The pain of social disconnection: examining the shared neural underpinnings of physical and social pain

Naomi I. Eisenberger

Abstract | Experiences of social rejection, exclusion or loss are generally considered to be some of the most 'painful' experiences that we endure. Indeed, many of us go to great lengths to avoid situations that may engender these experiences (such as public speaking). Why is it that these negative social experiences have such a profound effect on our emotional well-being? Emerging evidence suggests that experiences of social pain — the painful feelings associated with social disconnection — rely on some of the same neurobiological substrates that underlie experiences of physical pain. Understanding the ways in which physical and social pain overlap may provide new insights into the surprising relationship between these two types of experiences.

"… a sense of separation is a condition that makes being a mammal so painful." Paul MacLean[1]

Some of the most distressing experiences that we face involve the dissolution of our closest social bonds. Indeed, it is difficult to imagine a situation more upsetting than a relationship break-up or one more devastating than the loss of a loved one. In fact, according to one study, nearly three out of four people listed the loss of a close relationship (for example, through death or a relationship break-up) as the "single most negative emotional event" of their lives[2]. Interestingly, some individuals have gone so far as to describe these experiences of social loss or social separation as being 'painful'[1]. Given the intense emotional consequences of broken social bonds, one may ask why we react so strongly to the loss of our social ties.

Research over the past century, from social psychology to behavioural neuroscience, has demonstrated the importance of social bonds for mammalian well-being and survival[3–5]. Early in life, many mammalian infants are completely dependent on caregivers, relying on them exclusively for nourishment, care and protection[6]. Later on, connections to a social group aid survival through the shared responsibility for food acquisition, predator protection and care for offspring[3]. Owing to this profound reliance on others, threats to social connection may be just as detrimental to survival as threats to basic physical safety and thus may be processed by some of the same underlying neural circuitry. Specifically, it has been proposed[6–10] that experiences of 'social pain' — which is defined as the unpleasant experience that is associated with actual or potential damage to one's sense of social connection or social value (owing to social rejection, exclusion, negative social evaluation or loss) — may be processed by some of the same neural circuitry that processes physical pain (which is defined as the unpleasant experience that is associated with actual or potential tissue damage[11]). Given the importance of social connection for survival, the definition of social pain used here is intentionally broad and includes multiple experiences that signal the loss, or potential loss, of social connection or social value, therefore signifying an increased survival risk. Thus, social pain includes experiences in which a relationship is threatened or lost because the self is devalued (rejection or negative evaluation), as well as experiences in which a relationship is lost but the self is not implicated (death of a loved one), as both of these experiences signify a loss of a protective social bond.

This Review highlights the growing body of literature suggesting a possible overlap in the neural circuitry underlying physical and social pain. This article first summarizes the observational evidence that provides the starting point for the hypothesis that negative social experiences are painful and considers why the physical pain signal may have been co-opted to prevent social disconnection. The neurochemical and neural substrates that process physical pain are then reviewed, and research showing that some of these substrates also process social pain is summarized. Next, some of the

University of California, Department of Psychology, 4444 Franz Hall, Los Angeles, California 90095, USA.
e-mail: neisenbe@ucla.edu
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potentially surprising consequences of this shared neural circuitry are reviewed. Finally, the possible involvement of this neural circuitry in the link between social connection and both mental and physical health is discussed, as well as several remaining questions regarding the nature of social pain.

Observational evidence of social pain

> *"The intense, ever-increasing cathexis of the absent (lost) object generated by the child's unassuageable longing creates exactly the same economic conditions as does the pain-generated cathexis of an injured part of the body …" Sigmund Freud*[12]

Several early psychological thinkers, dating at least back to Freud, have drawn analogies between physical and social pain. However, one need look (or listen) no further than to our everyday language to see how physical and social pain are similarly conceptualized. Individuals use the same words to describe instances of physical and social injury, complaining of 'broken bones' and 'broken hearts' or 'hurt muscles' and 'hurt feelings'. In fact, experiences of social rejection or exclusion have been shown to elicit a discrete category of affective responses termed 'hurt feelings', which are described in a manner reminiscent of physical pain (for example, a "cutting stab" or a "sinking inner pain"[13]). Importantly, using physical pain words to describe experiences of social pain is a phenomenon common to many languages[10], suggesting a potentially universal overlap in the experience of physical and social pain.

Perhaps more convincing than a linguistic overlap, however, is the fact that experiences of social pain appear to be just as noxious and dreaded as experiences of physical pain. Suicide, one means to escape negative experience, is not only more prevalent in patients with chronic pain (in comparison to healthy controls)[14] but is also more common in those suffering from social isolation or social loss[15,16]. Anxiety disorders, characterized by a heightened focus on possible harm and its avoidance, have been shown to be rooted in two fundamental types of concerns: concerns about the possibility of physical harm (and thus physical pain) and concerns about the possibility of social harm, including rejection or evaluation (and thus social pain)[17].

In addition, behavioural evidence suggests that, in a similar way to experiences of physical injury, experiences of social injury result in self-reported pain. People recalling prior episodes of social pain report that they were just as painful (using a pain rating scale) as prior episodes of physical pain[18,19]. Moreover, following the death of a loved one — arguably one of the most devastating forms of social pain — bereaved people report feeling intense psychological pain and often complain of somatic symptoms[20,21].

Thus, there is considerable indirect evidence that social pain may be processed in a manner similar to physical pain. Considering the severe survival threat imposed by social disconnection, it makes sense that threats to social connection may utilize the same pain signal that signifies threats to the physical body. The pain signal interrupts ongoing behaviour; promotes quick responses aimed at terminating, reducing or escaping the source of threat; and serves as a punishment-based reinforcer to teach organisms to avoid threatening stimuli in the future[22]. Not surprisingly, individuals born without the ability to feel pain die significantly earlier[23]. Such a salient signal could be invaluable in signalling, terminating and later motivating the avoidance of threats to social connection as well. Consequently, the pain mechanisms involved in preventing physical harm may have been co-opted to prevent social separation[6], thereby increasing survival likelihood.

Neurochemical substrates of social pain

Perhaps the earliest evidence for an overlap in the systems underlying physical and social pain was the demonstration that opiates, best known for their pain-relieving effects, also reduce separation distress behaviours in non-human mammals[6]. Opiates, such as morphine, have well-documented analgesic (as well as euphoric) effects[24] and are part of the first line of defence for ameliorating severe physical pain. The pain-relieving effects of opiates appear to be mediated by the mu-opioid receptor, as mice lacking the mu-opioid receptor gene (*OPRM1*) are unresponsive to the pain-relieving effects of morphine and show increased sensitivity to painful stimuli[25].

In addition to their pain-relieving effects, opiates reduce behaviours associated with the distress of social separation, such as isolation calls, a type of distress vocalization emitted by infants upon maternal separation. Across multiple species, low, non-sedative doses of morphine, an opioid receptor agonist, reduce isolation calls in response to maternal separation, whereas naloxone, an opioid receptor antagonist, increases isolation calls[26–29]. Consistent with this evidence, mice lacking *OPRM1* show significant deficits in attachment behaviours, including reductions in isolation calls following mother–infant separation[30]. In these mice pups, the lack of mu-opioid signalling may reduce the rewarding experience associated with maternal interaction, resulting in little distress following maternal separation and thus fewer isolation calls. Opioid-related processes have also been shown to have a role in social affiliative processes. Opioid receptor agonists reduce time spent in close proximity with con-specifics[26,27,31], presumably because the opioids act as a substitute for the rewarding experience of social connection. Conversely, opioid receptor antagonists increase attempts at social connection through grooming[32], presumably in order to increase the experience of reward (through social means) that is being reduced by opioid receptor antagonists.

On the basis of these findings, it has been suggested that the social attachment system may have piggybacked onto the opioid substrates of the physical pain system to maintain proximity with others, eliciting distress upon separation (through low opioid receptor activity) and comfort upon reunion (through high opioid receptor activity)[6]. Indeed, given the robust effects of opiates on social attachment processes, some have drawn parallels between the nature of opiate addiction and social

Isolation calls
A type of distress vocalization produced by infant mammals in response to separation from a caregiver. These vocalizations function to facilitate reunion with the caregiver.

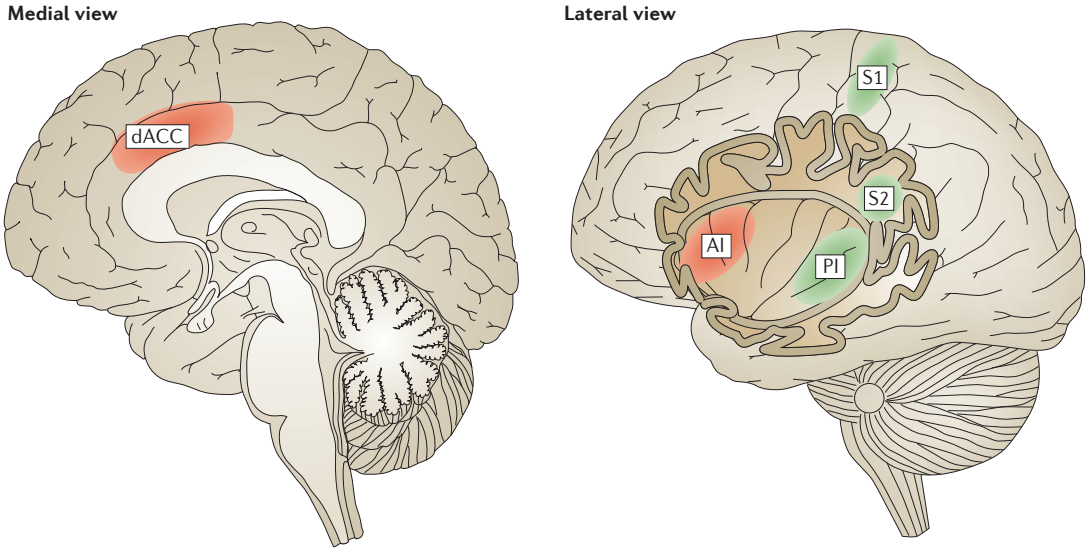


Figure 1 | **Cortical substrates of the affective and sensory components of physical pain.** The medial view on the left shows the dorsal anterior cingulate cortex (dACC). The lateral view on the right shows the primary somatosenory cortex (S1) on the outer surface of the brain, the secondary somatosensory cortex (S2) on the edge of the cut-out of the brain and the anterior insula (AI) and posterior insula (PI) in the middle of the cut-out of the brain. Sensory components are shown in green and affective components in red.

bonding, noting that both involve the development of strong attachments to a particular object (opiates or a loved one) and intense distress (including crying, irritability, depression and insomnia) to its withdrawal[6,26]. In sum, endogenous brain opioid systems, which are known to regulate the distress of physical pain, may be one of the neurochemical regulators of the distress associated with social separation, as well as the pleasure associated with social connection. Other neurochemical systems are likely to be involved as well[6].

Neural substrates of social pain

In addition to shared opioid substrates, experiences of social and physical pain rely on shared neural circuitry. To better understand the ways in which social pain might utilize physical pain-related neural circuitry, it is important to first elaborate on two components of the physical pain experience and their underlying neural substrates. Although physical pain 'feels like' a single, unified experience, pain researchers have subdivided pain into two dissociable (although highly interrelated) components: a sensory component involved in coding for stimulus localization (for example, arm versus leg), quality discrimination (such as stinging or burning) and intensity discrimination (the objective strength of the nociceptive signal); and an affective component associated with the unpleasant or distressing experience of pain (such as the subjective bothersomeness of the nociceptive signal) and the drive to terminate the stimulus causing this experience[33,34].

Given the significance of the affective component of pain for signalling an aversive state and motivating behaviour to terminate, reduce or escape the source of painful stimulation[22,34], it has been hypothesized that experiences of social pain rely on brain regions associated with the affective component of pain in order to warn against and prevent the dangers of social harm[8–10]. Sensory-related regions may also be involved, as 'somatic' symptoms are often reported following social pain[13,20]. However, the affective component of pain may be more directly implicated in social pain experience. In agreement with this assertion, a patient with congenital insensitivity to physical pain — which involves an impairment of the sensory (but not affective) component of pain — reported feeling pain for the first time shortly after the unexpected death of a younger sibling[35], suggesting that painful experience can arise from social loss even in the absence of sensory-related processing ability. Hence, the affective component of pain may be more crucial for experiencing the pain associated with negative social experiences.

Neural substrates of physical pain. The affective component of physical pain is processed cortically by the dorsal anterior cingulate cortex (dACC; defined here as Brodmann areas 24 and 32, superior and posterior to the genu of the corpus callosum) and the anterior insula (AI)[33,34] (FIG. 1). Following cingulotomy for the treatment of chronic pain, in which a portion of the dACC is surgically lesioned[36], patients are still able to localize pain sensations but report that the 'pain no longer bothers them'[37], highlighting a unique role for this region in the distressing experience of physical pain. Consistent with this, lesions to this region in animals result in reductions in affective pain responses (pain-induced conditioned place avoidance)[38] and impairments in learning to avoid noxious stimuli[39]. Insular lesions produce similar outcomes, leading to pain asymbolia, a condition in which pain is perceived but does not cause distress or suffering[40], or other disruptions of pain affect[41]. Neuroimaging

studies largely echo these neuropsychological findings. Hypnotic suggestions to increase the felt unpleasantness of pain lead to specific increases in dACC activity without altering activity in the somatosensory cortex, a sensory-related neural region[42]. Moreover, there is a direct correspondence between the magnitude of felt pain unpleasantness and activity in the dACC and AI[43–47]. Finally, given the profound capacity of opiates to reduce the affective component of pain[24], it is not surprising that both the dACC and AI have some of the highest densities of mu-opioid receptors in the central nervous system[48,49].

The sensory component of pain, however, is largely processed by the primary and secondary somatosensory cortices (S1 and S2, respectively)[50–52], as well as the posterior insula (PI)[44] (FIG. 1). Thus, patients with lesions to one or a combination of S1, S2 and PI show deficits in processing pain sensations as well as other sensory information (such as temperature discrimination)[41,53,54], but in some cases still describe the sensations as unpleasant, suggesting that the affective component of pain is intact[54]. Similarly, neuroimaging studies have shown that manipulations that augment the felt intensity of painful stimulation activate S1 as well as S2 and/or PI[44,45,51,55]. Using these pain-related neural substrates as a framework, animal and human research has demonstrated that some of the same regions — in particular, the affective neural regions — contribute to social pain.

Neural substrates of social pain in animals. Although animal studies cannot provide direct information regarding the experiential correlates of threats to social bonds, they provide important information about the neural regions associated with social separation-related behaviours. Two behaviours intimately linked with social separation in non-human mammals are isolation calls and maternal behaviour (including retrieving, crouching over and licking pups), both aimed at reducing mother–infant separation and thereby ensuring infant survival. Both of these behaviours seem to rely, in part, on neural activity in the dACC or more broadly in the ACC.

The ACC is well-positioned to contribute to the distress of social separation and behaviours aimed at reducing social separation. This region has no counterpart in the reptilian brain and thus, along with attachment-related and maternal behaviour, may distinguish the evolutionary transition from reptiles to mammals (and birds)[1,56]. Indeed, the thalamocingulate division of the brain — which includes the cingulate cortex and connected medial thalamic nuclei — is not only involved in mammalian attachment-related processes but is also directly involved in the affective component of physical pain[33,34], again highlighting the part that pain processes may play in maintaining social attachments.

As evidence for the role of the ACC in isolation calls, lesioning the ACC (dorsal and/or ventral to the genu) reduces these distress vocalizations[57,58], whereas electrically stimulating this region or its afferent inputs (from the mediodorsal thalamus) leads to the spontaneous production of these distress vocalizations[26,59,60]. Interestingly, lesions to the ACC (both dorsal and ventral to the genu) have also been shown to lead to reductions in social interactions and time spent in proximity with other animals[58], suggesting that this region may be crucial for registering the distress associated with social separation and motivating attempts at social reconnection.

In addition to isolation calls, the cingulate cortex has been shown to contribute to maternal behaviour aimed at pup retrieval (returning pups to the nest). For example, hamsters with lesions to the cingulate cortex retain most species-typical forms of behaviour but show severe deficits in maternal behaviour, failing completely in pup retrieval[61]. Mice and rats with cingulate lesions are similarly impaired[62,63]. Together, these studies demonstrate the critical role of the cingulate cortex generally, and the ACC more specifically, in behaviours that promote social bonds in non-human mammals.

Neural substrates of social pain in humans. Although there have been few studies examining the effect of neural lesions on social behaviour in humans, some studies support the idea that the dACC contributes to social motivation. Following cingulotomy, patients show decrements in self-consciousness[64,65] as well as a reduced concern about the opinions or social judgements of others[65]. To date, however, no studies have investigated the effect of dACC lesions on sensitivity to discrete types of socially painful experiences (such as social rejection). Instead, the majority of evidence for the role of the dACC and AI in social pain in humans comes from neuroimaging studies.

The first study to examine the neural substrates of social pain focused on neural responses to social exclusion[7]. In this study, participants believed they were playing a virtual game of catch, called 'Cyberball,' with two other individuals over the Internet (FIG. 2a). In reality, the other players were computer-controlled and the game was preset so that participants were first included in the game and then excluded when the two players stopped throwing them the ball. Notably, in response to social exclusion versus inclusion, participants showed increased activation in the dACC and AI (FIG. 2b). Moreover, greater activity in the dACC was associated with greater feelings of social distress (for example, "I felt rejected") in response to social exclusion (FIG. 2c).

Several additional studies have used the Cyberball task to examine the neural correlates of social exclusion from strangers. Many of these studies have shown increased activity in the dACC and/or AI in response to social exclusion[7,66–75] (BOX 1) and/or a positive correlation between neural activity in these regions and self-reported feelings of social distress in response to exclusion[7,67,69,70,73,76–78] (BOX 2). Moreover, factors typically associated with a greater sensitivity to social exclusion, such as low self-esteem[79], anxious attachment[77], interpersonal sensitivity[80] or a tendency to feel socially disconnected on a daily basis[81], have been shown to be associated with increased neural activity in the dACC and/or AI in response to social exclusion. Likewise, factors typically associated with a reduced sensitivity to social exclusion, such as social support[67,78] or avoidant attachment[77], have been shown to be associated with reduced activity in the dACC and/or AI.

Cyberball
A virtual ball-tossing game that can be used to induce social inclusion or exclusion, depending on the behaviour of the other virtual players (whether they toss the ball to the participant).

Anxious attachment
A style of relating to close others characterized by a heightened concern about being abandoned by close others and therefore an exaggerated sensitivity to signs of acceptance or rejection by others.

Avoidant attachment
A style of relating to close others characterized by an avoidance of seeking out support or closeness from others.

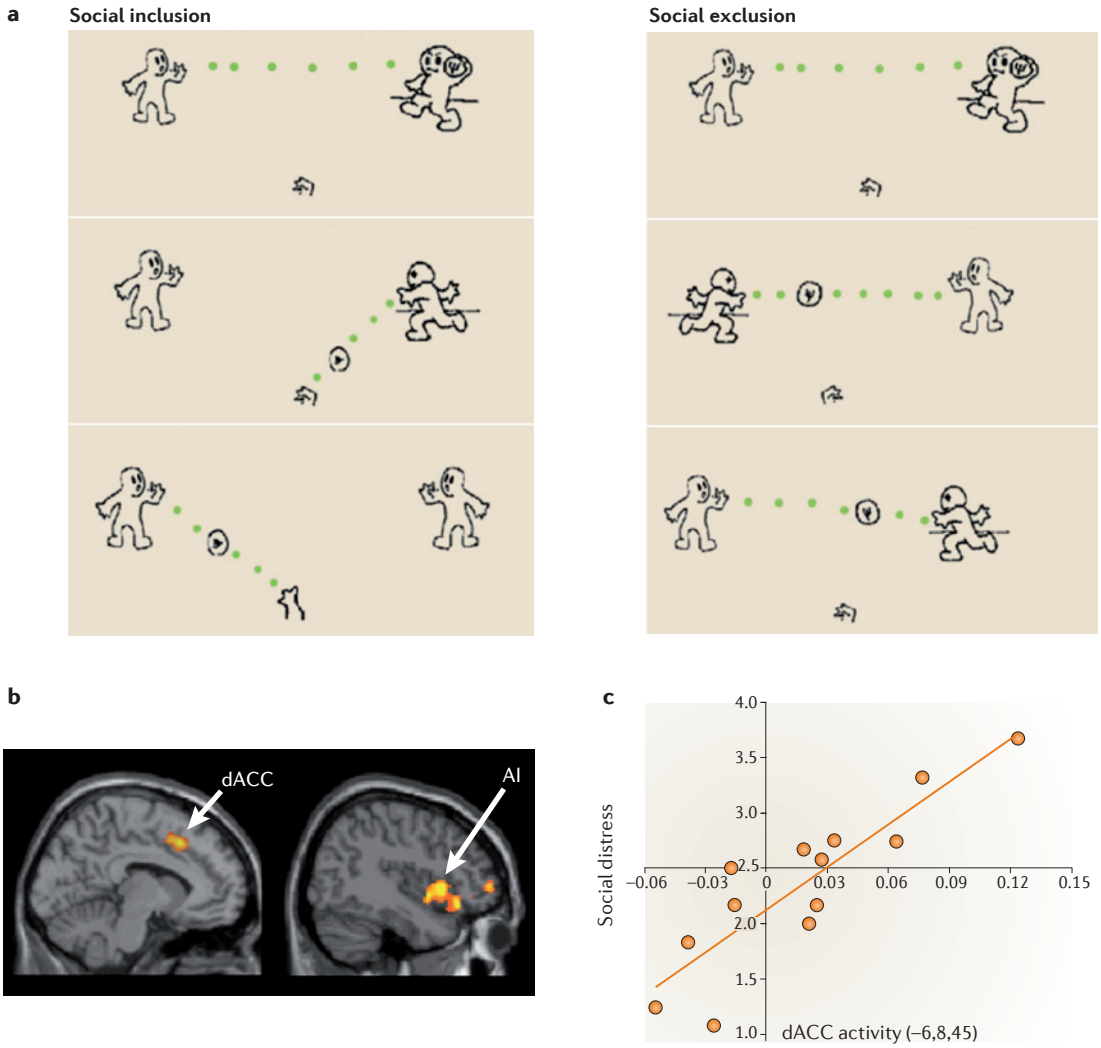


Figure 2 | **Neural responses to social exclusion. a** | Pictorial depiction of what participants see during the inclusion and exclusion rounds of the Cyberball game. On the left, the participant, depicted by the hand at the bottom of each screenshot, is included in the ball-tossing game with the two other players, depicted in the upper left and right hand corners of the screenshots. On the right, the participant is excluded when the two other players stop throwing the ball to the participant. **b** | Activity in the dorsal anterior cingulate cortex (dACC; coordinates: –8,20,40) and anterior insula (AI; coordinates: 42,16,1) that was greater during social exclusion than during social inclusion[7]. **c** | Activity in the dACC that correlated positively with self-reported distress in response to social exclusion[7]. Figure modified, with permission, from REF. 8 © (2004) Elsevier.

In addition, some Cyberball studies have found increased activity in the subgenual ACC (subACC) in response to social exclusion[68,71–75,82]. The subACC is a region implicated in affective processes[83] but not, typically, in physical pain. Although some studies have shown that greater activity in this region correlates with greater social distress[73,76], others have shown increased activity in this region in response to social acceptance rather than social rejection[84]. Moreover, many studies that find subACC activity have not examined correlations between self-reported distress and neural activity, and so it is not yet clear how this region contributes to the experience of social exclusion. Interestingly, as shown in BOX 1, subACC activity is more likely to appear in Cyberball studies that include adolescent participants. Indeed, some work has shown that subACC responses to exclusion are higher in adolescents and decrease with increasing age[72]. Thus, it is possible that subACC, rather than dACC, activity in response to social exclusion is indicative of an earlier developmental processing of exclusion. This is consistent with models that have suggested differential development in dorsal versus ventral emotion-processing systems and fits with prior work showing that dACC responses to threatening stimuli do not become evident until later in development[85]. Future studies, however, are needed to further examine the role of the subACC in social pain processes.

Studies of another form of social pain — feelings associated with being socially evaluated (which signals the possibility of being rejected by others) — have

Box 1 | **Summary of neural activations in social pain studies**

To identify the neural regions most frequently activated in response to social pain, studies examining neural responses to social exclusion (using the Cyberball method), social evaluation, rejection-themed images, romantic rejection and bereavement were reviewed. It is important to note that this was not a complete meta-analysis and, as such, no efforts were made to contact authors to identify unpublished null findings. The table illustrates the pattern of neural activity observed in response to various social pain tasks in several pain-related regions, including the dorsal anterior cingulate cortex (dACC), anterior insula (AI), thalamus (Thal), primary somatosensory cortex (S1), secondary somatosensory cortex (S2), posterior insula (PI) and periaqueductal grey (PAG), as well as the subgenual ACC (subACC; as this region is activated in some studies). Notably, dACC and AI activations were each observed in 67% of the 24 studies reviewed. Compared to these affective pain-related neural regions, sensory-related neural regions were not as consistently activated (Thal (13%); S1 (0%); S2 (4%); PI (25%)). The subACC was observed in 29% of these studies, all of which used the Cyberball methodology. Interestingly, 71% of the studies that showed subACC activation included adolescent participants; thus, it is possible that subACC activity to exclusion is more prevalent in developing samples. Indeed, when assessing only studies of adult participants, the dACC and AI were activated in 74% and 63% of the studies, respectively, whereas the subACC was activated in 100% of the studies that included adolescent participants.

Task	dACC	AI	subACC	Thal	S1	S2	PI	PAG	Refs
Adult samples									
Cyberball	↑	↑	-	-	-	-	-	-	7
Cyberball	↑	↑	-	-	-	-	-	-	66
Cyberball	↑	↑	-	-	-	-	-	-	67
Cyberball	↑	↑	↑	-	-	-	↑	-	68
Cyberball	↑	-	-	-	-	-	-	-	69
Cyberball	-	↑	-	-	-	-	-	-	70
Cyberball	↑	-	↑	-	-	-	↑	-	71
Cyberball	-	-	-	-	-	-	↑	-	76
Negative evaluation	-	↑	↓	-	-	-	-	-	84
Negative evaluation	↑	-	-	-	-	-	-	-	88
Evaluative threat	↑	-	-	-	-	-	-	-	86
Evaluative threat	-	↓	-	-	-	-	-	-	139
Rejection images	↑	↑	-	-	-	-	-	-	89
Disapproving faces	-	-	-	-	-	-	-	-	90
Romantic rejection	↑	↑	-	-	-	-	↑	-	91
Romantic rejection	↑	↑	-	↑	-	↑	↑	-	92
Bereavement	↑	↑	-	-	-	-	-	-	93
Bereavement	↑	↑	-	-	-	-	-	↑	94
Bereavement	↑	↑	-	↑	-	-	-	↑	95
Samples that included adolescents									
Cyberball	↑	↑	↑	↑	-	-	-	-	72*
Cyberball	-	-	↑	-	-	-	-	-	83*
Cyberball	-	↑	↑	-	-	-	-	-	73‡
Cyberball	↑	↑	↑	-	-	-	-	-	74‡
Cyberball	-	↑	↑	-	-	-	↑	-	75‡

'↑' indicates regions that were significantly activated by the task; '↓' indicates regions that were significantly less activated or deactivated by the task. In samples where two groups were compared (for example, autistic patients versus controls), the data from the control group are reported. '-' indicates that there were no significant effects reported for that region. *Participants included adolescents and adults. ‡All participants were adolescents.

yielded findings that are similar to those from studies of exclusion. Thus, during a social-evaluative task, in which participants prepared a speech that would later be evaluated by a panel, participants showed increased activity in the dACC[86]. Similarly, in response to being evaluated on a personal interview, feeling worse in response to negative social evaluative feedback ("you are boring") was associated with greater activity in the dACC and AI[87]. Moreover, when participants were made to evaluate themselves negatively, through an unfavourable comparison with a superior peer, they showed increased activity in the dACC[88].

Even subtle rejection cues that do not necessarily elicit feelings of social pain can activate some of these pain-related neural regions, perhaps attesting to the salience of social disconnection among humans. Thus, viewing rejection-themed paintings (by Edward Hopper) led to increased activity in the dACC and AI compared to viewing acceptance-themed paintings (by August Renoir)[89]. Also, viewing (non-personal) videos of individuals displaying disapproving facial expressions led to increased activity in the dACC for those more sensitive to rejection[90].

Although most studies examining social pain have focused on interactions with strangers, a few studies have examined the neural correlates of social rejection from a close other, which is likely to be a more socially painful experience. In these studies, participants who recently experienced an unwanted romantic relationship break-up were asked to view pictures of their ex-partner and think about the rejection experience[91,92]. In response to thinking about the ex-relationship partner versus a friend, participants showed increased activity in the dACC and AI, which are affective pain-related regions, as well as in the PI[91,92] and, in one study[92], the S2, which are regions associated with the sensory component of pain. In addition, one study[92] included a physical pain task alongside the social pain task and found overlapping neural activity to physical and social pain in each of these regions, again lending support to the idea that physical and social pain rely on shared neural circuitry.

Finally, although less work to date has focused on the neural correlates of social loss (such as the death of a close other), several studies have demonstrated that thinking about a lost loved one can activate affective pain-related neural regions. Thus, viewing pictures of a deceased loved one (versus a stranger) led to increased activity in the dACC and AI[93,94]. Moreover, females who lost an unborn child (versus those who delivered a healthy baby) showed greater activity in the posterior dACC when viewing images of smiling baby faces[95].

In sum, studies examining various situations that are likely to produce social pain — ranging from social exclusion to the loss of a loved one — have shown activity in several pain-related neural regions. Although the most commonly activated regions, particularly for adults, are the dACC and AI (BOX 1) — which are regions involved in the affective component of physical pain — some studies, such as those examining romantic rejection, have also shown activity in sensory-related neural regions (PI). It has been suggested that

Box 2 | **Correlations between neural activity and self-reported distress in response to social pain**

In addition to identifying the neural regions that show activity in response to socially painful events, it is important to explore how neural activity in these regions correlates with self-reported negative experience in response to these events. This is important, in part, because neural activity in response to a socially painful event could be indicative of several different responses, including negative affect or attempts at regulating negative affect ("I don't care what those people think about me anyway"). Examining correlations between neural responses to social pain and self-reported negative affect may provide some clues about whether the activated neural regions are involved in the negative experience associated with social pain. The table highlights the neural regions that correlate with self-reported social distress in response to certain tasks. Most of the studies that examine self-reported social distress used the Cyberball methodology and asked subjects to rate how they felt in response to being socially excluded (using items such as: "I felt rejected", "I felt meaningless" or "I felt invisible"). The most consistent pattern observed here is that greater feelings of social distress in response to socially painful tasks are associated with greater activity in the dorsal anterior cingulate cortex (dACC) and the anterior insula (AI). This is particularly true for the non-adolescent samples, in which dACC and AI activity are observed in 73% and 45% of the studies, respectively.

Task	Measure	dACC	AI	subACC	Thal	S1	S2	PI	PAG	Refs
Adult samples										
Cyberball	Social distress	↑	-	-	-	-	-	-	-	7
Cyberball	Social distress	↑	↑	-	-	-	-	-	-	67
Cyberball	Social distress	↑	-	-	-	-	-	-	-	69
Cyberball	Observer-rated distress	↑	↑	-	-	↓	-	-	-	70
Cyberball	Social distress	↓	-	-	-	-	-	-	-	71
Cyberball	Social distress	↑	-	↑	-	-	-	-	-	76
Cyberball	Social distress	↑	↑	-	-	-	-	-	-	77
Cyberball	Social distress	↑	-	-	-	-	-	-	-	78
Negative evaluation	'Feeling bad'	↑	↑	-	-	↓	-	↓	-	87
Evaluative threat	(No effects)	-	-	-	-	-	-	-	-	86
Rejection images	Distress	↓	↑	-	-	-	-	-	-	89
Samples that included adolescents										
Cyberball	Social distress	-	-	-	-	-	-	↑	-	72*
Cyberball	(No effects)	-	-	-	-	-	-	-	-	82*
Cyberball	Social distress	-	↑	↑	-	-	-	-	-	73‡
Cyberball	(No effects)	-	-	-	-	-	-	-	-	74‡

'↑' indicates regions that showed a positive correlation with self-reports; '↓' indicates regions that showed a negative correlation with self-reports; '-' indicates that there were no significant effects reported for that region. PAG, periaqueductal grey; PI, posterior insula; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; subACC, subgenual anterior cingulate cortex; Thal, thalamus. Studies that did not examine correlations with self-reports were not included. *Participants included adolescents and adults. ‡All participants were adolescents.

this sensory-related neural activity is due to the more intense experience of social pain that results from rejection from a close other[92]. Although this account seems plausible, it is at odds with the fact that studies of social loss or bereavement — some of the most intense experiences of social pain — have not typically yielded these types of activations. Still, it is possible that sensory-related neural regions are crucial for experiences of social pain that involve the devaluation of the self by others (being rejected) rather than experiences of social pain that involve the termination of a relationship but do not imply that the self is devalued (bereavement). Future work will be needed to fully examine whether, and under what circumstances, sensory regions are implicated in social pain processing. In addition, it will be important for future research to continue to examine how self-reported experience in response to socially painful events correlates with observed neural activity. Although not a perfect solution, self-reported experiences of distress may provide additional leverage in trying to determine whether the neural regions observed in response to socially painful events are involved in processing distress or in some other co-occurring process, such as the attempted regulation of this distress. Finally, additional research will be needed to determine the precise types of inputs to which the dACC and AI respond, as these regions have also been implicated in other types of psychological processes (BOX 3).

Box 3 | **Affective versus cognitive processing in the dACC**

Although substantial evidence supports the role of the dorsal anterior cingulate cortex (dACC) in negative affective experience (pain, fear and distress)[34,51], this concept is at least superficially at odds with an otherwise predominantly cognitive account of dACC activity. For example, research has highlighted the role of this region in conflict monitoring — detecting conflicting response tendencies (in the Stroop task, for example) or mismatches between produced and intended responses (that is, error detection) in order to signal the need for cognitive control[140]. On the basis of this, some have suggested that this region is involved in cognition, not affect[141]. However, another possibility is that these two accounts of dACC function are not incompatible, but rather work together as two components of a neural alarm system involved in the detection of discrepancies from a desired set point and the sounding of an alarm (which may include affective responses and autonomic activity) to recruit attention and resources aimed at fixing the discrepancy[8]. From this perspective, studies of conflict monitoring and error detection have examined the discrepancy detection function of the dACC, whereas studies on pain distress, fear or autonomic responding have focused on the alarm sounding function of the dACC. Indeed, recent meta-analyses have shown that negative affect, pain and tasks requiring cognitive control activate overlapping regions of the dACC[142,143]. Moreover, we have recently shown that fluctuations in the magnitude of dACC activity in response to errors during a cognitive stop-signal task were positively correlated with fluctuations in self-reported negative affect (frustration) across the task, even after controlling for various cognitive variables (number of errors, self-reported attention and effort)[149]. Thus, the dACC may perform both cognitive and affective functions that complement one another in supporting efficient goal-corrected behaviour.

Consequences of shared pain circuitry

One of the implications of this shared neural circuitry is that there should be predictable consequences of a physical–social pain overlap. Two hypothesized consequences are that individuals who are dispositionally more sensitive to one kind of pain should also be more sensitive to the other and that factors that increase or decrease one kind of pain should influence the other kind of pain in a similar manner (FIG. 3).

Individual differences. Although shared sensitivity to physical and social pain is not an obvious hypothesis, several lines of clinical research support this idea. Patients with chronic pain, who experience more physical pain, are also more sensitive to social pain than control subjects, as evidenced by greater fear and avoidance of social interactions and a greater incidence of social phobia[96]. Moreover, higher levels of daily pain affect are associated with higher levels of anxious attachment or a greater concern about being rejected by others[97]. Similarly, a large amount of work has demonstrated that those with a heightened sensitivity to social pain — such as those with an anxious attachment style or high levels of rejection sensitivity — report more somatic symptoms overall, including pain, than those with secure attachment styles[98–100].

Experimental work in healthy controls also supports this overlap. Individuals who are more sensitive to physical pain (assessed through experimental pain stimulation) also report higher levels of social pain in response to social exclusion[101]. In addition, participants with the rare form of the *OPRM1* polymorphism, which has previously been linked with increased physical pain sensitivity[102], demonstrate higher levels of rejection sensitivity and show greater activity in the dACC and AI in response to an experimental episode of social exclusion[103].

Rejection sensitivity
The tendency to anxiously expect, readily perceive and intensely react to experiences of social rejection.

Factors that enhance or reduce pain. A second consequence of a physical–social pain overlap is that factors that increase or decrease one kind of pain should have a similar effect on the other. For example, factors that typically increase social pain — such as social trauma, failure or exclusion — should also increase sensitivity to physical pain. Indeed, although there are some inconsistencies, several studies support this premise. Patients with somatoform pain disorder and fibromyalgia, who experience pain with no medical explanation, also report greater levels of early social trauma (including emotional abuse or family conflict)[104], suggesting a potential link between these early socially painful experiences and later reports of physical pain.

In addition, experiences of both failure and social exclusion are related to increased physical pain sensitivity. Experimental manipulations of failure (which may convey that one would not be liked or accepted by others) have been shown to increase pain ratings to a cold-pressor task, a painful task that involves immersing one's hand in ice water for extended periods of time[105,106]. Similarly, experiences of social exclusion have been shown to increase physical pain sensitivity[107], and those who report feeling more rejected in response to exclusion report higher physical pain ratings in response to a pain stimulus delivered at the end of the exclusion episode[101].

However, some studies have shown opposite effects. Paralleling the finding that endogenous analgesic systems can be triggered by the presence of physical threats[108,109], some work has shown that analgesic responses can also result from the presence of social threats. For example, being told that one will be alone in the future has been shown to reduce physical pain sensitivity[107,110]. Although it is not clear why social rejection and/or exclusion sometimes leads to increased physical pain and sometimes to reduced physical pain, these differences are not incompatible with the physical pain literature, which has shown both hyperalgesia and analgesia following nociceptive stimulation[109,111,112]. One possibility is that these differential pain outcomes may be due to the severity of the threatening stimulus[107]. In line with this possibility, it has been shown that exposure to a severe social injury (such as being told that one will be alone in the future) reduces physical pain sensitivity, whereas exposure to a less severe social injury (Cyberball exclusion) increases physical pain sensitivity[107]. Additional work will be needed to determine the precise conditions under which specific types of social pain increase or decrease physical pain, as well as how they are manifested neurobiologically.

More consistent findings have emerged from studies examining whether factors that typically increase physical pain also increase social pain. For example, it has long been noted that, in children, factors that increase the experience of physical pain (such as injury or sickness) also increase the child's sensitivity to the whereabouts of their caregiver, leading to more frequent experiences of distress upon separation[5]. Similarly, in adults, inflammatory activity, which is known to increase physical pain[113], can also increase social pain, leading to greater

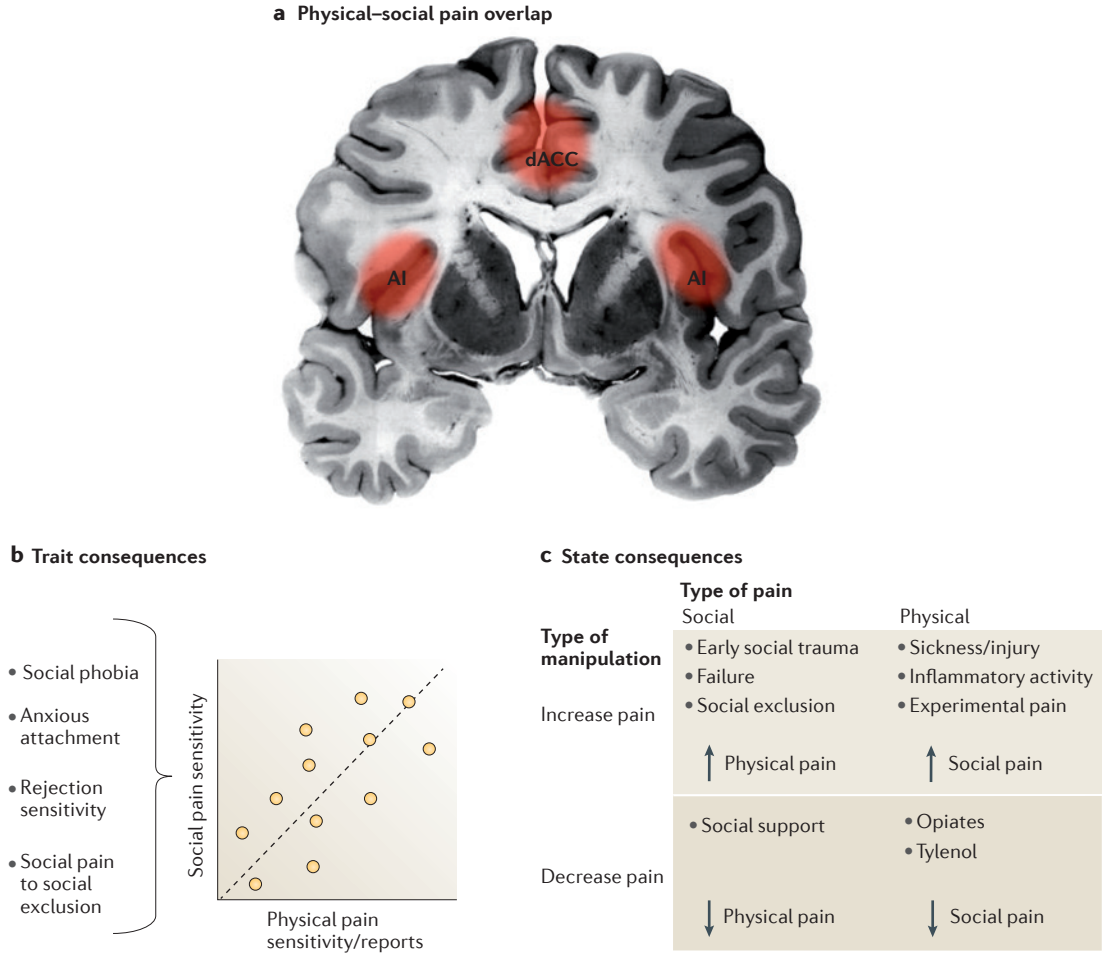


Figure 3 | **Model depicting the functional consequences of a physical–social pain overlap. a** | To the extent that physical and social pain rely on shared neural substrates (dorsal anterior cingulate cortex, (dACC) and anterior insula, (AI)), there should be trait and state consequences. **b** | The trait consequences of a physical–social pain overlap are that individual differences in sensitivity to one kind of pain should relate to individual differences in sensitivity to the other. The graph here shows the forms of social pain sensitivity that have been associated with physical pain sensitivity. **c** | The state consequences of a physical–social pain overlap are that factors that increase or decrease one kind of pain should affect the other in a similar manner. The box here lists the factors that are typically associated with altering one kind of pain (for example, Tylenol typically reduces physical pain) and have been shown to have the same effect on the other kind of pain (for example, Tylenol can also reduce social pain). Figure modified, with permission, from REF. 148 © (2012) Wolters Kluwer Health.

feelings of social disconnection[114]. Moreover, greater inflammatory activity in response to an inflammatory challenge has been shown to be associated with greater activity in the dACC and AI in response to an experimental episode of social exclusion[115]. Finally, although somewhat surprising, recent work has shown that experiences of physical pain can directly increase feelings of social exclusion even in the absence of being socially excluded; participants exposed to painfully cold water (versus warm water) reported feeling more ignored and excluded[19].

In addition to pain-enhancing effects, factors that reduce one type of painful experience should reduce the other as well. Along these lines, considerable research has shown that social support, typically associated with reduced perceptions of social harm, is related to reduced physical pain. Correlational research has demonstrated that individuals with more social support experience less pain across a number of different domains[116,117]. In addition, experimental work has demonstrated a causal effect of social support on pain[118–120]. For example, viewing a picture or holding the hand of a loved one (relative to a stranger or object) leads to reductions in self-reported pain[118–120], as well as reductions in pain-related neural activity (in the dACC and AI)[119,120]. Thus, the perception or presence of social support, presumably indicative of a lesser likelihood of social harm, appears to reduce physical pain as well.

Finally, factors that are known to reduce physical pain should also reduce social pain. In addition to research showing that opiates can reduce social as well as physical pain[6], other analgesic drugs typically used to manage physical pain have also been shown to reduce social pain. Thus, in a double-blind, placebo-controlled study, taking

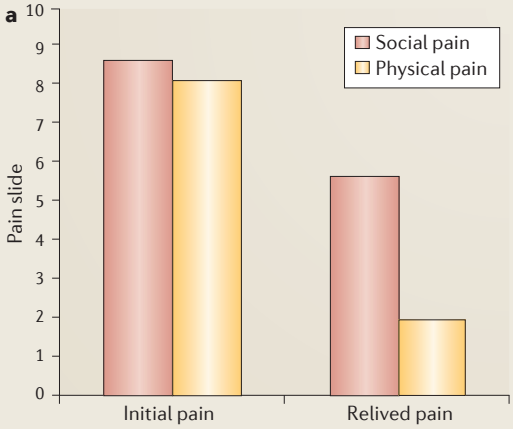
Tylenol (paracetamol; Johnson and Johnson), an over-the-counter pain reliever, for a 2-week period was shown to reduce daily self-reported hurt feelings and to reduce dACC and AI activity in response to an experimental episode of social exclusion[66].

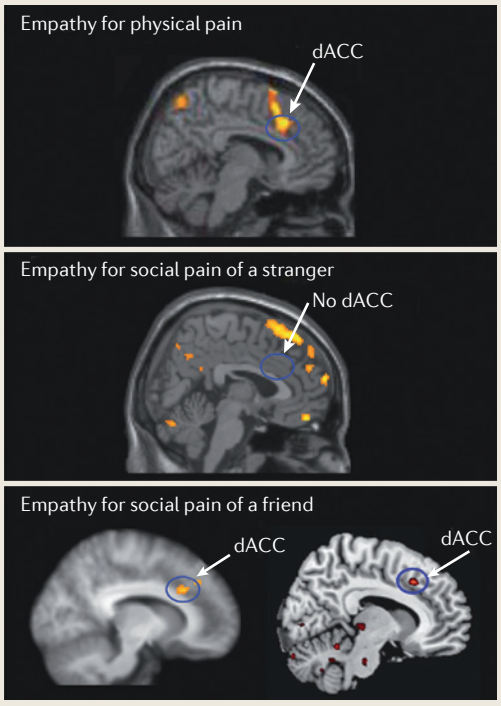
Together, these findings lend additional support to the hypothesis that physical and social pain processes overlap by highlighting some of the, sometimes surprising, consequences of such an overlap. Although it might seem objectively odd that social support would lessen physical pain or that a physical pain-reliever would ameliorate social pain, couching these findings within the larger framework of an overlap in the systems underlying physical and social pain helps to make sense of these relationships. Of course, experiences of physical and social pain are not identical and undoubtedly rely on distinct neural and neurobiological underpinnings as well. It will be crucial for future research to examine the boundary conditions for the extent of the physical–social pain overlap (BOX 4).

dACC and AI in health

In addition to being involved in social pain-related responding, the dACC and AI may have a key role in the relationship between experiences of social disconnection and health. Considerable research has shown links between social disconnection and health: for example, those higher in objective or subjective social

Box 4 | **Differences between physical and social pain**





Although the majority of the research reviewed in this article highlights an overlap in the systems underlying physical and social pain, there are important ways in which these experiences differ. One difference has to do with the way in which individuals experience pain in the absence of any direct threat to themselves — either through reliving prior experiences of pain or through observing the pain of others. With regard to reliving pain, studies have shown that reliving socially painful experiences elicits more pain. Thus, subjects reported feeling more pain after reliving a prior episode of social pain than after reliving a prior episode of physical pain, even though there were no differences in the amount of pain experienced at the time the event originally occurred ('initial pain', see the figure, part **a**)[18,19]. Interestingly, when it comes to observing the pain of others (empathy), the reverse pattern is observed. When observing others in physical pain, participants show increased activity in affective pain-related neural regions, such as the dorsal anterior cingulate cortex (dACC) and the anterior insula (AI)[135] (dACC activation shown in part **b** of the figure[144]), whereas these same neural responses are not present when observing others in social pain (mentalizing regions, such as the dorsomedial prefrontal cortex, are present instead; see part **c** of the figure)[145], unless the target of the social pain is a close friend (see part **d** of the figure)[146,147].

One way to understand these findings is to hypothesize that experiences of social pain may rely on more abstract types of social-cognitive processing that can be intentionally activated, whereas experiences of physical pain may rely on more low-level, automatic processes that are less accessible to intentional activation. If this were the case, it would make sense that social pain would be more easily relived than physical pain because the processes that elicit social pain can be more easily accessed than those that elicit physical pain. Moreover, to the extent that intentional social cognitive processing is required to experience others' social, but not physical, pain, it would make sense that observing anyone in physical pain would activate pain-related neural regions, but that these same neural regions might only be engaged in response to viewing close others (but not strangers) in social pain. Additional research is needed to further explore these possibilities.

disconnection (that is, those who have fewer social ties or greater perceived social isolation) have a greater risk of mortality and a greater incidence of physical health problems (such as coronary heart disease) and negative mental health-related outcomes (such as depression)[121,122]. Given that the dACC and AI are involved in responding to social disconnection, these regions may have a role in translating experiences of social disconnection into downstream physiological responses — such as heightened inflammatory activity, the immune system's first line of defence against foreign agents and infection — which have health implications. Indeed, several lines of research support this hypothesis.

Experiences of social disconnection have been shown to be associated with increases in various indices of inflammatory activity. Lonely individuals, who perceive greater levels of social disconnection on a daily basis, show an upregulation of pro-inflammatory response genes, which may contribute to their increased risk of inflammatory disease[123]. Social-evaluative stressors that involve the possibility of social rejection have been shown to increase pro-inflammatory activity, and this effect is heightened for those who feel more evaluated[124]. Finally, in guinea pigs, social (maternal) separation has been shown to lead to increases in the levels of pro-inflammatory cytokines[125].

In addition to being involved in responding to perceived social disconnection, the dACC and AI may contribute to inflammatory activity through their role in sympathetic responses, which have been shown to increase inflammatory activity[126,127]. Thus, activity in both the dACC and AI in response to effortful or socially stressful tasks has been shown to correlate with increases in measures of sympathetic activity[86,128,129]. Moreover, the dACC has been posited to play a part in the generation of these peripheral sympathetic responses, as patients with dACC lesions do not show the expected increase in sympathetic responses to mental stress[129]. Building on this evidence, a recent study demonstrated that greater activity in both the dACC and AI in response to social exclusion was associated with greater increases in pro-inflammatory cytokines in response to a separate social stressor[130]. Thus, these regions may have an important role in translating experiences of social disconnection into inflammatory-related responses.

Finally, inflammatory-related processes are known to relate to negative physical and mental health outcomes. Increased inflammatory activity has been linked with several chronic diseases of ageing (including cardiovascular disease and some types of cancer)[131]. In addition, considerable research has implicated enhanced inflammatory responding in depression. Depressed individuals show increased levels of pro-inflammatory cytokines[132], and healthy individuals exposed to an experimental inflammatory challenge show an increase in depressive symptoms[115,133].

Triangulating across these various lines of evidence suggests that the dACC and AI may be important mediators of the links between experiences of social disconnection and both physical and mental health[134]. People who are more sensitive to experiences of social disconnection may be more likely to activate the dACC and AI, which may be associated with greater increases in sympathetic and inflammatory activity, and such individuals may therefore be at greater risk of developing inflammatory-related diseases and depression.

Conclusions

In summary, evidence from animals and humans supports the hypothesis that there is an overlap in the neurobiological underpinnings of physical and social pain. This finding fits with other work showing that certain, basic neural systems (those involved in pain and reward) may have been co-opted to support more complex social experiences[135–138]. Focusing on the overlap between physical and social pain helps to make sense of several surprising findings, such as the reduction in physical pain that occurs in the presence of social support and the increase in feelings of social disconnection that accompanies physical pain. A better understanding of this overlap may provide a new way of thinking about the factors that contribute to physical pain and the methods that could be used to treat experiences of social pain or certain conditions, such as depression, that have strong links with both types of painful experience[16].

Nevertheless, several questions remain about the nature of the physical–social pain overlap. First, although the dACC and AI have been shown to activate in response to both physical and social pain, these two regions are also activated in response to many tasks that generate negative affect. Although it is certainly the case that some of these affective tasks induce negative affect through negative social experiences, not all of them do. Thus, it is possible that these regions have a broader role as a neural alarm system (BOX 3), which triggers affective, behavioural and autonomic responses[8] to various types of survival relevant threats — with indicators of social or physical harm being some salient examples. Further research is needed to determine the precise types of survival-relevant threats to which these regions are responsive.

Another remaining issue is whether experiences of social pain activate sensory, as well as affective, pain-related neural regions. Although most of the neuroimaging literature has shown that experiences of rejection or loss activate affective pain-related regions, some studies have also shown sensory-related neural activity in response to rejection. Given that socially painful experiences are sometimes described as being localized to a certain part of the body ('heartache'), it will be important to better understand how, and in what situations, social pain activates sensory-related neural regions. Furthermore, it will be important to identify the pathways whereby socially painful experiences become represented in or localized to the body.

More generally, the findings reviewed here highlight the counterintuitive nature of pain. We typically reify physical pain as 'real' pain and often dismiss social pain as 'psychological', but the connection between the two kinds of pain suggests that each of these lay theories is only half right. Physical pain is a deeply psychological

phenomenon that can be altered by expectations, mood and attention. Likewise, social pain is a deeply biological phenomenon that has been built into our brains and bodies over millions of years of mammalian evolution because of the crucial part it plays in our survival. A better understanding of the commonalities between these two types of painful experience may provide greater insight into the underlying nature of each.

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FURTHER INFORMATION
Naomi Eisenberger's homepage: http://sanlab.psych.ucla.edu/
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