prevents its activation.

Anxious attachment A style of relating to intimate others that is characterized by anxious and excessive preoccupation with close social relationships and hypervigilance for rejection cues.

Cingulotomy The surgical creation of lesions in the dorsal anterior cingulate cortex.

Cyberball A virtual ball-tossing game used to simulate experiences of social inclusion and exclusion, wherein

participants either receive ball tosses from virtual players or are ignored by them.

Distress vocalization A characteristic call produced by young animals when separated from their mothers or littermates and used by researchers as a measure of separation distress.

Hyperalgesia Enhanced sensitivity to pain.

Hypoalgesia Diminished sensitivity to pain.

mRNA A type of genetic material that mediates the translation of the genetic code into proteins.

Polymorphism Variation in the genetic sequence.

Rejection sensitivity A heightened tendency to expect, perceive, and overreact to social rejection.

All of us have, at one time or another, experienced negative social events that threaten our sense of social connection: divorce and breakups, exclusion from attractive groups, the deaths of loved ones. Interestingly, our descriptions of these experiences borrow heavily from the language of physical pain. We say, for example, that being left by a romantic partner causes 'heartache,' an insult is like a 'slap in the face,' and criticism from someone we admire is 'crushing.' This linguistic pattern is not peculiar to English; MacDonald and Leary (2005) observed that cultures around the world rely exclusively on physical pain terms to convey the emotional distress of being devalued by other people (i.e., what English speakers refer to as *hurt feelings*).

Research suggests that the reason these metaphors come so easily to us may be that social pain – the profound distress experienced when social ties are absent, threatened, damaged, or lost – is elaborated by the same neural and neurochemical substrates involved in processing physical pain (Eisenberger, 2012; Eisenberger & Lieberman, 2004; MacDonald & Leary, 2005; Panksepp, 1998). In other words, social disconnection (and the threat thereof) *hurts* in a very real way because it recruits some of the same neural mechanisms that respond to physical injury. Here, we explore this proposition by discussing the evolutionary value of social pain, reviewing evidence for the neurochemical and neural overlap between social and physical pain, and exploring some consequences of this overlap.

The Evolution of Social Pain

Humans are a deeply social species whose most joyful and despondent moments arise from the gratification and frustration of social belongingness needs (Jaremka, Gabriel, &

Carvalho, 2011). Our motivation to maintain stable and meaningful social relationships is rooted in evolutionary history (Baumeister & Leary, 1995). For our ancestors, group living was the primary survival tool that facilitated predator defense, hunting, foraging, mating, as well as childrearing (Baumeister & Leary, 1995; Brewer & Caporael, 1990), and provided a life-sustaining source of care during illness, injury (Hublin, 2009), and the utter dependency of childhood (Bowlby, 1969/1982).

As solitary individuals were ill-equipped to face the daunting challenges of their environment, the survival of our ancestors depended as much on the integrity of their social network as on the integrity of their physical body. Consequently, the evolutionarily ancient pain signal, which serves to limit damage to the body, may have been co-opted to alert humans and other social mammals to the possibility of damage to one's social relationships (Eisenberger & Lieberman, 2004; MacDonald & Leary, 2005; Panksepp, 1998). Just as physical pain protects animals by drawing attention to the site of the physical injury and motivating appropriate restorative action, social pain may signal potential estrangement from one's social network and motivate restoration of belongingness. In the next section, this idea is further explored, with the delineation of some of the neurochemical and neural systems that subservise both physical and social pain.

Neurochemical Evidence for an Overlap Between Physical and Social Pain

I must give due praise to the man who first extracted morphine from poppyheads. The pain stopped seven minutes after the injection ... and I forgot completely about the woman who deceived me. (Bulgakov, 1975, p. 125)

As in the semi-autobiographical account presented here, writers have long suggested that opioid drugs, a class of potent painkillers, also alleviate the ache of social loss. Indeed, the endogenous opioid system appears to play a key role in modulating both physical pain (Fields, 2007) and social affect (Panksepp, 1998). Morphine, whose pain-relieving effects are primarily mediated through the μ -opioid receptor subclass (Matthes et al., 1996), attenuates social separation distress (as indexed by a characteristic call termed a distress vocalization) in a variety of animal species (Carden, Hernandez, & Hofer, 1996; Carden & Hofer, 1990; Herman & Panksepp, 1978; Kalin, Shelton, & Barksdale, 1988; Kehoe & Blass, 1986; Panksepp, Herman, Conner, Bishop, & Scott, 1978; Panksepp, Vilberg, Bean, Coy, & Kastin, 1978; Sufka, Hughes, McCormick, & Borland, 1994). Importantly, this effect is observed with low, nonsedative doses of morphine that do not affect other behavioral responses. Conversely, opioid receptor antagonists, which are known to aggravate physical pain (Anderson, Sheth, Bencherif, Frost, & Campbell, 2002; Levine, Gordon, Jones, & Fields, 1978), increase distress vocalizations in isolated animals (Herman & Panksepp, 1978; Kehoe & Blass, 1986; Sufka et al., 1994) and slow the reduction in distress vocalizations typically seen when animals are reunited with their companions (Carden & Hofer, 1990; Carden et al., 1996; Herman & Panksepp, 1978; Martel, Nevison, Simpson, & Keverne, 1995; Panksepp, Bean, Bishop, Vilberg, & Sahley, 1980).

These findings suggest that the endogenous opioid system, a primary neurochemical system for regulating physical pain, also mediates social attachments (Panksepp, 1998; Panksepp, Sivi, & Normansell, 1985). Specifically, it is postulated that social separation causes a painful, low-opioid state that motivates social proximity seeking and is terminated once social contact is resumed, which prompts the release of endogenous opioids. Consistent with this view, elimination of the μ -opioid receptor through genetic engineering causes deficits in attachment, including lack of distress vocalizing (Moles, Kieffer, & D'Amato, 2004). In addition to suggesting a specific point of overlap between the physical and social pain systems, research on endogenous opioids also demonstrates that the elaboration of social attachment is contingent on the ability to experience social distress.

Neural Evidence for an Overlap Between Physical and Social Pain

Neural Substrates of Physical Pain

The experience of physical pain can be dissociated into two constituent components: the sensory-discriminative and the affective-motivational (Treede, Kenshalo, Gracely, & Jones, 1999). The sensory component provides information about the intensity, quality, and spatiotemporal characteristics of the pain stimulus, whereas the affective component is associated with the perceived unpleasantness of the stimulus, promotes focus on the pain stimulus, and provides the motivation to terminate the painful experience (Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999; Treede et al., 1999).

These two pain elements are subserved by different neural mechanisms (Craig, 2002; Price, 2000; Tölle et al., 1999; Treede et al., 1999). Pain sensation is processed in the primary and secondary somatosensory cortices (SI and SII) and the posterior insula (PI), whereas pain affect relies on the dorsal anterior cingulate cortex (dACC) and the anterior insula (AI) (see Figure 1). Although highly correlated, the dissociability of the two components of pain is evident in the fact that individuals with lesions to the dACC (Cohen et al., 2001) and the AI (Berthier, Starkstein, & Leiguarda, 1988) can still identify the presence of pain, but find it less bothersome and distracting. Given that social exclusion does not involve tissue damage but does require an efficient mechanism for capturing attention and motivating pain-terminating behavior, it is probable that the affective component of physical pain is more directly involved in social pain experience, although the sensory component has been shown to play a role in certain types of social pain as well (Kross, Berman, Mischel, Smith, & Wager, 2011).

Neural Substrates of Social Pain

Neuropsychological evidence

Paralleling the findings that the dACC mediates physical pain affect, several animal studies have found that the dACC regulates separation distress as well. For example, lesions of the dorsal and ventral sections of the ACC reduce distress vocalization rates (Hadland, Rushworth, Gaffan & Passingham,

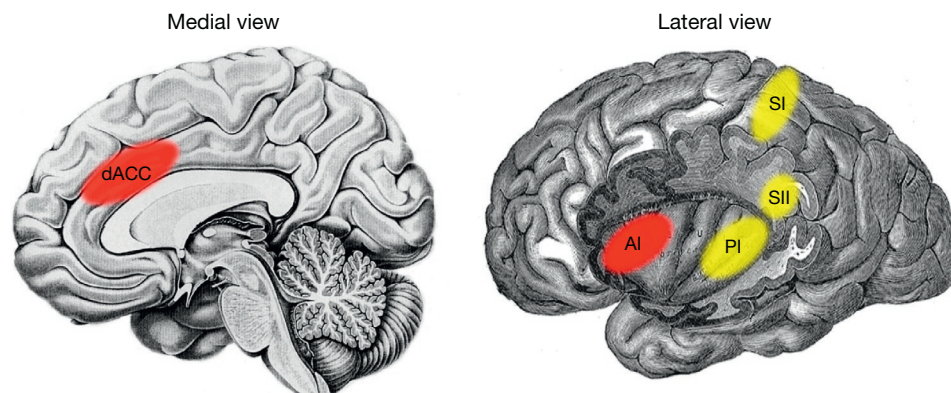


Figure 1 Cortical substrates of the affective and sensory components of pain. Regions displayed in red are hypothesized to be more strongly involved in the affective component of pain while regions displayed in yellow are hypothesized to be more strongly involved in the sensory component of pain. The medial view (on the left) shows the dorsal anterior cingulate cortex (dACC). The lateral view (on the right) shows the anterior insula (AI), posterior insula (PI), primary somatosensory cortex (SI), and secondary somatosensory cortex (SII).

2003; MacLean & Newman, 1988), whereas electrical stimulation of the ACC triggers distress vocalizations (Smith, 1945). Furthermore, cingulate ablation in mice causes deficits in maternal behavior (Murphy, MacLean, & Hamilton, 1981; Stamm, 1955), and lesions to the ACC (both dorsal and ventral regions) in monkeys leads to decreases in social interest and proximity seeking (Hadland et al., 2003), which may be expected given the link between separation distress and social motivation. Unfortunately, no neuropsychological studies have directly assessed the impact of cingulate cortex lesions on social distress in humans, although some investigators have observed that following cingulotomy, which involves lesioning the dACC, patients show a reduced concern for the opinions of others, decreased self-consciousness, and a social disinhibition (Tow & Whitty, 1953), all of which could be indicative of a lowered sensitivity to negative social consequences and social pain.

Neuroimaging evidence

Most of the evidence for the neural overlap between physical and social pain is derived from neuroimaging studies. In the first investigation of this kind, Eisenberger, Lieberman, and Williams (2003) took functional magnetic resonance imaging scans of participants' brains while they were engaged in a computerized ball-tossing game (Cyberball). Although the participants believed they were playing with real people via the Internet, they were actually playing with a computer program preset to exclude them partway through the game. The scan revealed that participants who stopped receiving ball tosses from their fellow players showed increased activation in the dACC and AI. Furthermore, participants' feelings of rejection positively correlated with dACC activation, such that those who felt most excluded showed the greatest activity in the dACC. These findings suggest, therefore, that brain structures involved in encoding physical pain unpleasantness may also elaborate feelings of social pain.

Subsequent neuroimaging studies have largely replicated the finding that Cyberball exclusion engages the dACC and/or AI (e.g., Bolling et al., 2011; Kawamoto et al., 2012; Krill & Platek, 2009; Masten, Telzer, & Eisenberger, 2011; Masten, Telzer, Fuligni, Lieberman, & Eisenberger, 2012; Moor et al., 2012). Additionally, dACC (DeWall et al., 2012; Eisenberger, Gable, & Lieberman, 2007; Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007; Onoda et al., 2009) and AI (DeWall et al., 2012; Masten et al., 2009) activity positively correlates with self-reported feelings of social exclusion, as well as levels of observer-rated social distress (Masten et al., 2011).

Other social pain induction paradigms have obtained similar findings. Kross et al. (2011) provided a direct comparison between a thermal pain condition, in which participants received painful heat stimuli on their arm, and a social pain condition, in which participants viewed a photograph of an ex-partner who had recently rejected them. The authors found overlapping activation in the dACC and AI, as well as the SII and PI in response to both types of pain, suggesting that some socially painful experiences may engage the sensory components of physical pain processing as well. Similarly, viewing pictures of a deceased relative engages the dACC and insula (Gündel, O'Connor, Littrell, Fort, & Lane, 2003; O'Connor et al., 2008). Even artwork conveying a sense of social disconnection and loneliness induces dACC and insula activation (Kross, Egner, Ochsner, Hirsch, & Downey, 2007),

and individuals higher on rejection sensitivity display greater dACC responses to disapproving facial expressions (Burklund, Eisenberger, & Lieberman, 2007). Finally, decreases in state self-esteem that accompany negative social evaluation – for example, being told that you are boring – similarly relate to increased dACC and AI activity (Eisenberger, Inagaki, Muscatell, Byrne Haltom, & Leary, 2011).

In addition, factors that are associated with decreased or increased sensitivity to social pain show the expected relationships with pain-related neural activity. For example, social support, which is known to mitigate social and emotional distress (Mikulincer & Shaver, 2008), is associated with reduced activity in the dACC and AI. Thus, individuals who spent more time with friends in adolescence showed less exclusion-related activity in the dACC and AI (Masten et al., 2012) and those who reported higher levels of daily social support showed reduced activity in the dACC in response to social exclusion (Eisenberger et al., 2007b). Likewise, individual difference factors that increase sensitivity to social pain increase neural sensitivity in these regions. Individuals who are high in rejection sensitivity (Masten et al., 2009), high in anxious attachment (chronic preoccupation about the availability of social support figures; DeWall et al., 2012; Gillath, Bunge, Shaver, Wendelken, & Mikulincer, 2005), or low in self-esteem (Onoda et al., 2010) show greater dACC and/or AI activity during social pain induction.

In sum, research findings across a variety of social pain induction paradigms provide support for a neural overlap between physical and social pain. Although neuroimaging studies most commonly show social exclusion-related activation in the dACC and AI, other brain regions, including the SII, PI, subgenual ACC, thalamus, and periaqueductal grey may also be involved in the experience of social pain (see Eisenberger, 2012, for a recent review). In the next section, some of the implications of this neural overlap are reviewed. Namely, we will explore whether sensitivity to physical and social pain are related, and whether manipulations that enhance or reduce one type of pain affect perception of the other type of pain in a corresponding manner.

Implications of the Neurobiological Overlap Between Physical and Social Pain

Shared Sensitivity to Physical and Social Pain

One corollary of the idea that physical and social pain systems are governed by overlapping neurobiological mechanisms is that individuals who exhibit a greater sensitivity to one type of pain will also be more susceptible to the other type of pain. Indeed, an experimental test of this hypothesis (Eisenberger, Jarcho, Lieberman, & Naliboff, 2006) showed that greater baseline sensitivity to physical pain (assessed with the application of a thermal stimulus to participants' forearms) corresponds to heightened self-reported feelings of rejection during Cyberball exclusion.

Another line of evidence for the shared sensitivity hypothesis comes from investigations of the μ -opioid receptor gene (OPRM1). The A118G polymorphism of this gene is believed to be a loss-of-function allele that lowers mRNA expression and receptor protein translation rates (Zhang, Wang, Johnson, Papp, & Sadée, 2005). Paralleling findings that A118G

corresponds to greater physical pain susceptibility (Sia et al., 2008), Way, Taylor, and Eisenberger (2009) observed that G allele carriers exhibit a higher dispositional rejection sensitivity, as well as a greater dACC and AI reactivity to Cyberball exclusion. Furthermore, A118G has also been linked to increased childhood withdrawal (a correlate of rejection sensitivity; Bertoletti, Zanoni, Giorda, & Battaglia, 2012), and its primate analog is associated with more pronounced and persistent separation distress in monkeys (Barr et al., 2008). Altogether, these research findings support the idea of shared sensitivities to physical and social pain and make a particular argument for the involvement of the endogenous opioid system in the regulation of social pain.

Mutually Influential Effects of Physical and Social Pain

A further prediction arising from the neural overlap theory of physical and social pain is that any factor that enhances or decreases one type of pain should exert parallel effects on the other type of pain experience. In the next section, evidence for this hypothesis is reviewed by examining various manipulations that either potentiate or downregulate social and physical pain.

Factors that enhance social pain

Would it hurt more if a stranger shoved you on purpose rather than by accident? Commonsense tells us that these factors should not make a difference; however, Gray and Wegner (2008) showed that intentionally inflicted pain does indeed hurt more than incidental pain of the same intensity. Such findings are consistent with the hypothesis that social pain potentiating factors should enhance physical pain sensitivity as well. In fact, it has been shown that Cyberball exclusion leads to pain hypersensitivity (Bernstein & Claypool, 2012), and that the participants who *feel* most excluded report higher pain ratings (Eisenberger et al., 2006).

Conversely, other social exclusion manipulations have been shown to reduce physical pain. Specifically, both interactions with a standoffish individual (Borsook & MacDonald, 2010) and a bogus forecast that one is going to end up alone in life (DeWall & Baumeister, 2006) induce hypoalgesia. Some have posited that the intensity of the social exclusion manipulation may partially account for this discrepancy, such that milder exclusion (Cyberball) enhances physical pain while more extreme exclusion (being told that one will end up alone) causes pain numbing (Bernstein & Claypool, 2012). It is also possible that different types of exclusion experiences elicit different motivations that may play a role in amplifying or reducing pain. Molden, Lucas, Gardner, Dean, and Knowles (2009) have demonstrated that explicit social rejection (Cyberball) leads to prevention-focused behavioral responses, such as social withdrawal (and possibly increased pain), whereas being ignored actuates promotion-focused responses, such as renewed attempts at social contact (and possibly reduced pain). Insofar as engagement of physical analgesia is a function of the motivational context in which injury occurs (Fields, 2007), further research is needed to establish whether different types of social exclusion engage different biological processes to support divergent goals (e.g., seeking out a new friend or avoiding further social injury).

Although physical pain responses to social threat are complex, it is evident that social and physical injuries influence pain responses in parallel ways. Notably, studies that observed hypoalgesia after social exclusion did not find increases in emotional distress (Borsook & MacDonald, 2010; DeWall & Baumeister, 2006), whereas studies that observed hyperalgesia after social exclusion did (Eisenberger et al., 2006). Therefore, certain social threats may evoke both physical and emotional numbing, which may be adaptive in particular contexts – as when, for example, pain is too overwhelming (Bernstein & Claypool, 2012) or is inconsistent with the current motivational context (Fields, 2007).

Factors that enhance physical pain

A separate program of research also suggests that physical pain may, in turn, influence perceptions of social connection. It is well known that inflammation, the immune system's first line of defense against harmful stimuli such as pathogens, leads to exaggerated sensitivity to physical pain, which presumably aids survival by promoting rest and other recuperative behaviors (Watkins & Maier, 2000). Along these lines, research has shown that in response to an experimental inflammatory challenge that elicited a temporary inflammatory response, participants reported greater feelings of social disconnection and interpersonal sensitivity (Eisenberger, Inagaki, Mashal, & Irwin, 2010). In addition, among individuals exposed to an inflammatory challenge, those who showed the greatest increase in inflammatory activity correspondingly exhibited the greatest dACC and AI reactivity to social exclusion (Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009). These findings suggest that factors typically associated with hyperalgesia may also enhance social pain sensitivity, which is an important consideration for clinicians working with pain patients.

Factors that decrease social pain

Sensitive social support is perhaps the greatest source of relief from emotional distress, including social pain (Bowlby, 1969/1982; Mikulincer & Shaver, 2008); however, it may also be true that social support alleviates physical pain. For example, correlational research has shown that spousal support during labor is associated with decreased pain (Cogan, Henneborn, & Klopfer, 1976). In an experimental investigation of the social support–physical pain link, females undergoing a thermal pain task experienced less pain when holding their romantic partner's hand or viewing their partner's photograph (Master et al., 2009). Furthermore, the pain-reducing effect of social support is accompanied by decreased signaling in the dACC and AI to physical pain (Eisenberger et al., 2011; Younger, Aron, Parke, Chatterjee, & Mackey, 2010).

Factors that decrease physical pain

Another hypothesis suggested by the physical–social pain overlap is that factors that reduce physical pain should exert a similar effect on social pain. Earlier, we reviewed research evidence showing that opioid drugs, which are commonly used to treat physical pain, decrease separation distress in animals. Expanding on this research, a recent study (DeWall et al., 2010) tested the effect of Tylenol – a popular painkiller – on social pain in humans. Participants were given Tylenol or a

placebo daily for 3 weeks and asked to record the amount of hurt feelings they experienced during their daily social interactions. After day 15, individuals in the Tylenol condition reported lower levels of hurt feelings relative to the placebo group. Furthermore, a separate group of participants who took Tylenol daily for 3 weeks exhibited less dACC and AI activation during Cyberball exclusion.

Conclusion

In this article, evidence for a neurobiological overlap between social and physical pain has been presented with a review of their common neurochemical and neural correlates. Furthermore, it has been argued that the confluence between these two systems manifests in shared sensitivities to both types of pain, as well as in the mutual influences of various social- and physical-pain regulating factors. This research suggests that commonplace laments of broken hearts and hurt feelings are not empty metaphors; rather, they reflect a true and evolutionarily deep aspect of the human social experience. Because maintenance of social ties provided a great survival advantage for our ancestors, the social attachment system likely piggybacked on preexisting physical pain circuits to signal the possibility of social exclusion and motivate restoration of social ties.

Such considerations remind us that, while the sting of rejection may feel devastating, social pain responses are ultimately adaptive. For example, the pain of exclusion may benefit us by providing the motivation to secure new social connections (Maner, DeWall, Baumeister, & Schaller, 2007), and the voicing of hurt feelings within a romantic relationship may open up new levels of intimacy (Frey, Holley, & L'Abate, 1979). Just as individuals with congenital insensitivity to physical pain have difficulty avoiding physical injury (e.g., Fath, Hassanein, & James, 1983), an inability to feel distress in response to social threat would deprive us of an essential tool for navigating our social world.

See also: INTRODUCTION TO CLINICAL BRAIN MAPPING: Emotion and Stress; INTRODUCTION TO SOCIAL COGNITIVE NEUROSCIENCE: Neurocognitive and Physiological Mechanisms Linking Stress and Health; INTRODUCTION TO SYSTEMS: Pain: Acute and Chronic.

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