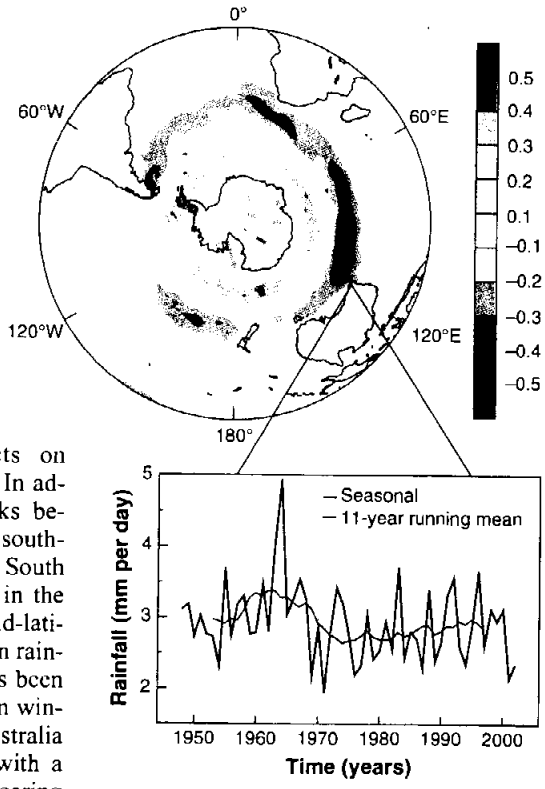
sure at mid-latitudes and decreased pressure at high latitudes (*1*). Increasing greenhouse gases have probably contributed to the observed Southern Hemisphere warming at mid- and lower latitudes and to the observed circulation changes (strengthening of the SAM) in winter. However, the magnitude of the circulation response in these climate models is not nearly as strong as that found in the observations or in the ozone-forced model response in summer (*3*).

The recent changes in the Southern Hemisphere circulation at high latitudes have clear impacts on Antarctica and the Southern Ocean. In addition, there may be important links between SAM variations and rainfall in southern Australia, New Zealand, and South America (see the figure). Increases in the SAM, with increasing pressure at mid-latitudes, are associated with decreases in rainfall between 35° and 50°S. There has been a substantial reduction (15 to 20%) in winter rainfall in southwest Western Australia over the past 50 years, associated with a southward shift in the winter rain-bearing weather systems (*5*). Fyfe has noted this southward shift in Southern Hemisphere extratropical cyclones in both observational data and model responses to increasing greenhouse gases (*6*).

The observed rainfall trends in southwest Western Australia are much greater than expected from most climate model simulations with increasing greenhouse gases. Furthermore, they occur in a season when there is likely to be little influence from stratospheric ozone depletion. Hence, natural decadal climate variations are likely to be an important factor in these rainfall decreases.



Climate connections. (Top) Relation between variations of the southern annular mode (SAM) and rainfall in the Southern Hemisphere, based on data from a long control climate model simulation (*7*). Similar results are obtained with the climate model of Gillett and Thompson (*3*). **(Bottom)** Time series of winter rainfall in southwest Western Australia. The decrease in rainfall is consistent with the observed increasing trend in the SAM.

Recent climate changes in the Southern Hemisphere are likely to result from a complex combination of natural climate processes (associated with interactions between the atmosphere, oceans, and sea ice) and human influences (including decreases in stratospheric ozone and increases in atmospheric greenhouse gases and aerosols).

Untangling the separate contributions is crucial for understanding recent regional climate variations, such as the rainfall trends in Western Australia, and for predicting how climate is likely to change in the future. Gillett and Thompson (*3*) have taken an important step in this direction in showing that the recent summer circulation changes in the Southern Hemisphere high latitudes are likely to be caused by stratospheric ozone depletion.

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NEUROSCIENCE

Feeling the Pain of Social Loss

Jaak Panksepp

The Greek philosopher Zeno of Citium (356 to 264 B.C.), the founder of Stoicism, considered pain to be one of nine forms of grief. We often speak about the loss of a loved one in terms of painful feelings, but it is still not clear to what extent such metaphors reflect what is actually happening in the human brain? Enter Eisenberger and colleagues (*1*) on page 290 of this issue with a bold neuroimaging experiment that seeks to discover whether the metaphor for the psychological pain of social loss is reflected in the neural circuitry of the human brain. Using functional magnetic resonance imaging (fMRI), they show that certain human brain areas that "light up" during physical pain are also activated during emotional pain induced by social exclusion.

You might wonder how one measures the feeling of social exclusion while the subject is lying in an MRI machine. Eisenberger *et al.* circumvented this obvious problem in a clever way. In their study, the 13 participants observed a virtual ball-tossing video game while brain blood flow was monitored by MRI. During a baseline period, subjects were led to believe that they were only observing the game. During the experimental phase, however, they became active participants in the game. Within a few throws of the ball, the two other "players" (actually computerized stooges) stopped throwing the ball to the subjects, leading them to feel excluded (*2*). The subjects experienced emotional distress as indicated by substantial blood-flow changes in two key brain areas. One of these areas, the anterior cingulate cortex, has been implicated in generating the aversive experience of physical pain. Eisenberger and colleagues demonstrate that the greater the feeling of social distress, the more this brain area becomes activated. The other brain region, in the prefrontal cortex, showed an opposite pattern of activity, becoming more active when the distress was least. In other words, the two brain areas involved in the distressing feelings of social exclusion responded in op-

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posite ways to the degree of social pain experienced. This suggests that the anterior cingulate is more important for elaborating feelings of emotional distress, whereas the prefrontal cortex, already implicated in emotional regulation (*3*), counteracts the painful feeling of being shunned.

These results are consistent with the idea that aversive feelings of social exclusion and physical pain arise, in part, from the same brain regions. They dovetail nicely with what we know about separation distress in other animals. In our work a quarter of a century ago, we examined the neurochemistry of social attachments in animals (*4*, *5*). We found that the same neurochemicals that regulate physical pain also control the psychological pain of social loss. Indeed, plant opioids (such as morphine) as well as endogenous brain opioids (especially endorphins)—known to alleviate physical pain—also alleviated separation distress (as measured by isolation cries) in dogs, guinea pigs, chicks, rats, and primates (*6*).

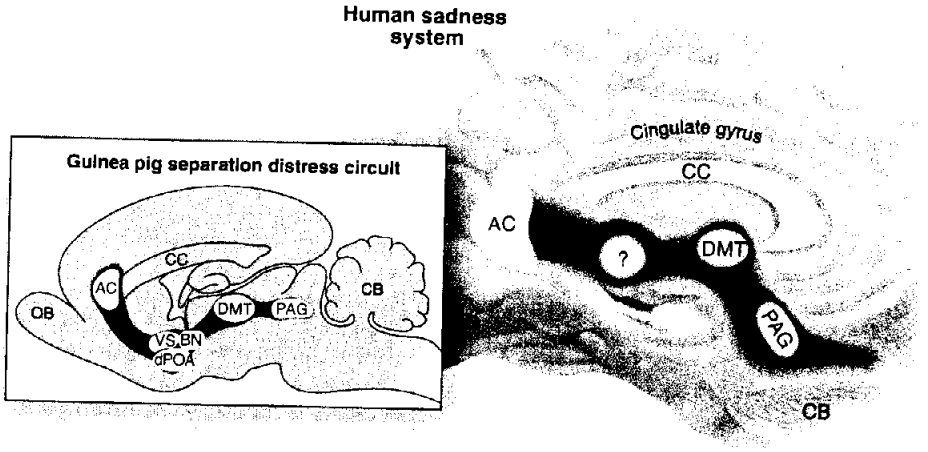
How can we further elucidate the neural mechanisms that underlie the emotional pain induced by social exclusion? Two strategies might help. If the participants in the Eisenberger *et al.* study were to be given opioids, one would predict that they would feel less distress at being shunned, and that the brain areas implicated in elaborating such feelings would not be as profoundly activated. The administration of opioid receptor antagonists should intensify both effects. Other brain chemicals, such as oxytocin and prolactin (*6*) that are also powerful regulators of separation distress in animals, may have effects similar to those of opioids but they are too difficult to manipulate experimentally in humans.

Brain imaging has yielded a plethora of neural correlates of affective states (*3*) including the response to breathlessness (*7*), the craving for chocolate (*8*), winning the lottery (*9*), the sex-specific appeal of pretty faces (*10*), the ecstasy of peak musical experiences (*11*), human sympathy (*12*), male sexual arousal (*13*), and even rectal distension (*14*). The human brain areas implicated by Eisenberger *et al.* in feelings of social pain have many other functions. The cingulate gyrus (a long ribbon of tissue at the brain's midline) contains two distinct "emotional" zones: The far anterior region elaborates negative feelings, whereas posterior regions elaborate positive feelings. The antidepressant effects of mood-elevating drugs and placebos both depend on reducing the activity of the (subgenual) anterior cingulate and increasing the activity of the posterior cingulate (*15*). The most profound effects observed by Eisenberger *et al.* seem to be centered in the central cingulate region that is known to integrate emotion and cognition. This region is activated during male sexual arousal (*12*) and during stressful cognitive tasks requiring attention (*16*).

The feelings induced by experimental games in the laboratory, such as "CyberBall" in the Eisenberger *et al.* study, are a pale shadow of the real-life feelings that humans and other animals experience in response to the sudden loss of social support. It will be interesting to study more intense emotional states arising from profound personal loss with fMRI, which should allow us to probe even deeper into the regions of the mammalian brain that control separation distress (*6*). A step in this direction is the visualization by positron emission tomography of regions of the human brain activated during sadness (*17*) (see the figure). These regions correspond to some of the deeper brain areas activated during separation distress in animals. Localized electrical stimulation of many subcortical brain sites provokes separation cries in mammals (*6*, *18*, *19*). These sites include not only the anterior cingulate, but also the bed nucleus of the stria terminalis, the ventral septal and dorsal preoptic areas, the dorsomedial thalamus, and the periaqueductal central gray area the brain stem (see the figure). The latt two areas are known to control feelings physical pain. Psychological pain in h mans, especially grief and intense lone ness, may share some of the same neur pathways that elaborate physical pai Given the dependence of mammalia young on their caregivers, it is not hard comprehend the strong survival value co ferred by common neural pathways th elaborate both social attachment and the a fective qualities of physical pain.

Throughout history poets have writte about the pain of a broken heart. It seem that such poetic insights into the huma condition are now supported by neurophysiological findings. Will the opposite also prove to be the case—that socially supportive and loving feelings reduce the sting of pain (*20*, *21*)? A reasonable working hypothesis is that social feelings such as love are constructed partly from brain neural circuits that alleviate the feelings of social isolation. Will we eventually discover that the feeling of a broken heart arises from the rich autonomic circuits of the brain's limbic system that control cardiac neurodynamics? Will we find that people we consider "cold" or "warm" influence different thermoregulatory neural pathways in our brains?

As exemplified by the Eisenberger *et al.* study, such poetic insights garner some support from neurophysiological research,



The emotional pain of social loss. There are remarkable similarities between regions of the guinea pig brain that when activated provoke separation distress and areas of the human brain that are activated during feelings of sadness. During separation distress in guinea pigs, the most responsive brain areas are the anterior cingulate (AC), the ventral septal (VS) and dorsal preoptic areas (dPOA), the bed nucleus of the stria terminalis (BN), the dorsomedial thalamus (DMT), and the periaqueductal central gray area of the brain stem (PAG) (*18*, *19*). In humans experiencing sadness (*17*), it is the anterior cingulate that is most responsive, but other areas that are also activated include the DMT, PAG, and insula. The correspondence between the brain regions activated during human sadness and those activated during animal separation distress suggests that human feelings may arise from the instinctual emotional action systems of ancient regions of the mammalian brain. OB, olfactory bulb; CC, corpus callosum; CB, cerebellum.

subtilis (fig. S2). The RLP of *B. subtilis* includes both those amino acid residues of RuBisCO that are responsible for binding the phosphate on C1 of RuBP and those required for activation by CO_2. However, the residues of RuBisCO that are responsible for binding the other phosphate group of RuBP and the residues of loop 6, which are essential for RuBisCO activity (*2*, *3*), are replaced by different amino acids in RLP (Fig. 1B). The reaction catalyzed by RuBisCO consists of three sequential, partial reactions: enolization, carboxylation or oxygenation, and hydrolysis (*2*, *3*, *26*). Deletion of loop 6 from RuBisCO prevents it from catalyzing the carboxylation/oxygenation reactions (*27*). However, it retains the ability to catalyze the enolization reaction (*27*). This observation supports the hypothesis that the RLP-catalyzed enolization of DK-MTP-1-P does not require the amino acid residues that bind the phosphate group on C5 of RuBP and the loop 6. Moreover, the structure of DK-MTP-1-P is very similar to that of RuBP. In photosynthetic RuBisCO, these additional structures may hinder the DK-MTP-1-P enolase reaction, and they may also explain the slow growth of *ykrW /rbc*L$^+$ cells (Fig. 4C). In this context, our results with the RLP of *B. subtilis* suggest that RLPs of other bacteria may also catalyze a reaction similar to one of the partial reactions of RuBisCO in a bacterial metabolic pathway.

Our analysis shows that RLP of *B. subtilis* functions as a DK-MTP-1-P enolase, which has no RuBP-carboxylation activity, in the methionine salvage pathway. Moreover, this function of RLP is conserved in the RuBisCO from a photosynthetic bacterium. In a standard phylogenetic tree of the large subunits of RuBisCO, the RLP from *B. subtilis* is not included on any branches that include RuBisCO or on branches that include other RLPs with RuBP-carboxylation activity (Fig. 1A). The codon usage and the G + C content of the gene for RLP are typical of the organism. The literature (*28*) suggests that genes such as the gene for RLP were probably not derived by lateral transfer of a gene for a RuBP-carboxylating enzyme from another unrelated organism, for example, in this case, an archaeon or photosynthetic bacterium. Thus, it is possible that the gene for RLP, which in *B. subtilis* is part of the methionine salvage pathway, and the gene for photosynthetic RuBisCO originated from a common ancestral gene (supporting online text). However, bacteria and Archaea that have RLPs first appeared on Earth (*29*) long before the Calvin cycle developed in photosynthetic bacteria (*30*), thus we suggest that RLPs may be the ancestral enzymes of photosynthetic RuBisCO.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/302/5643/286/DC1
Materials and Methods
SOM Text
Figs. S1 and S2
References

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Does Rejection Hurt? An fMRI Study of Social Exclusion

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A neuroimaging study examined the neural correlates of social exclusion and tested the hypothesis that the brain bases of social pain are similar to those of physical pain. Participants were scanned while playing a virtual ball-tossing game in which they were ultimately excluded. Paralleling results from physical pain studies, the anterior cingulate cortex (ACC) was more active during exclusion than during inclusion and correlated positively with self-reported distress. Right ventral prefrontal cortex (RVPFC) was active during exclusion and correlated negatively with self-reported distress. ACC changes mediated the RVPFC-distress correlation, suggesting that RVPFC regulates the distress of social exclusion by disrupting ACC activity.

It is a basic feature of human experience to feel soothed in the presence of close others and to feel distressed when left behind. Many languages reflect this experience in the assignment of physical pain words ("hurt feelings") to describe experiences of social separation (*1*). However, the notion that the pain associated with losing someone is similar to the pain experienced upon physical injury seems more metaphorical than real. Nonetheless, evidence suggests that some of the same neural machinery recruited in the experience of physical pain may also be involved in the experience of pain associated with social separation or

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rejection (*2*). Because of the adaptive value of mammalian social bonds, the social attachment system, which keeps young near caregivers, may have piggybacked onto the physical pain system to promote survival (*3*). We conducted a functional magnetic resonance imaging (fMRI) study of social exclusion to determine whether the regions activated by social pain are similar to those found in studies of physical pain.

The anterior cingulate cortex (ACC) is believed to act as a neural "alarm system" or conflict monitor, detecting when an automatic response is inappropriate or in conflict with current goals (*4–6*). Not surprisingly, pain, the most primitive signal that "something is wrong," activates the ACC (*7, 8*). More specifically, dorsal ACC activity is primarily associated with the affectively distressing rather than the sensory component of pain (*7–9*).

Because of the importance of social bonds for the survival of most mammalian species, the social attachment system may have adopted the neural computations of the ACC, involved in pain and conflict detection processes, to promote the goal of social connectedness. Ablating the cingulate in hamster mothers disrupts maternal behavior aimed at keeping pups near (*10*), and ablating the cingulate in squirrel monkeys eliminates the spontaneous production of the separation cry, emitted to reestablish contact with the social group (*11*). In human mothers, the ACC is activated by the sound of infant cries (*12*). However, to date, no studies have examined whether the ACC is also activated upon social separation or social rejection in human subjects.

Right ventral prefrontal cortex (RVPFC) has been implicated in the regulation or inhibition of pain distress and negative affect (*13–16*). The primate homolog of VPFC has efferent connections to the region of the ACC associated with pain distress (*17, 18*), suggesting that RVPFC may partially regulate the ACC. Additionally, electrical stimulation of VPFC in rats diminishes pain behavior in response to painful stimulation (*19*). More recently in humans, heightened RVPFC activation has been associated with improvement of pain symptoms in a placebo-pain study (*16*).

Given that even the mildest forms of social exclusion can generate social pain (*20*), we investigated the neural response during two types of social exclusion: (i) explicit social exclusion (ESE), in which individuals were prevented from participating in a social activity by other players engaged in the social activity, and (ii) implicit social exclusion (ISE), in which participants, because of extenuating circumstances, were not able to join in a social activity with other players.

fMRI scans were acquired while participants played a virtual ball-tossing game ("CyberBall") with what they believed to be two other players, also in fMRI scanners, during which the players eventually excluded the participant (*21*). In reality, there were no other players; participants were playing with a preset computer program and were given a cover story to ensure that they believed the other players were real (*22*).

In the first scan (ISE), the participant watched the other "players" play CyberBall. Participants were told that, because of technical difficulties, the link to the other two scanners could not yet be made and thus, at first, they would be able to watch but not play with the other two players. This cover story was intended to allow participants to view a scene visually identical to ESE without participants believing they were being excluded. In the second scan (inclusion), participants played with the other two players. In the final scan (ESE), participants received seven throws and were then excluded when the two players stopped throwing participants the ball for the remainder of the scan (~45 throws). Afterward, participants filled out questionnaires assessing how excluded they felt and their level of social distress during the ESE scan (*22*).

Behavioral results indicated that participants felt ignored and excluded during ESE ($t = 5.33$, $P < 0.05$). As predicted, group analysis of the fMRI data indicated that dorsal ACC (Fig. 1A) ($x = -8$, $y = 20$, $z = 40$) was more active during ESE than during inclusion ($t = 3.36$, $r = 0.71$, $P < 0.005$) (*23, 24*). Self-reported distress was positively correlated with ACC activity in this contrast (Fig. 2A) ($x = -6$, $y = 8$, $z = 45$, $r = 0.88$, $P < 0.005$; $x = -4$, $y = 31$, $z = 41$, $r = 0.75$, $P < 0.005$), suggesting that dorsal ACC activation during ESE was associated with emotional distress paralleling previous studies of physical pain (*7, 8*). The anterior insula ($x = 42$, $y = 16$, $z = 1$) was also active in this comparison ($t = 4.07$, $r = 0.78$, $P < 0.005$); however, it was not associated with self-reported distress.

Two regions of RVPFC were more active during ESE than during inclusion (Fig. 1B) ($x = 42$, $y = 27$, $z = -11$, $t = 4.26$, $r = 0.79$, $P < 0.005$; $x = 37$, $y = 50$, $z = 1$, $t = 4.96$, $r = 0.83$, $P < 0.005$). Self-reported distress was negatively correlated with RVPFC activity during ESE, relative to inclusion (Fig. 2B) ($x = 30$, $y = 34$, $z = -3$, $r = -0.68$, $P < 0.005$). Additionally, RVPFC activation ($x = 34$, $y = 36$, $z = -3$) was negatively correlated with ACC activity ($x = -6$, $y = 8$, $z = 45$) during ESE, relative to inclusion ($r = -0.81$, $P < 0.005$) (Fig. 2C), suggesting that RVPFC may play a self-regulatory role in mitigating the distressing effects of social exclusion.

ACC activity ($x = -6$, $y = 8$, $z = 45$) mediated the direct path from RVPFC ($x = 34$, $y = 36$, $z = -3$) to distress (Sobel test, $Z = 3.16$, $P < 0.005$). After controlling for ACC activity, the remaining path from RVPFC to distress was no longer significant ($\beta = -0.17$, $P > 0.5$). This mediational model is nearly identical to the results from previous research on the self-regulation of physical pain (*16*).

ISE, relative to inclusion, also produced significant activation of ACC ($x = -6$, $y = 21$, $z = 41$; ($z = 41$, $t = 4.34$, I = 0.78, $P < 0.005$). To preserve the cover story, self-reported distress was not assessed after this condition, and thus we could not assess the relation between ACC activity during ISE and perceived distress. However, no RVPFC activity was found in this comparison, even at a $P = .05$ significance level, suggesting that the ACC registered this ISE but did not generate a self-regulatory response.

In summary, a pattern of activations very similar to those found in studies of physical pain emerged during social exclusion, providing evidence that the experience and regulation of social and physical pain share a common neuroanatomical basis. Activity in dorsal ACC, previously linked to the experience of pain distress, was associated with increased distress after social exclusion. Furthermore, activity in RVPFC, previously linked to the regulation of pain distress, was associated with diminished distress after social exclusion.

The neural correlates of social pain were also activated by the mere visual appear-

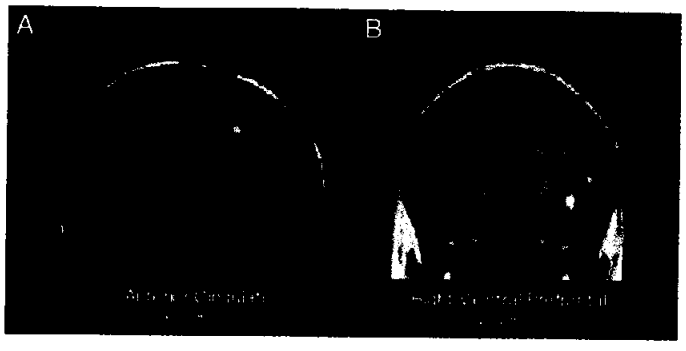

Fig. 1. (**A**) Increased activity in anterior cingulate cortex (ACC) during exclusion relative to inclusion. (**B**) Increased activity in right ventral prefrontal cortex (RVPFC) during exclusion relative to inclusion.

ance of exclusion in the absence of actual exclusion. The pattern of neural activity associated with ISE and ESE provides some challenges to the way we currently understand exclusion and its consequences. Although the neural correlates of distress were observed in both ISE and ESE, the self-regulation of this distress only occurred in response to ESE. Explicit awareness of exclusion may be required before individuals can make appropriate attributions and regulate the associated distress.

Dorsal ACC activation during ESE could reflect enhanced attentional processing, previously associated with ACC activity (*4*, *5*), rather than an underlying distress due to exclusion. Two pieces of evidence make this possibility unlikely. First, ACC activity was strongly correlated with perceived distress after exclusion, indicating that the ACC activity was associated with changes in participants' self-reported feeling states. Second, although inclusion is likely to require greater attentional processing than does ISE to facilitate participation in the game, there was greater ACC activity during ISE than during inclusion, indicating that the ACC activity was not fully attributable to heightened attention.

Because of the need to maintain a realistic situation in which participants would genuinely feel excluded, the study did not contain some of the controls typical of most neuroimaging studies. For instance, the conditions were always implemented in the same order so as to keep expectations consistent from one scan to the next across participants. It was especially critical that ESE came last to prevent expectations of possible exclusion from contaminating the other conditions. There was only a single ESE period to preserve ecological validity. This modification, however, diminishes, rather than increases, the likelihood of Type I errors.

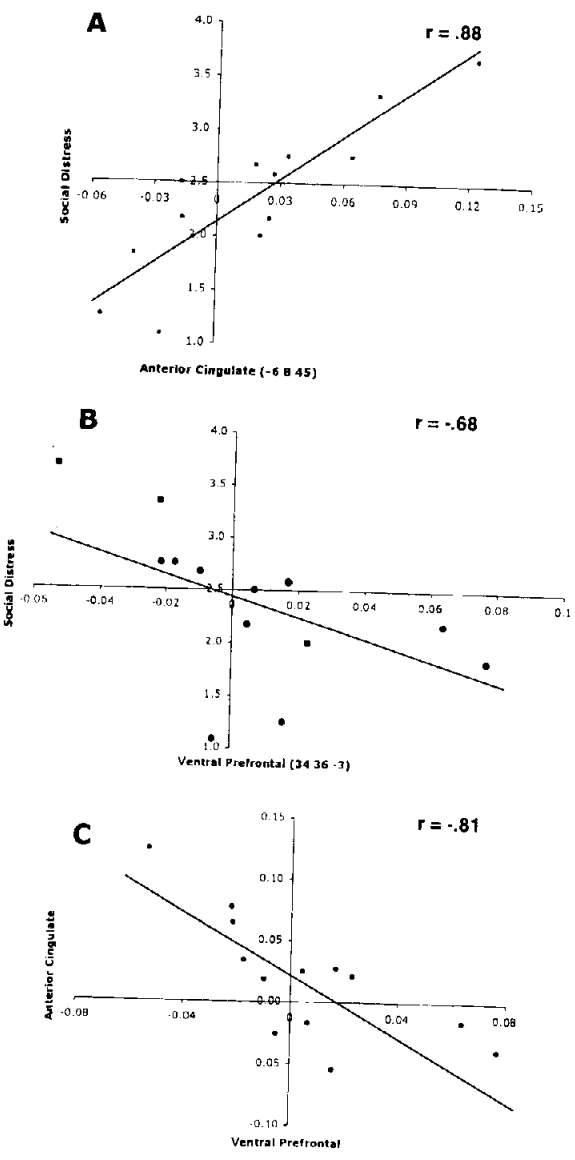

Fig. 2. Scatterplots showing the relation during exclusion, relative to inclusion, between (**A**) ACC activity and self-reported distress, (**B**) RVPFC and self-reported distress, and (**C**) ACC and RVPFC activity. Each point represents the data from a single participant.

This study suggests that social pain is analogous in its neurocognitive function to physical pain, alerting us when we have sustained injury to our social connections, allowing restorative measures to be taken. Understanding the underlying commonalities between physical and social pain unearths new perspectives on issues such as why physical and social pain are affected similarly by both social support and neurochemical interventions (*2*, *3*, *25*), and why it "hurts" to lose someone we love (*1*).

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22. Materials and methods are available as supportive material on *Science* Online.
23. The correction for multiple comparisons was carried out with an uncorrected P value of 0.005 and a cluster size threshold of 10, corresponding to a per-voxel false positive probability of less than 0.000001 (*24*).
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Supporting Online Material

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Materials and Methods

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