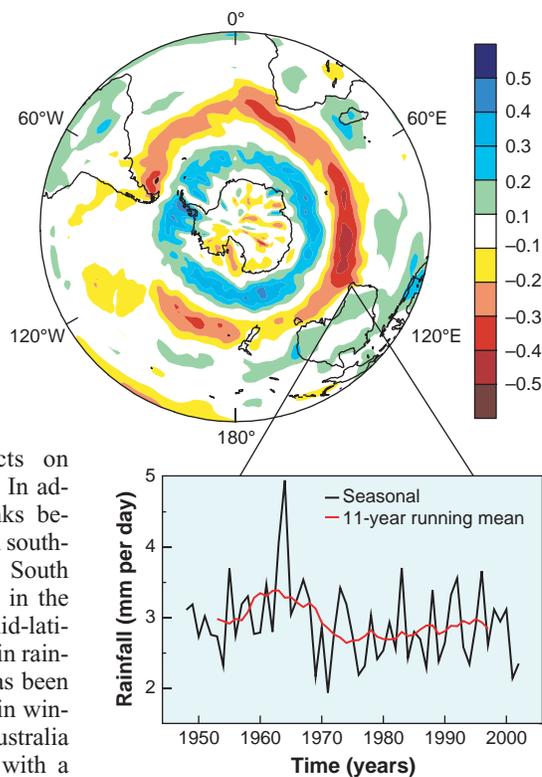


sure at mid-latitudes and decreased pressure at high latitudes (1). Increasing greenhouse gases have probably contributed to the observed Southern Hemisphere warming at mid- and lower latitudes and to the observed circulation changes (strengthening of the SAM) in winter. However, the magnitude of the 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.

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).

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.

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 neu-

roimaging 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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PERSPECTIVES

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.

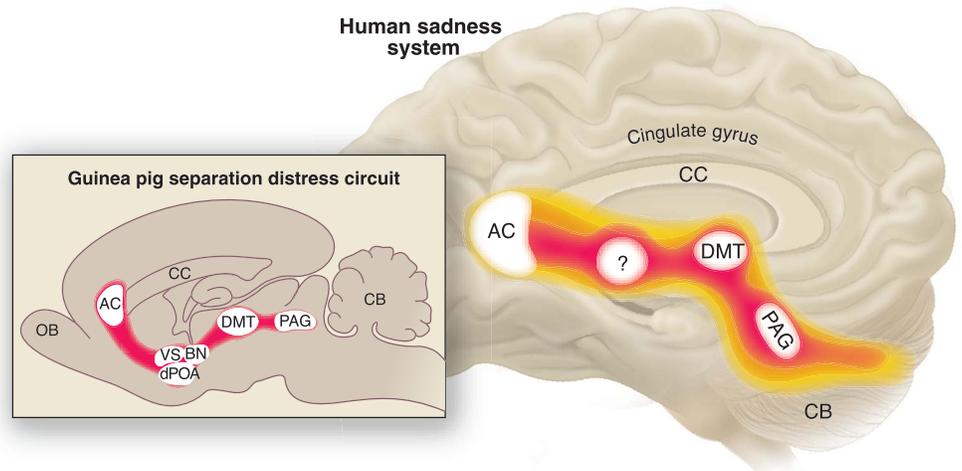
Brain imaging has yielded a plethora of neural correlates of affective states (3) including the response to breathlessness (7), the craving for chocolate (8), winning the lottery (9), the sex-specific appeal of pretty faces (10), the ecstasy of peak musical experiences (11), human sympathy (12), male 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 re-

ducing 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

and the periaqueductal central gray area of the brain stem (see the figure). The latter two areas are known to control feelings of physical pain. Psychological pain in humans, especially grief and intense loneliness, may share some of the same neural pathways that elaborate physical pain. Given the dependence of mammalian young on their caregivers, it is not hard to comprehend the strong survival value conferred by common neural pathways that elaborate both social attachment and the affective qualities of physical pain.

Throughout history poets have written about the pain of a broken heart. It seems that such poetic insights into the human



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.

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,

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,

adding a humanistic touch to the mind-brain sciences. Feelings of love and loneliness, and the thoughts they provoke, are constructed in part from neural pathways in the brain that regulate core emotional responses, such as playfulness, sexuality, and friendship, as well as separation distress in our fellow creatures (6).

Of course, scientists should continue to be skeptical about such hypotheses until they are supported by solid research such as that carried out by Eisenberger and co-workers. Although there are many species differences in the emotional systems that we share as ancestral gifts with other animals (6, 22, 23), the field of neuroscience will be more productive if it remains open to the similar nature of human and animal affective experiences.

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21. When I lost my daughter 12 years ago in a horrendous traffic accident, among her papers I found a poem that is now carved on her tombstone. The last stanza is particularly pertinent to the question of whether love can reduce the emotional pain of loss.
*When your days are full of pain,
And you don't know what to do,
Recall these words I tell you now
—I will always care for you*

Full poem is published in A. Miller, *A Road Beyond Loss* (Memorial Foundation for Lost Children, Bowling Green, OH, 1995).

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CHEMISTRY

The Motions of an Enzyme Soloist

Michel Orrit

On page 262 of this issue, Yang *et al.* report a fluorescence study of the conformational fluctuations of a single enzyme molecule (1). As we can observe every time we boil an egg, proteins are not static. Conformational flexibility at various levels of their hierarchical structure enables proteins to fulfill a wide range of complex biological functions. Yang *et al.* now follow these fluctuations over a range of time scales at equilibrium, and not in response to some initial large disturbance.

Most proteins are highly complex macromolecules (2). Driven by Brownian motion, they wander in an intricate multidimensional energy landscape, featuring multitudes of interconnected wells and dells, valleys and passes. Hopping from well to well can be as fast as tens of femtoseconds for fast backbone vibrations, or as slow as hours and even days for folding and maturation in large proteins—a range of time scales spanning 18 orders of magnitude.

To make matters worse, protein functions such as catalytic reactions are determined by short-range atom-atom interactions and critically depend on tiny atomic displacements. Understanding of such sub-

tlety and complexity is still in its infancy. Numerical simulations (3) can handle ever more complexity, but the longest simulations do not exceed a few nanoseconds. Moreover, computations must eventually be compared with experiments.

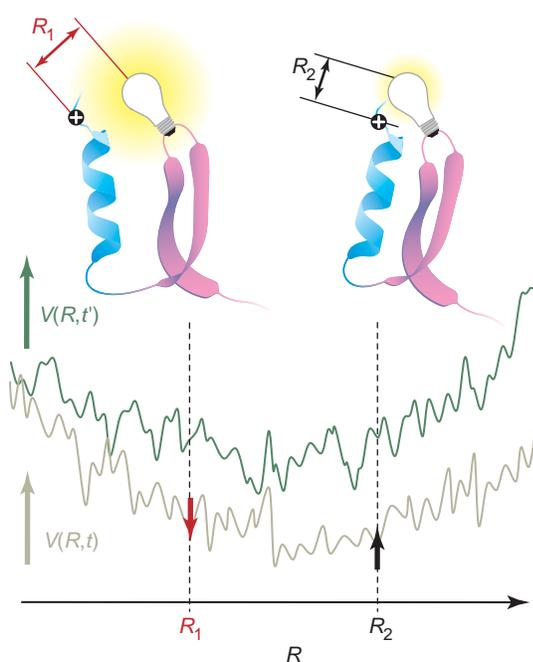
Current experiments to explore protein dynamics are of two kinds. First, fluctuation amplitudes may be measured with a range of techniques, each of which has a

characteristic time window. The diffraction of x-rays and neutrons falls into this group, as do various spectroscopies, including nuclear or electronic magnetic resonance (4, 5), Mössbauer absorption (6), infrared, and Raman spectroscopy. NMR is particularly powerful because it can distinguish each amino acid residue in the sequence, but it does not cover all fluctuation time scales.

Second, an ensemble of molecules may be synchronously brought out of equilibrium, and its subsequent relaxation monitored as a function of time. The initial disturbance in such kinetic measurements can be a temperature jump, a sudden concentration change, or—on much shorter time scales—the breaking of a bond by a laser pulse (7). Under such strong perturbations, however, proteins may no longer be close to equilibrium. Furthermore, synchronization is short-lived. Because different individual molecules follow different pathways in the energy landscape,

Monitoring dynamics via fluorescence.

Variations of the distance R between an emitting fluorophore (flavin, sketched as a light bulb) and an electron acceptor and quencher (tyrosine, sketched as a black ball) cause variations of the fluorescence intensity and lifetime. The wiggly curve schematically represents a cut of the potential energy of the enzyme along R . Because the multidimensional potential depends on many other time-dependent atomic coordinates, the one-dimensional potential is time dependent and is shown here at two different times. The coexistence of low and high barriers in the transient potential generates stretched kinetics with a broad range of relaxation times.



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