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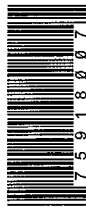
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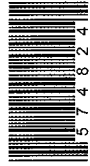
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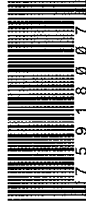
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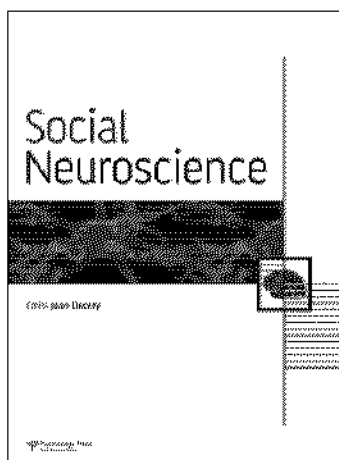
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## Social Neuroscience

Publication details, including instructions for authors and subscription information:  
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### I feel your pain: Emotional closeness modulates neural responses to empathically experienced rejection

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First published on: 10 March 2011

**To cite this Article** Beene, Joseph E. , Franklin Jr., Robert G. , Levy, Kenneth N. and Adams Jr., Reginald B.(2011) 'I feel your pain: Emotional closeness modulates neural responses to empathically experienced rejection', Social Neuroscience,, First published on: 10 March 2011 (iFirst)

**To link to this Article:** DOI: 10.1080/17470919.2011.557245

**URL:** <http://dx.doi.org/10.1080/17470919.2011.557245>

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# I feel your pain: Emotional closeness modulates neural responses to empathically experienced rejection

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Empathy is generally thought of as the ability to share the emotional experiences of others. In scientific terms, this is usually operationalized as an ability to vicariously feel others' mental and emotional experiences. Supporting this account, research demonstrates that watching others experience physical pain activates similar brain regions to the actual experience of pain itself. First-hand experience of social rejection also activates this network. The current work extends these findings by examining whether the "pain" network is similarly implicated in witnessing rejection, and whether emotional closeness modulates this response. We provide evidence for each of these suppositions, demonstrating: (a) that the pain network is activated when watching a friend suffer social rejection, and (b) that interpersonal closeness with that friend modulates this response. Further, we found that the inferior frontal gyrus, critical for representing others' mental and emotional states, mediates the relationship between emotional closeness and neural responses to watching the rejection of a friend.

**Keywords:** Empathy; Peer rejection; Social exclusion; Mirror neurons; Pain; Functional magnetic resonance imaging.

In 1992, presidential hopeful Bill Clinton famously responded to an AIDS activist's contention that "we're not dying of AIDS as much as . . . government neglect" with a statement that became a centerpiece of his campaign: "I feel your pain." The comment unwittingly forecast important scientific insights into empathy that were to come, namely that we can vicariously feel the pain of others. Indeed, watching others in physical pain activates many of the same brain regions involved in the direct experience of pain (Singer et al., 2004). Likewise, experiencing social pain, such as when ostracized, also activates these same brain regions (Eisenberger, Lieberman, & Williams, 2003). Still the question remains: Do we also feel others' social pain the way we vicariously feel their physical pain, as Clinton suggests in the above statement? And if so, what processes moderate and mediate how we empathize with those in social pain?

Physical pain reliably activates a network of brain regions, termed the "pain matrix," which include sensory components such as the somatosensory cortex as well as affective components including the dorsal anterior cingulate cortex (dACC) and the anterior insula (AI) (Peyron, Laurent, & Garcia-Larrea, 2000). The dACC is thought to be involved in a neural alarm system and is central to processing the distress involved with pain (Eisenberger & Lieberman, 2004), while the insula is involved with processing vicarious feelings involved with pain (Ostrowsky et al., 2002; Singer et al., 2004). Social pain also elicits activation in the affective components of the pain matrix, including the insula and dACC (Eisenberger & Lieberman, 2004; Eisenberger et al., 2003), indicating that social pain shares some similarities with the actual experience of physical pain. Thus, the "sting of rejection" may not be simply metaphorical. In fact, highlighting this point,

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This research was supported by a Social Science Research Institute research grant, Pennsylvania State University, to Reginald B. Adams, Jr. The authors declare no competing financial interests. Joseph E. Beeney and Robert G. Franklin, Jr., contributed equally to this publication and are co-primary authors.

the painkiller acetaminophen has been found to reduce both self-reports of social pain and neural responses in the dACC and insula to social rejection (Dewall et al., 2010).

As humans, we have highly developed abilities to empathize. According to the perception-action model of empathy (PAM) (Preston & de Waal, 2002), seeing or imagining another person's experience activates our own representations of that experience, and this helps generate the actual physiological and sensory experience of shared feelings. Extending the PAM to physical pain, numerous researchers (e.g., Avenanti, Buetti, Galati, & Aglioti, 2005; Bufalari, Aprile, Avenanti, Di Russo, & Aglioti, 2007; Cheng et al., 2007; Cheng, Yang, Lin, Lee, & Decety, 2008; Decety, Michalska, & Akitsuki, 2008; Gu & Han, 2007; Lamm, Batson, & Decety, 2007; Lamm, Nussbaum, Meltzoff, & Decety, 2007) found that watching another in pain elicited activation in many of the same brain regions involved in the experience of actual physical pain, including the insula, dACC, and somatosensory cortex (see also Han et al., 2009). Recently, Masten, Eisenberger, Pfeifer, and Dapretto (2010) examined the neural correlates of empathy for social exclusion of strangers among adolescents, but, interestingly, did not find activation of the pain network as previously found for empathy for physical pain. Rather, in both studies, watching another person be rejected prompted greater activation in brain areas related to mentalizing (medial prefrontal cortex (PFC), dorsomedial PFC, and precuneus). These findings may suggest that empathy for social exclusion, distinct from empathy for physical pain, relies on seeking to understand the minds of others, rather than activation of shared representations.

However, the PAM predicts that how familiar or close we are with another should modulate empathic responses. According to this view, greater emotional closeness with another should afford us richer representations of that person's internal states, which would then directly impact the extent to which we are capable of empathizing with them. To date, few studies have examined how relationship quality affects empathy, and no studies to date have examined if representations of others affect empathy. Instead, most studies have focused on empathic responses among strangers, and even when investigating familiar others, the role of emotional closeness has not been explored (e.g., Singer et al., 2004). This may be due in part to findings from twin studies revealing a strong genetic basis for our empathic responses to strangers (Plomin et al., 1993), suggesting that emotional closeness with another is not a necessary ingredient for the empathic response.

However, some existing evidence suggests otherwise. For instance, contextual factors can influence

empathic responses, even to strangers, and empathy tends to be higher for cultural ingroups than outgroups (Mathur, Harada, Lipke, & Chiao, 2010; Xu, Zuo, Wang, & Han, 2009). Likewise, Cheng, Chen, Lin, Chou, and Decety (2010) found that imagining a loved one versus imagining a stranger affected empathy-related responses. In their study, ACC and AI responses for perceiving physical pain were higher when participants perceived those imagined to be loved ones than those imagined to be strangers. These findings suggest a link between shared experience and empathy. If it is indeed correct that empathy for social pain depends on emotional closeness, it would both explain the absence of pain-related neural activation in Masten et al.'s (2010) research and provide elaboration on our understanding of empathy for social pain.

Finally, the PAM also speculates that the premotor mirror neuron system (MNS) is pivotal to our ability to simulate others' internal states and may provide the neural basis for our representations of others. Several brain regions comprise the putative MNS, with the premotor cortex within the posterior inferior frontal gyrus (IFG) consistently implicated in mirroring others' responses (Iacoboni et al., 1999), and in socioperceptual theory of mind tasks such as the reading the mind in the eyes task (Adams et al., 2010; Baron-Cohen et al., 2006; Platek, Keenan, Gallup, & Mohamed, 2004; Russell et al., 2000). Recent reviews of the MNS suggest that its role in empathy may not be as extensive as previously thought, as many studies of facial emotion perception do not elicit IFG activation (Decety, 2010), and many that do, suffer from limitations that prevent those studies from concluding that IFG activation represents the MNS (Turella, Pierno, Tubaldi, & Castiello, 2009).

However, indirect evidence does implicate the IFG MNS in empathy for others, especially involving understanding others' facial expressions. IFG regions are thinner in those with autism (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006) and less active when imitating and observing emotional expressions (Dapretto et al., 2005). Both imitating and perceiving disgusted, fearful, and happy faces also elicit activation in the IFG (van der Gaag, Minderaa, & Keyers, 2007). Likewise, those with higher levels of empathy, as measured by the Empathy Quotient self-report measure, show more left IFG activation when perceiving dynamic displays of facial emotions (Chakrabarti, Bullmore, & Baron-Cohen, 2006), suggesting a role for the IFG in some part of empathizing with another's expression. Further, the IFG has also been found to be more active in those with higher trait levels of empathy when watching others' motor movements, suggesting a link between mirror neurons and empathy (Kaplan

& Iacoboni, 2006). Together, these findings suggest that the IFG is likely important for empathy of others' expressions, especially in mirroring the motor responses and goal-directed actions of others, while other regions may form a more extended MNS for other emotional states (Keysers & Gazzola, 2006; Van der Gaag et al., 2007).

Much of the existing research on the IFG implicates it in the direct mirroring of the actions of others, but no studies to date have directly demonstrated that the MNS is critical to understand others' mental states (Saxe, 2009), as proposed by the PAM. Still, indirect research does show that the human MNS, particularly the IFG, is more responsive when encoding goals related to actions rather than simply mirroring the actions themselves (Iacoboni et al., 2005). The IFG is also more responsive when people perceive actions with discernible goals versus those without discernible goals (Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni, 2006).

Thus, despite some weakness in the evidence linking mirror neurons to empathy, there is still reason to believe the IFG might meaningfully contribute to empathy. If the IFG is a generator of the shared mental representations that the PAM proposes are essential to the empathic response, then activity in this region should predict empathy-related responses, such as those found in the dACC. Additionally, given that emotional closeness allows for richer representations of others, it should also be positively associated with activity in the IFG. Finally, if the IFG is critical in simulating the complex mental representations of known others, then, according to this model, activation in this region should at least partially mediate the proposed relationship between emotional closeness and empathic neural responses to social pain.

In sum, the current research examines three hypotheses derived from the PAM regarding the nature of social empathy. First, we hypothesized that the brain network previously found for the experience of pain, both empathic and actual, would be activated when watching a friend experience social rejection. Second, we predicted that these empathic responses would vary as a function of emotional closeness with that friend. Finally, we predicted that the IFG would mediate the relationship between emotional closeness and activation in the pain matrix.

## METHOD

### Participants

We recruited 20 pairs of same-sex participants (10 female) and their same-sex friends. Friendship pairs

varied from work acquaintances to very close friends. Twenty-four (60%) of the participants were Caucasian. Ages ranged from 18 to 35 years ( $M = 24.6$ ,  $SD = 5.8$ ). Participants signed consents approved by the Pennsylvania State University Institutional Review Board and were paid \$20 each for their participation.

### Procedure

Functional magnetic resonance images (fMRI) were collected while participants watched as their friend was included and then excluded in a ball-toss game (Williams, Cheung, & Choi, 2000), ostensibly by two other participants. Participants were told that two other friendship pairs in the same configuration (one in the scanner, one outside the scanner) were participating in the ball-toss game at another location. One member of the friendship pair was scanned while the other member was seated in a separate room in front of a computer. The ball-toss paradigm used in this study elicits feelings of rejection and distress in past research (Williams et al., 2000). Each of the participants oriented in the scanner watched as their friend was included in one round of the game, and excluded in another. In the inclusion run, the participant had an equal chance of having the ball tossed on any given throw (60 throws). On the second, the participant was excluded after seven throws. Each run lasted 2.45 min and consisted of three avatars tossing the ball, with photographs of the participant's friend and two others representing the other purported friendship pairs. Following both runs, the participants were individually debriefed and carefully probed for suspicion of the hypothesis of the research.

Following the study, participants filled out an adapted version of the Friendship Quality Questionnaire (Parker & Asher, 1993). This measure operationalizes emotional closeness by the degree of sharing of emotional information ("My friend and I are always telling each other about our problems"), degree of interdependency ("When I'm mad about something, I can always talk to my friend about it"), and emotional support ("My friend makes me feel good about my ideas"). The 21-item scale was altered slightly in order to make all items appropriate for adults.

### fMRI data acquisition and analysis

Functional data were collected with a 3T Siemens Tim-Trio Whole Body MRI machine, (Siemens, Munich, Germany) with two runs of 51 T2\* images (TR: 3,000 ms, TE: 25 ms, 36 interleaved slices,

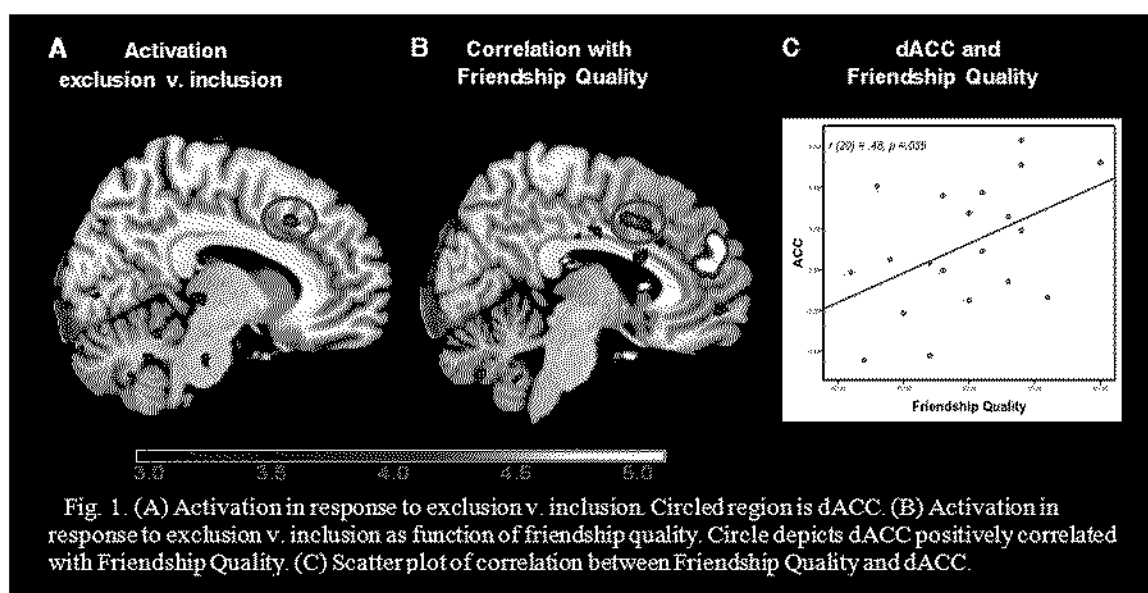
transverse orientation, 3-mm slice thickness, no gap). Data were preprocessed by SPM5 software (Wellcome Institute, London, UK) with a six-parameter rigid realignment, coregistration of mean functional image to a T1 anatomic image, normalization of the T1 image to MNI template and application of these normalization parameters to the functional images, and 8-mm FWHM smoothing with a Gaussian kernel. Analysis used a mass-univariate GLM contrasting activation to exclusion versus inclusion, and contrasts derived for this were used as the basis for second-level analysis and regression (height:  $p < .005$ , uncorrected; extent threshold: 41 voxels, equivalent to  $p < .05$  corrected) (Forman et al., 1995; Vul, Harris, Winkelman, & Pashler, 2009). Regions of interest (ROI) were pulled as mean beta signal for each region, with the ACC defined as activity for rejection to baseline in the ACC. Prefrontal mirror neurons were defined by the Talarach Daemon (Lancaster et al., 2000) to select mean signals for neurons in Brodmann area (BA) 45 (for a similar approach, see Aziz-Zadeh et al., 2006). Rizzolatti, Fadiga, Gallese, & Fogassi, (1996) argued that BA 45 is a human homolog of monkey area F5 (see also Geyer, Matelli, Luppino, & Zilles, 2000), which contains the most consistent evidence for the MNS in monkey single-cell recordings (e.g., Gallese, Fadiga, Fogassi, & Rizzolatti, 1995). BA 45 is also implicated in action imitation in man (e.g., Buccino et al., 2001; Grezes, Costes, & Decety, 1998; Rizzolatti et al., 1996).

## RESULTS

In line with our first hypothesis, we found that when participants watched their friends be rejected, there was striking overlap in brain regions activated with those previously found for the actual experience of social rejection, as well as for actual and empathic experiences of physical pain, most notably involving the right dACC, bilateral anterior insula, and right anterior PFC. Activity was also found in the cerebellum, IFG, and superior temporal sulcus (STS), all of which are regions previously found to be involved in empathic responses to others (see Figure 1).

Consistent with our second hypothesis, when examined as a subject-level regressor, emotional closeness was positively associated with activation in the same primary ROI (see Table 1), namely the right dACC, bilateral anterior insula, and right anterior PFC. In addition, emotional closeness was associated with activation in the bilateral fusiform gyrus, IFG, cerebellum, left ventromedial PFC, temporal pole, and STS, all of which have previously been found to be involved in empathic responses to others.

Finally, we examined whether activity in the IFG mediated the relationship between emotional closeness and dACC activity. Using beta values pulled from clusters of our primary ROI based on our own exclusion > inclusion contrast, we subjected our data to the four conditions for mediation (Baron & Kenny, 1986). Specifically, we found that emotional closeness



**Figure 1.** Activation maps for exclusion versus inclusion and friendship quality entered as a regressor. ACC: anterior cingulate cortex.

TABLE 1

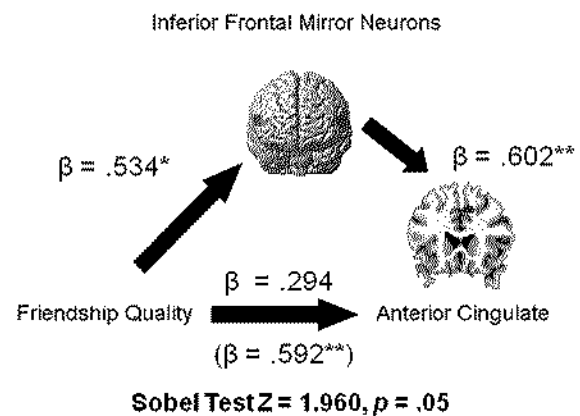
Regions active for the main effect of exclusion minus inclusion and regions active with friendship quality as a regressor. Regions are reported posterior to anterior.

Brain region	MNI coordinates			t-value	Cluster size
	x	y	z		
<b>A. Exclusion minus inclusion</b>					
R. precuneus	14	-82	40	3.75	56
R. cuneus	16	-80	0	4.07	71
L. cerebellum	-10	-76	-50	5.11	964
R. cerebellum	14	-76	-12	4.53	116
R. posterior insula	48	-38	18	3.84	67
R. middle temporal gyrus	44	-28	-8	4.61	99
R. thalamus	12	-28	4	3.61	46
R. insula	44	-10	-10	3.44	46
R. anterior cingulate	12	20	40	4.05	81
<b>B. Exclusion minus inclusion with friendship quality as regressor</b>					
R. cerebellum	24	-62	-46	4.57	42
L. cerebellum	-2	-52	-44	3.68	118
L. fusiform gyrus	-40	-40	-12	4.31	70
R. fusiform gyrus	30	-40	-6	4.15	47
L. superior temporal sulcus	-66	-38	6	4.6	117
L. inferior frontal gyrus	-44	-10	60	4.08	65
L. insula	-44	-6	12	6.79	943
R. inferior frontal gyrus	66	-4	24	4.13	57
R. putamen	24	0	14	4.92	46
L. anterior cingulate	-14	14	42	5	163
L. temporal pole	-40	16	-28	4.77	61
L. ventromedial prefrontal cortex	-6	36	-10	4.96	230
L. anterior prefrontal cortex	-10	48	42	4.45	50
R. medial prefrontal cortex	4	52	30	4.29	127
R. anterior cingulate	28	62	10	5.43	68

was positively associated with the IFG and the dACC. Additionally, activity in the IFG was positively associated with the dACC when controlling for emotional closeness. When controlling for activity in the IFG, however, the relationship between emotional closeness and the dACC was reduced to statistical nonsignificance (see Figure 2).

## DISCUSSION

We found evidence supporting each of our three hypotheses. When we see someone else we know suffer a rejection, it prompts activation in brain areas underlying the affective experience of pain. Moreover, rather than empathy being a fixed, genetically influenced, trait-like response, closeness of the friendship pair was found to be a powerful moderator of this response. Finally, we found that activation in the IFG mediated the relationship between level of closeness and activation in the dACC when viewing a friend



**Figure 2.** Mediation of the relationship between friendship quality and ACC activation by Brodmann area (BA) 45. An anatomically defined area for the inferior frontal gyrus mediated the relationship between friendship quality and the anterior cingulate cortex.

being socially ostracized, consistent with the proposed role of the IFG as the neural basis for some of the perceptual representations that give rise to empathy for social pain. In sum, these findings suggest that knowing a person better allows us to construct



a richer representation of that individual's rejection experience, leading to greater empathic responses.

Consistent with our first hypothesis, we found that when participants watched a friend be rejected their brain activation showed striking overlap with regions activated previously for the actual experience of social rejection, as well as for actual and empathic experiences of physical pain (Eisenberger et al., 2003; Singer et al., 2004, 2006; Xu et al., 2009), most notably involving the right dACC and the right anterior insula. We also found activity in the cerebellum, IFG, and STS. These regions have also previously been found to be involved in understanding what others are thinking (theory of mind) and in empathic responses to others (Decety & Jackson, 2004).

We found activation in the pain matrix when watching the rejection of a friend, something that Masten et al. (2010) did not find, despite the use of nearly identical tasks. Though we also included pictures of the other participants, while Masten et al. did not, the most obvious and theoretically relevant difference between the two studies is the relationship between the participant and the individual experiencing social rejection. It seems highly likely that the difference between the study of Masten et al. and ours can be explained by differences in witnessing the experience of social rejection of a friend versus a stranger. This conclusion gains greater credence when we consider that friendship quality directly moderated this effect. Importantly, this finding suggests that when we witness a friend experience social rejection, we may simulate pain-related neural activation, whereas we may instead recruit more cognitive mentalizing strategies when watching the social rejection of a stranger. This is consistent with the PAM, which suggests that familiarity moderates empathy through the development of more richly shared representations.

In line with our second hypothesis, emotional closeness modulated brain responses to vicarious rejection in the bilateral anterior insula and the dACC. This confirms a vital prediction of the PAM that closeness should modulate the empathic response (Preston & de Waal, 2002). In addition, our finding that closeness modulates empathy suggests that although empathy for strangers is likely a genetically influenced trait (Plomin et al., 1993), empathy for known others develops over the course of a relationship.

We also found that emotional closeness modulated activation in the ventromedial PFC such that closer friends showed greater activation in these regions to vicarious rejection. Each of these regions is critical in theory of mind, or decoding what others are thinking. More ventral regions of the medial PFC are thought to

be involved in decoding the emotional states of others (Amodio & Frith, 2006). This is especially the case with similar others, as understanding the mental states of similar others (Mitchell, Macrae, & Banaji, 2006) and emotional perspective taking (Hynes, Baird, & Grafton, 2006) both elicit ventromedial PFC activation. This suggests that we may understand closer friends by taking their perspective to a greater degree. This may contribute to our greater empathy for them.

In seeking to identify a potential mechanism of this relationship, we examined our third hypothesis that the IFG would at least partially mediate the relationship between emotional closeness and dACC activation. Our analysis confirmed this proposition, suggesting that the path through which closeness influences dACC responses to watching a friend be rejected is through the IFG. Since the dACC is pivotal to processing the affective nature of pain and is central to our empathy for social pain (Eisenberger & Lieberman, 2004), this provides evidence of the involvement of regions known to be part of the MNS in affective responses to social exclusion.

However, this study does not conclusively implicate the involvement of the MNS in empathy. One critique of research looking into the role of the MNS in empathy is that many tasks that examine the MNS do not use a task to localize the MNS by functionally determining the regions involved in both producing and observing others' actions (Turella et al., 2009). Given that we did not functionally determine the MNS in the IFG in the present study, it is impossible to rule out other interpretations of this data. Along with being involved in mirroring others' actions, the IFG is also known to be involved in several other cognitive tasks, such as language processing (e.g., Binder et al., 1997), in task switching, and in tasks involving choosing between competing responses, such as the flanker task (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Hazeltine, Bunge, Scanlon, & Gabrieli, 2003; Hazeltine, Poldrack, & Gabrieli, 2000).

Although our *a priori* rationale for examining the IFG stemmed from theoretical considerations surrounding its putative mirror-neuron properties, its role in empathy may be more broadly construed. Nonetheless, the evidence here suggests an important role of the IFG in empathy, especially in how relationship quality affects empathy. Therefore, further investigation is necessary to determine whether the IFG does contain representations of others that are critical for empathy, as the PAM suggests, or whether our findings may be due to other factors involving IFG responses. The evidence contained here at the very least implicates the IFG as playing a critical role in

mediating the effects of friendship quality on neural responses to empathic rejection. Other limitations of this research include a relatively small sample size and the use of correlational measures rather than a direct manipulation of emotional closeness. Further research of this type will be necessary to clarify the precise nature of these findings.

In sum, we found that empathy for emotional pain activated brain areas overlapping with the direct experience of physical pain and social rejection, and that friendship quality modulated this brain activity. Further, this study suggests that empathy develops through the growth of the relationship itself, and is not simply a fixed trait response of the individual. As we grow closer to a person, forming a more complex and elaborated understanding of that person, our empathic neural responses to their experiences increases, offering crucial evidence to support current theoretical assertions that empathy depends on the relationships and shared experiences we have with another.

Original manuscript received 22 July 2010  
Revised manuscript accepted 7 December 2010  
First published online

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