CHAPTER 16
Social Pain: Experiential, Neurocognitive, and Genetic Correlates

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> "There is much suffering in the world…from hunger, from homelessness, from all kinds of diseases. But the greatest suffering is being lonely, feeling unloved, having no one. I have come more and more to realize that it is being unwanted that is the worst disease that any human being can ever experience."—Mother Theresa

Mother Theresa's statement comes as no surprise to most observers of human nature, trained and untrained alike. Experience suggests that the pain of being socially estranged can be just as (if not more) distressing as the pain of hunger or the pain of cold. In fact, the "need to belong" has been identified by social psychologists as a fundamental human motivation that, when unsatisfied, leads to a variety of negative consequences, such as poor health and compromised well-being (Baumeister & Leary, 1995). However, is the pain that results from feeling unloved or unwanted the same kind of pain as that which results from feeling cold or hungry, or is Mother Theresa being metaphorical when she describes a lack of social connection as being "painful?" Can a lack of social connection actually lead to real pain experience, in the same manner that a lack of other basic needs can lead to pain experience? In the present chapter, I suggest, like others have previously (Baumeister & Leary, 1995), that the need for social connection is a fundamental need and that like other basic needs, a lack of social connection can feel "painful," an experience that has been termed "social pain" (Eisenberger & Lieberman, 2004, 2005; MacDonald & Leary, 2005).

The notion that a lack of social connection can lead to painful experience is not new. Rather, it is based on the hypothesis that over the course of mammalian evolution, the social attachment system, responsible for maintaining social connection, may have piggybacked directly onto the physical pain system, borrowing the pain signal to signify and thus prevent the danger of social separation (Panksepp, 1998). Because most mammals are born relatively immature without the capacity to feed or fend for themselves, it is necessary for mammalian infants to maintain close social contact with a caregiver to acquire the appropriate nourishment and protection. An overlap in the neural systems that support physical and social pain experience may have proved invaluable in this endeavor. To the extent that being separated from a caregiver threatens the survival of the infant, feeling "hurt" by separation from a caregiver may be an adaptive way to prevent future separation.

A review of the literature supports this hypothesized physical–social pain overlap and suggests that physical and social pain may share more than just metaphorical similarity. Observational, pharmacological, and neuropsychological evidence together suggest that physical and social pain processes share similar experiential, behavioral, and neural underpinnings.

Perhaps the most accessible source of data supporting a physical–social pain overlap comes from the English language. When individuals feel rejected or left out, they often describe their feelings with physical pain words, complaining of "*hurt* feelings," "*broken* hearts," or "feeling *crushed*." In fact, the English language has no direct synonym for these "hurt feelings," suggesting that the only way that English speakers can describe these feelings of social estrangement are with physical pain words. Indeed, the use of physical pain words to describe episodes of social estrangement is common to many languages (MacDonald & Leary, 2005), highlighting a potentially universal phenomenon.

Pharmacological research also supports the notion that physical and social pain share common substrates by showing that certain drugs have similar effects on both types of pain. For example, opiate-based medications (such as morphine or codeine), which are thought of primarily as "painkillers," also alleviate social pain (Herman & Panksepp, 1978; Kalin, Shelton, & Barksdale, 1988; Panksepp, 1998; Panksepp, Herman, Conner, Bishop, & Scott, 1978). Similarly, antidepressants, which are typically prescribed to treat anxiety and depression (often related to social stressors) are also effective in alleviating physical pain (Nemoto et al., 2003; Shimodozono, Kamishita, Ogata, Tohgo, & Tanaka, 2002; Singh, Jain, & Kulkarni, 2001) and are now commonly prescribed to treat chronic pain conditions.

Research from health psychology supports a physical–social pain overlap as well, demonstrating that changes in one type of pain experience correspond with changes in the other. For example, individuals with more social support (who should presumably experience less social pain) experience less cancer pain (Zaza and Baine, 2002), are less likely to suffer from chest pain following coronary artery bypass surgery (King, Reis, Porter, & Norsen, 1993; Kulik and Mahler, 1989), report less labor pain, and are less likely to use epidural anesthesia during childbirth (Chalmers, Wolman, Nikodem, Gulmezoglu, & Hofmeyer, 1995; Kennell, Klaus, McGrath, Robertson, & Hinkley, 1991). In addition, an experimental study has shown that compared to unsupported individuals, individuals who received social support from either a friend or stranger reported experiencing less pain during a cold pressor task, a task in which the participant's arm is submerged in ice water (Brown, Sheffield, Leary, & Robinson, 2003).

Finally, neuropsychological and neuroimaging research suggests that some of the same neural structures may underlie both physical and social pain. For example, the dorsal portion of the anterior cingulate cortex (dACC) is one neural region that seems to be involved in both forms of pain.[1] With regard to physical pain, the dACC is associated with the *affective* as opposed to the *sensory* component of pain. For example, following cingulotomy for chronic pain, a procedure in which a portion of the dACC is removed, patients report still being able to feel the intensity of pain but report that the pain no longer bothers them (Foltz & White, 1968), highlighting the role that this structure plays in registering the distressing, rather than the purely sensory, component of the pain experience. In line with this, several neuroimaging studies have shown that dACC activity correlates with perceived pain unpleasantness, whereas primary somatosensory cortex activity correlates with perceived pain intensity from cutaneous stimulation (Peyron, Laurent, & Garcia-Larrea, 2000; Ploghaus, et al., 1999; Rainville, Duncan, Price, Carrier, & Bushnell, 1997, Sawamoto et al., 2000). Thus, the dACC seems to be involved in the "distressing," or what is sometimes referred to as the "suffering," component of painful experience.

Although human research has focused on the role of the dACC in physical pain processes, animal research highlights a role for the ACC in social pain processes, such as those involved in preventing social estrangement and promoting

[1] The dACC has also been shown to play a role in more purely cognitive processes, such as "conflict monitoring," when behavioral response tendencies or expectations conflict (Botvinick, Cohen, & Carter, 2004), or "error detection" (Brown & Braver, 2005). These different roles will be discussed more fully at the end of the chapter.

social connection. Specifically, in nonhuman mammals, the ACC has been shown to play a role in the production of "distress vocalizations," a type of vocalization that is produced by infants upon separation from a caregiver. Distress vocalizations are considered to be the most primitive and basic mammalian vocalization with the original purpose of maintaining mother–infant contact (MacLean, 1985). Although it is impossible to determine whether these vocalizations are the product of painful or distressing experiences for the animal that is producing them, these vocalizations represent a behavioral indicator of sensitivity to social separation, which in humans may be a precursor for social pain experience.

To demonstrate the role that the ACC plays in distress vocalizations specifically, it has been shown that ablation of the ACC in squirrel monkeys leads to decreases in distress vocalizations but not other kinds of vocalizations (Hadland, Rushworth, Gaffan, & Passingham, 2003; MacLean & Newman, 1988), whereas electrical stimulation of the ACC in rhesus monkeys leads to the spontaneous production of distress vocalizations (Robinson, 1967; Smith, 1945). In addition, highlighting the specific role of the ACC rather than other neural regions in producing distress vocalizations, stimulation of the area corresponding to Broca's area, an area known to be involved in speech production, elicits movement of the vocal chords but no distress vocalizations in monkeys and apes (Leyton & Sherrington, 1917; Ploog, 1981). Thus, distress vocalizations seem to be uniquely related to ACC activation and not to the activation of neural regions typically involved in speech production. Finally, the cingulate gyrus (of which the ACC is a part) appears for the first time, phylogenetically, in mammalian species (MacLean, 1985) and thus may play a role in certain behaviors that also appear for the first time in mammals, such as those aimed at maintaining close social contact by producing distress or distress-related behaviors upon separation.

In sum, these lines of evidence support the notion that physical and social pain processes overlap by demonstrating that both types of pain rely on common experiential, behavioral, and neural substrates. However, there are still questions that remain. First, although it seems clear from the preceding review that the dACC is involved in the distress of physical pain experience in humans as well as in separation distress in nonhuman mammals, it is not clear if the dACC is also involved in socially painful experience in humans. Moreover, although there is some suggestion that physical and social pain share similar computational substrates and thus similar sensitivities, the extent to which sensitivity to social pain directly relates to sensitivity to physical pain has not been fully explored.

In the next section, I will review some of our own work that has examined these questions more closely. Two of these studies utilized functional neuroimaging methodologies to examine whether the dACC is sensitive to: *(1)* the experience of social pain in humans (social exclusion; Eisenberger, Lieberman, & Williams, 2003) and *(2)* cues that predict social pain in humans ("disapproving facial expressions;" Burklund, Eisenberger, & Lieberman, 2007). A third study examined the extent to which sensitivity to one type of pain relates to sensitivity to the other, as well as whether activating one type of pain heightens sensitivity to the other (Eisenberger, Jarcho, Lieberman, & Naliboff, 2006).

I will then highlight some of the extensions of this work by reviewing three studies that examined whether neural responses to social pain relate to and can help us understand real-world social phenomena. In other words, these studies utilized neural responses to social pain to help elucidate several unresolved questions regarding specific socio-emotional processes. The first study examined whether neural responses to experimental social rejection related to real-world feelings in social interactions, such as how rejected or accepted individuals tended to feel on a daily basis or the extent to which these feelings impacted more global judgments of social standing (Eisenberger, Gable, & Lieberman, 2007). The second study used neural sensitivity to social rejection, along with measures of social support and physiological stress reactivity, to better understand why social support is consistently related to reduced physiological stress reactivity and positive health

outcomes (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007). The final study used neural sensitivity to social rejection to help understand the possible socio-emotional mechanisms that linked a specific genetic polymorphism to aggressive or antisocial behavior (Eisenberger, Way, Taylor, Welch, & Lieberman, 2007). Following this, I identify some of the questions that remain for understanding the neural correlates of social pain experience. I also highlight some key areas that will be critical for future research on social pain.

Investigating the Physical–Social Pain Overlap in Humans

The "Pain" of Social Exclusion

Based on the involvement of the dACC in physical pain distress in humans and in separation distress in nonhuman mammals, we investigated whether this neural region was also involved in the distress associated with social exclusion in humans. At the time that this study was conducted, no work had investigated the neural correlates associated with socially painful experience in human subjects.

In this study (Eisenberger, Lieberman, & Williams, 2003), participants were led to believe that they would be playing a virtual ball-tossing game called "Cyberball" (Williams, Cheung, & Choi, 2000) with two other players over the Internet while in the fMRI scanner. During one scan, participants played with the two computer players for the entire duration of the game. In a subsequent scan, participants were excluded from the ball-tossing game partway through the game when the two computer players stopped throwing the ball to them.

Upon being excluded from the game, compared to when being included, participants reported feeling significant levels of social distress (e.g., "I felt rejected," "I felt invisible") and showed increased activity in a region of the dACC, very similar to the region of the dACC associated with the unpleasantness of physical pain experience. Moreover, the magnitude of dACC activity correlated significantly with self-reports of social distress felt during the exclusion episode, such that individuals who showed greater dACC activity in response to social rejection also reported feeling more distressed by the rejection episode. Participants also showed increased activity in the insula, a region known to be involved in processing visceral sensation (e.g., visceral pain) as well as negative affective states (Aziz, Schnitzler, & Enck, 2000; Cechetto & Saper, 1987; Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Phan, Wager, Taylor, & Liberzon, 2004; Philips et al., 1997); however, insular activity did not correlate significantly with self-reported social distress in this study.

In addition, in response to social exclusion (vs. inclusion), participants showed increased activity in the right ventral prefrontal cortex (RVPFC), a region of the brain typically associated with regulating physical pain experience or negative affect (Hariri, Bookheimer, Mazziotta, 2000; Lieberman et al., 2004; Lieberman, Eisenberger, Crockett, Tom, Pfeifer, & Way, 2007; Petrovic & Ingvar, 2002). Consistent with this region's role in regulatory processes, greater activity in the RVPFC was associated with lower levels of self-reported social distress in response to the ball-tossing game, suggesting that this region may also be involved in regulating the distress of being socially excluded. Finally, we found that the dACC was a significant mediator of the RVPFC–distress relationship, such that RVPFC may be related to lower levels of social distress by downregulating the activity of the dACC.

Thus, neural responses to an episode of social exclusion recruited some of the same neural regions that are involved in the distress (dACC) and regulation (RVPFC) of physical pain experience. In fact, when comparing the neural activations in this study of social pain with those from a study of physical pain in patients with irritable bowel syndrome (Lieberman et al., 2004), very similar regions of activation in the dACC and RVPFC are observed (*see* Fig. 16–1; the left panel displays *social* pain, the right panel displays *physical* pain). Moreover, these two studies also demonstrate similar patterns of correlations between neural activity and pain distress, such that in both cases, greater dACC

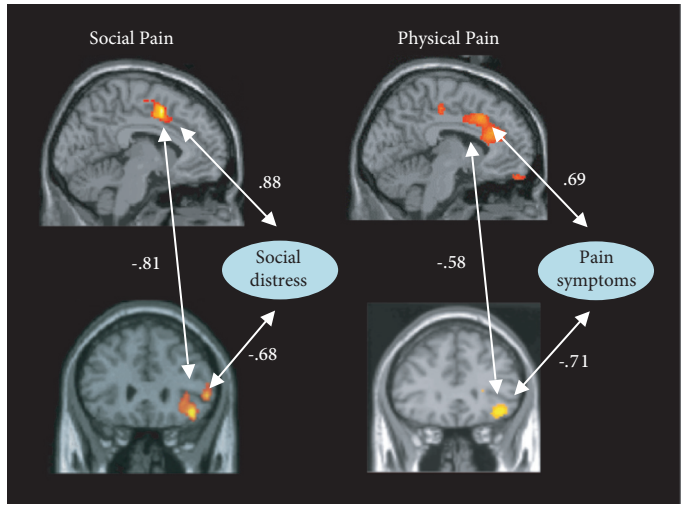

Fig. 16–1 The left side of the panel displays the neural activity during social exclusion, compared to social inclusion, that correlates with self-reported social distress. (From Eisenberger NI, Lieberman MD, & Williams KD (2003). Does rejection hurt? An fMRI study of social exclusion. *Science, 302***, 290–292. Reprinted with permission from AAAS.). The right side of the panel displays the neural activity during painful visceral stimulation, compared to baseline, that correlates with self-reported pain experience. (From Lieberman, Jarcho, Berman, Naliboff, Suyenobu, Mandelkern, & Mayer, 2004).**

activity is associated with greater reports of social pain or physical pain distress, whereas greater RVPFC activity is associated with lower reports of distress and less dACC activity. Thus, not only do physical and social pain recruit some of the same neural regions, but for both types of pain, these neural regions relate to painful or distressing experience in similar ways.

As further evidence that social pain processes recruit pain-related neural regions, additional work has shown that other types of socially painful experience, such as bereavement or relationship dissolution, can lead to dACC activation as well. In one study (Gundel, O'Connor, Littrell, Fort, & Lane, 2003), bereaved participants were scanned while viewing pictures of their deceased first-degree relative or a stranger. In response to viewing pictures of the deceased, compared to pictures of a stranger, participants showed greater activity in regions of the dACC and insula. Similarly, in a study investigating the neural responses associated with grieving a romantic relationship, women whose romantic relationship ended within the preceding 4 months showed greater activity in several neural regions, including the dACC, when thinking about their relationship compared to when thinking about another individual (Najib, Lorberbaum, Kose, Bohning, & George, 2004). However, there were many neural regions activated in response to thinking about the former partner, and thus it is difficult to clearly identify which neural activations were specifically related to feelings of social pain. Nonetheless, together these studies support the notion that various types of socially painful experience activate pain-related neural regions such as the dACC.

The Face of Rejection

Based on our neuroimaging study of social exclusion as well as other studies of socially painful experiences, there is increasing evidence to suggest that the dACC is involved in the distressing experience associated with social pain experience in humans. Our next question was whether this neural region was also involved in responding to cues that signaled the possibility of socially painful experience. To examine this question, we investigated

whether the dACC was involved in responding to "disapproving" facial expressions, a facial display that signified the possibility of social rejection (Burklund, Eisenberger, & Lieberman, 2007). Although many previous neuroimaging studies have investigated the neural responses associated with viewing specific emotional expressions (e.g., fear, anger, disgust), this is the first to explore the neural responses associated with viewing a disapproving face. We also examined whether there were differences in neural sensitivity to disapproving faces based on an individual's level of rejection sensitivity, an individual difference measure that should increase sensitivity to cues that signal social rejection (Downey & Feldman, 1996).

Participants were scanned while viewing a series of 3-second film clips depicting individuals making different emotional expressions. Participants viewed disapproving emotional expressions as well as angry and disgusted emotional expressions for comparison. Although all of these facial expressions can signal a threat to social connection, the "disapproving" facial expression is the only expression that has no other meaning but a threat to social connection. Thus, although anger and disgust expressions typically indicate physical and contamination threats, respectively, disapproval does not have a nonsocial interpretation.

Similar patterns of neural activity were found in response to each of the three facial expression conditions; participants showed significant activity in the amygdala and various regions of the PFC when viewing each of these emotional expressions compared to when viewing a neutral crosshair fixation. However, when examining individual differences in rejection sensitivity, we found that individuals who scored higher in rejection sensitivity showed greater dACC activity while viewing the disapproving faces but not while viewing the anger or disgust faces, highlighting a specific role for the dACC in responding to disapproving faces among rejection-sensitive individuals. Moreover, rejection sensitivity correlated specifically with dACC activity to disapproving faces but not with other limbic system activity (e.g., amygdala, insula), suggesting that dACC activity, rather than more general limbic system activity, may be specifically responsive to these cues of rejection.

This increased dACC activity to disapproving facial expressions among rejection-sensitive individuals could result from several factors. First, it is possible that rejection-sensitive individuals are more likely to feel socially distressed while viewing disapproving facial expressions and thus exhibit increases in distress-related dACC activity. Alternatively, it is possible that the dACC activity observed here is not directly related to the experience of social distress but, rather, that it is related to detecting cues that predict social distress, which may be more salient for rejection-sensitive individuals. Future research will be needed to disentangle between these two alternatives. In addition, future research will be needed to better understand why dACC activity in response to disapproving faces was limited to those high in rejection sensitivity and was not seen for the sample as a whole. It is possible that there was no main effect for dACC activity because the stimuli were not interpreted as personally relevant, except for those high in rejection sensitivity.

We also found that when viewing disapproving facial expressions, individuals who scored lower in rejection sensitivity exhibited greater activity in the subgenual ACC (subACC), a neural region that has been shown to play a role in the extinction of conditioned fear responses in humans (Phelps, Delgado, Nearing, & LeDoux, 2004) as well as in signaling a less threatening interpretation of a negative stimulus (Kim, Somerville, Johnstone, Alexander, & Whalen, 2003). Thus, it is possible that those low in rejection sensitivity may have shown greater subACC activity to disapproving faces because they were better able to regulate their negative responses to these disapproving facial expressions or better able to generate less threatening interpretations of these stimuli.

Finally, we found that neural activity in the subACC and dACC were negatively correlated with each other, such that individuals who showed greater activity in the subACC while viewing disapproving faces, compared to rest, also showed a corresponding reduction in

dACC activity. These results are similar to previous findings showing an inverse relationship between subACC and amygdala activity when assessing the valence of certain stimuli (Kim et al., 2003). In that study, to the extent that surprised facial expressions were interpreted more positively, participants showed increased subACC activity and reduced amygdala activity; conversely, to the extent that surprised facial expressions were interpreted more negatively, participants showed reduced subACC activity and greater amygdala activity. In a similar manner, the present findings may suggest that individuals who interpret the disapproving facial expressions more positively (i.e., those low in rejection sensitivity) show greater subACC and reduced dACC activity, whereas individuals who interpret the disapproving facial expressions more negatively (i.e., those high in rejection sensitivity) show reduced subACC and greater dACC activity.

Shared Sensitivities to Physical and Social Pain

The studies reviewed thus far have used neuroimaging techniques to examine whether social pain processes in humans rely on some of the same neural structures that are involved in physical pain processes in humans and separation distress behaviors in nonhuman mammals. To examine the physical–social pain overlap in a different way, we conducted a behavioral study in which we used a measure of physical pain to investigate the extent to which people show similar patterns of sensitivity to physical and social pain. Specifically, we investigated: *(1)* whether individuals who are more sensitive to physical pain are also more sensitive to social pain and *(2)* whether inducing social pain potentiates sensitivity to physical pain stimuli, as triggering one type of pain should activate the underlying neural system that supports both types of pain processes (Eisenberger, Jarcho, Lieberman, & Naliboff, 2006).

Upon arriving in the lab, participants provided a baseline measure of sensitivity to heat pain by rating the temperature at which they perceived a painful heat stimulus delivered to their volar forearm to be very unpleasant (a 10 on a scale from 0 ["no sensation"] to 20 ["unbearable"]; Gracely, McGrath, & Dubner, 1978). After this, participants completed one round of the Cyberball game in which they were either included, not included (couldn't play with the two other players because of technical difficulties), or overtly excluded (stopped receiving the ball from the two virtual players midway through the game) in a between-subjects manner. During the last 30 seconds of the Cyberball game, participants were exposed to three painful heat stimuli (at the temperature they reported to be "very unpleasant") and were asked to rate the unpleasantness of each. They were also asked to rate how rejected they felt during the Cyberball game (level of social distress).

Results demonstrated that individuals who were more sensitive to physical pain at baseline (e.g., lower baseline pain thresholds) were also more distressed during social rejection (either non-inclusion or overt exclusion) but not during social inclusion, suggesting that individual sensitivity to one type of pain is related to sensitivity to the other. In addition, this relationship remained significant after controlling for neuroticism, suggesting that this relationship cannot simply be explained by a general tendency to report higher levels of negative experience. In addition, we found that individuals who felt the most distressed by the social rejection episodes also reported the highest pain ratings in response to the heat stimuli that were delivered at the end of the rejection episodes. Note that these heat stimuli were calibrated based on each subject's baseline pain threshold, and thus this result is independent of the previous one. Although this finding was correlational, it suggests that augmented sensitivity to one type of pain is related to augmented sensitivity to the other. This relationship remained after controlling for neuroticism as well.

It should be noted that these findings are somewhat different from those of another study that examined the effect of social exclusion (using a different manipulation) on physical pain sensitivity (DeWall & Baumeister, 2006). In this study, social exclusion was manipulated by telling participants that they

would be alone in the future. Participants in this "future alone" condition, compared to those who were given no feedback or who were told that they would have satisfying relationships in the future, showed a reduced (rather than an increased) sensitivity to physical pain. These different findings could result from the fact that the "future alone" manipulation may induce more depression-like affect, thus reducing pain sensitivity, whereas the Cyberball manipulation may induce more anxiety-like affect, making an increase in pain sensitivity more likely. Nonetheless, it is important to note that in both studies, sensitivity to physical pain still correlated directly with sensitivity to social pain. Thus, even among subjects in the "future alone" condition, those who showed the greatest sensitivity to physical pain also showed the greatest sensitivity to social pain as indicated by higher levels of empathy toward a rejected target individual. In other words, although the exclusion manipulations (future alone vs. Cyberball) had different effects on pain sensitivity, in both studies, sensitivity to physical pain still remained positively correlated with sensitivity to social pain.

Thus, overall, physical and social pain share not only similar neural substrates but similar experiential sensitivities as well, such that individual differences in sensitivity to physical pain experience covaried with individual differences in sensitivity to socially painful experience. Showing that social and physical pain experience track one another provides additional, behavioral evidence for the notion that physical and social pain share experiential, computational, and neural substrates.

Correlates of Neural Responses to Social Pain

Knowing that dACC responses to social rejection relate to feelings of social distress may help us to better understand the mechanisms underlying other phenomena that are likely to utilize this neural system. In the next section, I review three studies that utilized neural responses to social pain to help to better understand specific real-world social phenomena.

Cyberball and the Real World

Several studies now support the notion that experiences of social exclusion in the scanner lead to dACC activity and that the magnitude of dACC activity is associated with the degree to which individuals feel rejected or excluded. What is less clear, however, is whether these scanner-based responses to social rejection relate to how individuals experience real-world social interactions. In other words, do individuals who show greater dACC reactivity to social rejection in the scanner also report feeling more socially rejected or estranged in their real-world social interactions? In addition, are individuals who show greater dACC reactivity to scanner-based social rejection more likely to integrate their experiences of rejection into more negative global beliefs about themselves and their social worlds? Because it is not yet possible to directly assess whole-brain neural activity during naturalistic, real-world social encounters, we investigated whether neural responses during an experimental episode of social rejection within the fMRI scanner correlated with real-world experiences during ongoing social interactions (Eisenberger, Gable, & Lieberman, 2007).

To examine whether neural activity to social rejection in the scanner related to moment-to-moment feelings of social rejection in real-world interactions, participants completed the Cyberball social exclusion task in the scanner (as done in a previous sample; Eisenberger et al., 2003) and, at a separate point in time, completed a 10-day experience-sampling study in which they were randomly signaled at different times during the day and asked to report on their feelings of social distress in their most recent social interaction (*momentary social distress*: e.g., "I felt accepted/rejected by my interaction partner").

Results revealed that individuals who showed greater dACC activity to the Cyberball task in the scanner also reported feeling greater levels of momentary social distress during their real-world social interactions across the 10-day experience-sampling study. In addition, individuals who showed greater activity in response to social exclusion in the amygdala, a neural

region involved in affective processing (Davis & Whalen, 2001), and in the periaqueductal gray (PAG), a neural region involved in pain processing and attachment-related behaviors (Bandler & Shipley, 1994), also reported feeling greater levels of momentary social distress across this 10-day period. This is a notable finding given that this neural activity was assessed during a brief episode of social rejection that is probably quite unlike what most individuals experience in their daily lives (presumably most real-world social interactions do not involve such overt social exclusion, at least in adults). However, the strong correlation between neural responses to scanner-based social rejection and self-reports of social distress during real-world interactions suggests a core sensitivity to experiences of social rejection, such that those who are the most sensitive to an experimental episode of social rejection are also the most sensitive to these types of experiences in their everyday lives.

As a second goal of the study, we were also interested in whether neural activity to social rejection in the scanner related to the extent to which momentary social distress was integrated into end-of-day global assessments of social disconnection. To examine this, participants provided a global assessment of social disconnection (*end-of-day social disconnection*: e.g., "Today, I generally felt accepted by others: strongly agree [1] to strongly disagree [7]") at the end of each of the 10 days, and correlations were computed between momentary social distress and end-of-day social disconnection ratings across the 10-day period. This correlation provided an index of the extent to which momentary social distress scores corresponded with and perhaps contributed to end-of-day social disconnection ratings. Thus, individuals with a large, positive correlation were more likely to feel socially disconnected at the end of the day if they felt a lot of social distress during their moment-to-moment social interactions during the day, whereas individuals with a small correlation were those who showed no clear relationship between momentary and end-of-day reports. We then investigated how neural activity during social rejection in the scanner related to this correspondence measure. Thus, we were interested in the neural processes that occurred during an episode of social rejection that predict whether that experience will figure prominently into one's later feelings about the whole day.

Here, activity in the dACC, amygdala, and PAG in response to experimental social rejection did *not* significantly relate to the correspondence between momentary social distress and end-of-day social disconnection; instead, activity in the left hippocampus and medial prefrontal cortex (mPFC; Brodmann's Area [BA] 10) did. Individuals who showed greater hippocampal and mPFC activity during an experimental episode of social rejection demonstrated a greater correspondence between momentary social distress and end-of-day social disconnection, such that individuals who felt more social distress during their social interactions reported feeling more socially disconnected at the end of the day. Notably, the neural regions associated with this correspondence between momentary and retrospective reports are similar to those found in neuroimaging studies of memory encoding (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al., 1998) as well as self-referential or autobiographical memory encoding (Cabeza et al., 2004; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004). In these studies, individuals who demonstrated greater activity in the hippocampus when viewing presented stimuli or in the mPFC when viewing self-relevant stimuli were more likely to remember those stimuli in a subsequent memory test. In a similar fashion, the present data suggest that social experiences that are more deeply encoded when they occur may then be more easily retrieved when making global assessments of social disconnection in retrospective reports.

In sum, this study demonstrates that neural responses to an experimental episode of social rejection have meaningful real-world correlates, such that those who showed the greatest neural responses to social rejection in the scanner also reported feeling the most socially rejected in their real-world social interactions. In addition, these findings point to a double dissociation in the neural systems underlying momentary and retrospective reports of social

disconnection (Lieberman, 2007). The neural regions associated with momentary social distress (dACC, amygdala, PAG) were not significantly associated with the correspondence between momentary and end-of-day assessments of social disconnection, and the neural regions associated with the correspondence between momentary and end-of-day social disconnection (mPFC, hippocampus) were not significantly associated with momentary social distress. These findings map nicely onto previous behavioral work demonstrating that moment-to-moment and retrospective reports of affect do not necessarily correspond (Fredrickson & Kahneman, 1993; Kahneman, Fredrickson, Schreiber, & Redelmeier, 1993; Redelmeier & Kahneman, 1996; Updegraff, Gable, & Taylor, 2004) and suggest that part of the reason for this may result from the fact that these processes rely on the computational substrates of two separate neural systems. Future studies that continue to examine the relationships between neural responses within the fMRI scanner and real-world experiences may provide important information regarding how individuals experience their social worlds and the neurocognitive processes that underlie these experiences.

dACC Mediates the Effect of Social Support on Health-Related Outcomes

Although animal and human research has consistently demonstrated a relationship between a lack of social support and an increased risk of morbidity and mortality, the mechanisms underlying this relationship remain unknown and the neurocognitive mechanisms have been largely unexplored in humans. One hypothesis that has garnered some support is that social support reduces physiological stress reactivity (such as the release of cortisol, a neuroendocrine stress hormone) to threatening situations, which, over time, can have deleterious health consequences (Uchino et al., 1996).

Social support may modulate stress responses at two different points in the chain of events that lead from potential stressors to physiological stress responses (Cohen & Wills, 1981). First, social support may alter the appraisal or perception of potentially threatening conditions such that they are no longer perceived as stressful. Thus, feeling supported and cared for may lead an individual to be less likely to appraise certain conditions as threatening, preventing the onset of physiological stress reactivity. To the extent that social support downregulates threat-related reactivity, social support may be associated with less activity in limbic structures that are typically involved in responding to negative or threatening experiences, such as the amygdala, insula, or dACC. The second point at which social support may reduce physiological stress reactivity is after an event has been appraised as stressful but prior to the onset of prolonged physiological stress responses. Thus, individuals with greater social support may be better able to cope with or regulate negative stressful experiences, leading to reduced physiological stress responses through reappraisal or regulatory processes. To the extent that social support is important for regulating negative responses to stressors, social support may relate to increased activity in regions that are typically involved in regulating negative affect, such as VLPFC and mPFC (Ochsner & Gross, 2005).

To investigate the types of neural processes that underlie the stress-protective effects of social support, we investigated how daily levels of social support related to both neurocognitive and cortisol reactivity to a social rejection stressor. To assess daily levels of social support, participants completed a signal-contingent daily experience-sampling task, in which they were loaned a PalmPilot device and, for 10 days, were signaled at random times during the day to report on the degree to which their most recent interaction partner was someone they perceived to be generally supportive. To assess neural reactivity to social rejection, participants completed the Cyberball task within the fMRI scanner. To assess cortisol reactivity to a social stressor, all participants completed the Trier Social Stress Task (TSST; Kirschbaum et al., 1993), a task that requires participants to deliver an impromptu speech and perform mental arithmetic aloud in front of a nonresponsive, rejecting panel and, in a meta-analysis, has been shown to

reliably elicit cortisol responses (Dickerson & Kemeny, 2004).[2]

Results showed that individuals who interacted regularly with supportive individuals across a 10-day period showed reduced activity in the dACC as well as reduced activity in BA 8 in the dorsal superior frontal gyrus, a region previously associated with the distress of social separation (Rilling, Winslow, O'Brien, Gutman, Hoffman, & Kilts, 2001). Moreover, reduced activity in these neural regions was associated with reduced cortisol reactivity to a social stressor. In addition, we found that individual differences in dACC and BA 8 reactivity mediated the relationship between high daily social support and low cortisol reactivity, such that supported individuals showed reduced neurocognitive reactivity to social stressors, which in turn was associated with reduced neuroendocrine stress responses. Thus, in the present study, social support related to reduced physiological stress reactivity by way of attenuated activity in neural regions that have previously been associated with distressing experience (dACC, BA 8), rather than by way of increased activity in regions previously associated with effortful, controlled processing or with regulating negative affect (LPFC, mPFC; Ochsner & Gross, 2005). Understanding how neural activity relates to social support and physiological stress reactivity thus helps to inform our understanding of the ways in which social support may relate to better health outcomes.

Using Neural Responses to Social Pain to Understand a Genetic Precursor to Aggression

In the past decade, there has been a surge of interest in understanding the genetic precursors of behavior and behavioral disorders. Neuroimaging techniques have played an integral role in this endeavor by allowing for the investigation of the neurocognitive mechanisms that may underlie gene–behavior relationships. For example, individuals with the short form of the serotonin transporter promoter polymorphism (5LC6A4), who are at a greater risk for anxiety disorders, have been shown to have stronger amygdala responses to negative stimuli (Hariri et al., 2002) and thus may be more dispositionally sensitive to fear-related stimuli. The implication of findings such as these is that neuroimaging techniques can be used to better understand the cognitive mechanisms that underlie gene–behavior or gene–disorder relationships.

Along these lines, we recently investigated whether neural responses to social rejection could inform our understanding of why individual differences in a gene that encodes monoamine oxidase-A (MAOA) relate to aggressive behavior (Eisenberger, Way, Taylor, Welch, & Lieberman, 2007). Previous work has demonstrated a link between MAOA, an enzyme that degrades monoamines such as serotonin (Caspi et al., 2002), and aggressive behavior. For example, MAOA-deficient men from a single Dutch kindred demonstrated elevated levels of impulsive aggression, arson, and attempted rape (Brunner, Nelen, Breakefield, Ropers, & van Oost, 1993). In addition, when exposed to early adversity, men with the low-expression allele (MAOA-L) of the 30-bp variable number tandem repeats polymorphism in the MAOA promoter (MAOA-uVNTR) were more likely to develop antisocial behavior than men with the high-expression allele (MAOA-H; Caspi et al., 2002). Despite mounting evidence suggesting a relationship between the MAOA-uVNTR and aggressive behavior, it is unclear how this genetic polymorphism predisposes individuals to aggressive behavior.

There are many possible mechanisms supporting this functional relationship between the MAOA polymorphism and aggressive behavior. We examined two possibilities, each related to social pain sensitivity. One possibility is that MAOA-L individuals show *blunted* socio-emotional sensitivity, making them

[2] Although it would have been ideal to assess cortisol and neural responses simultaneously, the paradigm needed to produce cortisol responses was not amenable to the fMRI scanner. Previous research has demonstrated that the social-evaluative component of the TSST, the possibility that one could be evaluated and rejected, is critical for cortisol responses (Dickerson & Kemeny, 2004). Because of the difficulty in recreating an evaluative panel within the fMRI scanner, the Cyberball task, which has been shown to elicit feelings of rejection and is amenable to the fMRI scanner (Eisenberger et al., 2003), was used instead.

less concerned with the feelings of others, less empathic, and thus more likely to commit violent crimes because they care less about harming others or the repercussions of doing so. Another possibility is that MAOA-L individuals show *heightened* socio-emotional sensitivity, making them more sensitive to negative social experiences like social rejection and more likely to respond to these experiences with defensively aggressive behavior. Numerous studies have shown that social rejection can trigger aggressive responses against the rejector (Crick & Dodge, 1996; Dodge et al., 2003; Dodge & Pettit 2003; Twenge, Baumeister, Tice, & Stucke 2001; Twenge, 2005).

To investigate these possibilities, we examined how different allelic variants in the MAOA polymorphism related to neural responses to the Cyberball game as well as to self-report measures of trait interpersonal hypersensitivity and trait aggression. To the extent that the MAOA–aggression link reflects *blunted* socio-emotional sensitivity, MAOA-L individuals should report less trait interpersonal hypersensitivity and show less dACC activity to social rejection than MAOA-H individuals. Alternatively, to the extent that the MAOA–aggression link reflects *heightened* socio-emotional sensitivity, MAOA-L individuals should report greater trait interpersonal hypersensitivity and show greater dACC activity to social rejection than MAOA-H individuals. In either case, MAOA-L individuals should report higher levels of trait aggression than MAOA-H individuals.

Consistent with previous work, we found that MAOA-L individuals did report higher levels of trait aggression than MAOA-H individuals. To examine the experiential or neurocognitive mediators of this gene–behavior link, we next investigated how the MAOA polymorphism related to trait interpersonal hypersensitivity and dACC activity to social rejection. Results indicated that MAOA-L individuals, compared to MAOA-H individuals, reported greater levels of trait interpersonal hypersensitivity as well as greater dACC responses to social rejection (*see* Fig. 16–2), suggesting that the relationship between MAOA and trait aggression may result from heightened, rather than blunted, socio-emotional sensitivity. We also found that the relationship between the MAOA polymorphism and trait aggression was partially mediated by self-reported trait interpersonal

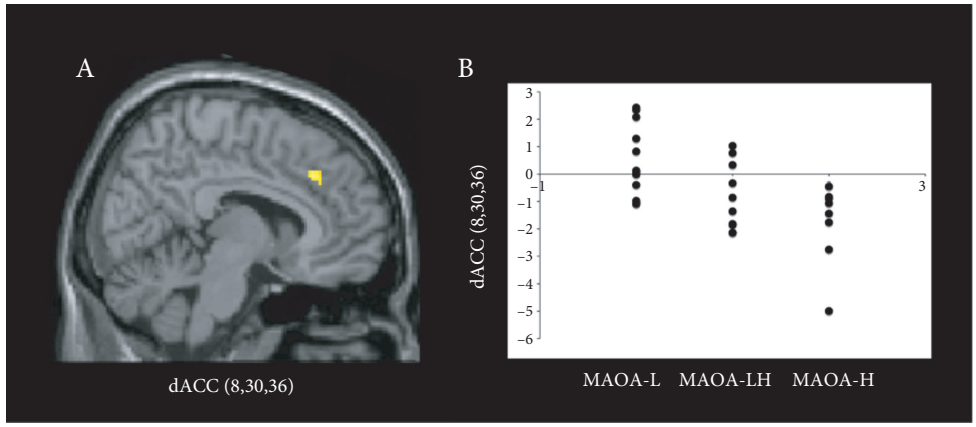

Fig. 16–2 dACC activity (8,30,36) that varies as a function of the MAOA polymorphism. (A) Activity in the dACC, during social exclusion vs. inclusion, that correlates with individual differences in the MAOA polymorphism (maximum activation at 8,30,36) and shows greater activity for MAOA-L, compared to MAOA-H or MAOA-LH (females with one low expression and one high expression allele), individuals. (B) Scatterplot showing the relationship between the MAOA polymorphism and dACC (8,30,36) responses to social exclusion vs. inclusion.

hypersensitivity as well as by dACC responses to social rejection.

These findings not only identify a possible genetic precursor to social pain sensitivity, but they also help to clarify some of the intervening mechanisms that link MAOA with aggressive behavior. Thus, instead of assuming that MAOA-related aggression results from psychopathy or a lack of social concern, it seems instead that MAOA-related aggression may be more closely tied to a heightened sensitivity to negative social cues, like social rejection, which may then trigger defensively aggressive behavior. Clarifying the underlying socio-emotional mechanisms that link MAOA to aggression is critical for both understanding the experience of individuals at risk for aggression and for identifying appropriate interventions for treating these aggressive behaviors. Moreover, identifying a genetic correlate of social pain sensitivity may aid not only in the identification and treatment of aggressive disorders but in the identification and treatment of other clinical disorders that relate closely to sensitivity to social pain as well (e.g., social anxiety, depression).

Summary

The studies reviewed here have several implications. First, they provide additional support for the notion that social pain and physical pain share some of the same experiential and neural substrates. We have shown that social pain in humans activates some of the neural structures that are involved in physical pain processing (Eisenberger et al., 2003), that cues of social rejection activate these regions among those who are the most rejection-sensitive (Burklund et al., 2007), and that sensitivity to physical pain is directly related to sensitivity to social pain (Eisenberger, Jarcho, Lieberman, & Naliboff, 2006). To the extent that these results point to common neural and behavioral mechanisms underlying physical and social pain, they support the notion that a lack of social connection can lead to pain experience and further the suggestion that social connection is indeed a fundamental need (Baumeister & Leary, 1995).

We have also shown that dACC activity during an experimental episode of social exclusion both relates to and helps us to understand real-world social experience and behavior. Thus, in one study, we demonstrated that neural responses to social rejection in the scanner corresponded strongly with the extent to which individuals felt socially rejected in their real-world social interactions (Eisenberger, Gable, & Lieberman, 2007). In a second study, we demonstrated that one way that social support relates to reduced physiological stress reactivity is through attenuated distress-related neural activity in regions like the dACC (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007). Finally, in a third study, we were able to use an assessment of neural activity to social rejection to elucidate a link between the MAOA gene and aggressive behavior. Here, we found that MAOA-related aggression was more closely related to heightened, rather than reduced, sensitivity to negative social experience, as evidenced by increased interpersonal sensitivity and increased dACC reactivity to social exclusion, among those with the low expression allele (Eisenberger, Way, Taylor, Welch, & Lieberman, 2007). Nonetheless, there are still unresolved issues regarding the role of the dACC in social pain processes and additional research that needs to be done. The final section of this review addresses one of the unresolved issues facing social pain research and highlights some key areas for future research.

Unresolved Issues and Future Directions in Social Pain Research

Relation of dACC Activity to Cognitive Processes

Finding such strong relationships between dACC activity and a negative socio-emotional experience like social rejection is somewhat at odds with previous cognitive neuroscience research. The most popular conceptions of dACC function have focused on its role in specific cognitive processes. For example, one prominent view of dACC function emphasizes

its role in "conflict monitoring," in which the dACC monitors for conflicting response tendencies or goal representations to alert executive resources to implement cognitive control (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Botvinick, Cohen, & Carter, 2004; Carter, Braver, Barch, Botvinick, Cohen, & Noll, 1998; Carter et al., 2000; MacDonald, Cohen, Stenger, & Carter, 2000). This view is also closely related to a hypothesis suggesting that the dACC plays a role in error detection, detecting discrepancies between actual and intended events (Brown & Braver, 2005; Ito, Stuphorn, Brown, & Schall, 2003). Still, others have emphasized a role for the dACC in attentional processes more generally (Pardo, Pardo, Janer, & Raichle, 1990; Posner & Petersen, 1990). Moreover, a very influential review paper posited that the dorsal subdivision of the ACC is primarily involved in cognitive processes (i.e., conflict monitoring, attention-related processes), whereas the rostral-ventral subdivision of the ACC (rACC) is primarily involved in affective processes (Bush, Luu, & Posner, 2000). Indeed, this view has led some to suggest that the dACC activity seen in response to social exclusion during the Cyberball game may result from the fact that this exclusion is unexpected and that it is the ventral or subgenual portion of the ACC (subACC) that should be more directly activated by social rejection. However, in a study that attempted to dissociate expectancy violation from rejection, there was little evidence for the subACC playing a role in rejection-related distress; rather, subACC showed greater activity to the extent that subjects were accepted (Somerville, Heatherton, & Kelley, 2006).

Needless to say, although the proposed role for the dACC in cognitive processes specifically has been quite influential, it is at odds with the work reported here, showing a relationship between dACC activity and social pain, an experience that is undoubtedly affective in nature. Moreover, it is at odds with the work showing a relationship between dACC activity and physical pain distress (Price, 2000; Rainville, 2002; Rainville et al., 1997), anxiety (Bystritsky, Pontillo, Powers, Sabb, Craske, & Bookheimer 2001; Kimbrell et al., 1999; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006), and perceived stress (Wang et al., 2005). As can be seen in Figure 16–3, all of the activations reported in the present manuscript (related to social pain processes) fall within the dorsal, rather than the rostral-ventral, subdivision of the ACC, suggesting that the

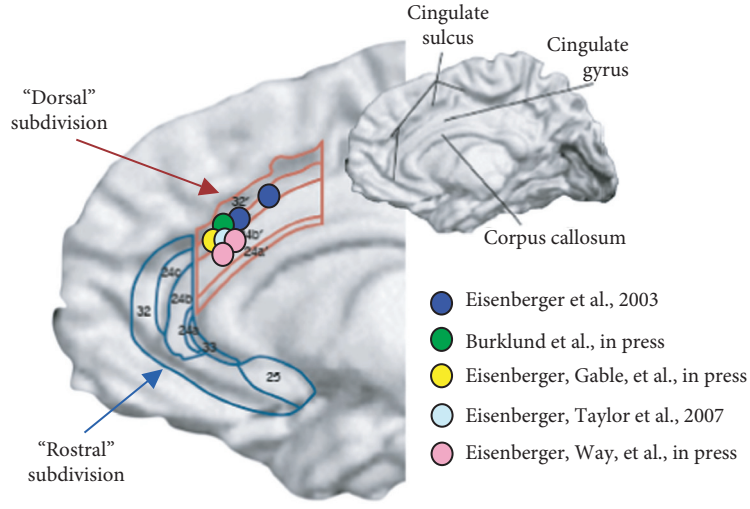

Fig. 16–3 A picture of the ACC adapted from Bush, Luu, & Posner (2000), showing dorsal and rostral-ventral subdivisions as well as how the neural responses reviewed in the present chapter map onto this figure.

dACC may be involved in affective processes as well.

As additional evidence supporting a role for the dACC in affective processes, numerous studies have shown that lesions to the dACC consistently result in reductions in distressing or anxious affective experience across many different patient populations (Baer et al., 1995; Ballantine, Bouckome, Thomas, & Giriunas, 1987; Ballantine, Cassidy, Flanagan, & Marino, 1967; Cohen, Paul, Zawacki, Moser, Sweet, & Wilkinson, 2001; Dougherty et al., 2002; Foltz & White, 1968); however, the data are less consistent with regard to how dACC lesions influence cognitive processes such as conflict monitoring. Across several studies that have examined Stroop performance (a task that assesses reaction times to trials containing conflicting information) following cingulotomy or naturally occurring dACC lesions, some studies have found reductions in conflict monitoring (as evidenced by reduced interference scores; Cohen, Kaplan, Moser, Jenkins, & Wilkinson, 1999; Cohen et al., 1999), one found increases in conflict monitoring (Ochsner et al., 2001), and some have found no differences in conflict monitoring (Fellows & Farah, 2005; Naccache et al., 2005; Turken & Swick, 1999) compared to controls. Thus, although cingulate lesions seem to relate uniformly to reductions in distressing affective experience, their impact on cognitive processes, like conflict monitoring, are still not well-understood.

Based on these additional data, it seems that this previous distinction between a "cognitive" and "affective" subdivision of the ACC needs to be revised and that the dominant focus on the role of the dACC in cognitive processes needs to be expanded. Rather than suggesting that the dACC is specifically involved in cognition or affect *per se*, we have posited that the dACC may be involved in both more basic cognitive processes, such as conflict monitoring or error detection, as well as in painful or distressing experience (Eisenberger & Lieberman, 2004). Thus, the dACC may function more generally as a "neural alarm system" that is involved in both detecting discrepancies from a desired standard (i.e., detecting threats to social connection) as well as in the phenomenological experience of distress (e.g., social pain experience) that is associated with bringing attention to the relevant problem and recruiting resources to fix or manage it. If the dACC functions more generally as a type of neural alarm system, it should be activated in response to the detection of simple discrepancies from desired standards (e.g., error detection), as suggested by research from cognitive neuroscience, and it should be activated in response to more complicated distressing experience (e.g., social rejection) that may represent a discrepancy from a desired standard (e.g., being socially connected), as suggested by the research reported here. Future research will be needed to determine whether these two processes, discrepancy detection and distressing experience, activate the same or different regions of the dACC.

Future Directions

Although some progress has been made in understanding the neural correlates of social pain processes in humans, there are still many issues that warrant further investigation. First and foremost, a careful examination needs to be carried out to investigate the specific overlap in the neural structures underlying physical and social pain experience by examining both of these processes within the same individuals. Identifying the overlap in the neural regions that underlie physical and social pain experience would be important for more clearly identifying the similarities and differences between these two processes. Some complicating issues with this approach include identifying a physical pain paradigm that most closely resembles social pain experience, as some types of physical pain (e.g., visceral pain) may approximate social pain more closely than others (e.g., somatosensory pain).

It will also be important to identify whether the neural responses to social exclusion are similar to or different from neural responses to other socially painful experiences. Neural responses to the Cyberball game provide us with information about the neural correlates associated with feeling rejected by individuals that one does not have

a meaningful relationship with and presumably will not have future contact with. It is not yet clear if these are the same neural responses that would be seen with more self-relevant forms of socially painful experience. For example, do neural responses to experiences of discrimination look like neural responses to Cyberball or are discrimination-related neural patterns unique in some way? Are the neural correlates associated with the experience of bereavement the same as those involved in social rejection but more intense, or does bereavement activate different neural structures, based on specific processes that are unique to the loss an attachment figure? These questions are just beginning to be addressed (Gundel et al., 2003; Najib et al., 2006) and remain important and timely questions for future investigation.

In addition, there are presumably many more neural structures involved in the experience of social pain that have yet to be identified. For example, the insula is a neural structure that is involved in the processing of visceral sensation as well as negative affective experience (Aziz et al., 2000; Cechetto & Saper, 1987; Lane et al., 1997; Phan et al., 2004; Philips et al., 1997) and thus may play a role in social pain experience. Indeed, we found anterior insular activation in response to social exclusion in a previous study (Eisenberger et al., 2003). The PAG is another neural region that may play a role in social pain processes, as it has been shown to be involved in pain processing and attachment-related behaviors (Bandler & Shipley, 1994; Dunckley et al., 2005). Consistent with this, we found that PAG activity during social exclusion correlated with real-world reports of social distress in daily social interactions (Eisenberger, Gable, & Lieberman, 2007). Finally, the RVPFC, although not the primary focus of this chapter, is typically involved in regulating the distress of physical pain or negative affective experience (Hariri et al., 2000; Lieberman et al., 2007; Lieberman et al., 2004; Petrovic & Ingvar, 2002) and has been shown to play a role in regulating the distress of social pain as well (Eisenberger et al., 2003). Future studies will be needed to more completely identify the neural correlates of social pain experience.

Conclusions

Although we now know more about the neural correlates of social pain processes than we did 10 years ago, there is still much to learn. Regardless, it has been made clear across many different areas of research that social connection is critical for survival and well-being. From the earliest studies of mother–infant separation in rhesus monkeys (Harlow, 1958; Harlow & Zimmerman, 1959), demonstrating the importance of the mother–infant bond for normal socio-emotional development, to our present-day studies of the neural correlates of social pain, it is revealed over and over again that social relationships sustain, regulate, and promote physical, psychological, and emotional well-being. Although it can be debated as to whether a lack of social connection can truly engender pain experience, it is hard to argue with the notion that it "hurts" to be without the ones we love. Continuing to explore the neural substrates underlying our need for social connection may help us to better understand why.

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