14

Loneliness and the Social Bond

The Brain Sources of Sorrow and Grief

I have perceiv'd that to be with those I like is enough,
To stop in company with the rest at evening is enough,
To be surrounded by beautiful, curious, breathing, laughing flesh is enough, . . .

I do not ask any more delight, I swim in it as in a sea.
There is *something* in staying close to men and women and looking on them,
and in the contact and odor of them, that pleases the soul well,

All things please the soul, but these please the soul well.

Walt Whitman, "I Sing the Body Electric" (1855)

CENTRAL THEME

One of the great mysteries of psychology is the nature of the "something" that Walt Whitman extols in his masterpiece "I Sing the Body Electric." That subtle feeling of social presence is almost undetectable, until it is gone. We simply feel normal and comfortable when we are in the midst of friendly company, and that same feeling becomes warmer when we are among those we love deeply, especially when we have not seen them for some time. We often take these feelings, like air itself, for granted. But we should not, for when this feeling of normalcy is suddenly disrupted by the undesired loss of a lover or the unexpected death of a loved one, we find ourselves plunged into one of the deepest and most troubling emotional pains of which we, as social creatures, are capable. In everyday language, this feeling is called sorrow or grief, and it can verge on panic in its most intense and precipitous forms. At a less acute but more persistent level, the same essential feeling is called loneliness or sadness. This psychic pain informs us of the importance of those we have lost. In psychological terms, "importance" is not easy to define, but in evolutionary terms it is. We grieve most when we lose those in whom we have invested a great deal of genetic effort (our children) or those who have helped us to thrive (our parents, friends, and relatives)—in short, when we lose those with whom we have social bonds. Obviously, the loss of a parent is most acute when one is young and still dependent; the pain is less intense and protracted when a grown child loses an elderly parent. On the other hand, when adults lose a child, their genetic and emotional future is compromised forever, and their pain is as intense and lasting as that of a child who loses a nurturant caregiver. This type of psychic pain probably emerges from a brain emotional system that evolved early in the mammalian line to inform individuals about the status of their social environment and to help create our social bonds. Neuroscience is struggling to come to terms with the nature of such intrinsic brain processes, and it is becoming clear that several ancient emotional systems control our social inclinations. In the course of brain evolution, the systems that mediate separation distress emerged, in part, from preexisting pain circuits. Here we will call this neural system the PANIC circuit. It becomes aroused when young animals are separated from their social support systems. We can measure this arousal in several ways, perhaps most effectively by monitoring the separation calls young animals emit when left alone in strange new places. Since opioid systems had already evolved to modulate the intensity of physical pain, it is not surprising that these same neurochemistries can soothe the pain evoked by social isolation. As mentioned in the previous chapter (see Figure 13.5), this work was initiated by the realization that there are remarkable similarities between the dynamics of opiate addiction and social dependence. Other systems that are important in quelling this emotion are oxytocin- and prolactin-based neural activities. We now know where PANIC circuits are situated in the brain, and which neurochemistries transmit the message of distress. This knowledge addresses the essence of our

nature as social creatures, allowing us to construct credible hypotheses about which neurochemistries contribute to creating the emotional bonds that link us with our fellows. The existence of such brain systems may eventually help explain the sources of human empathy, altruism, and love, as well as depression and autism.

On the Nature of the Social Bond

Imagine an archetypal situation: The life of a young sea otter is completely dependent on the care provided by its mother. After his sexual contribution, the father pays little heed to his young. It is the mother's job to be both caretaker and food provider, as often as not, on the open sea. The pup's life revolves around maternal devotion. When she dives beneath the dark surface of the water for food, being absent from her infant's side for many minutes at a stretch, the young otter begins to cry and swim about in an agitated state. If it were not for those calls of distress among the rising and falling waves, young otters might be lost forever. Their security and future are unequivocally linked to the audiovocal thread of attachment that joins them to their mothers. It is the same for all mammals. At the outset, we are utterly dependent creatures whose survival is founded on the quality of our social bonds—one of the remaining great mysteries, and gifts, of nature.

Only a few decades ago, behavioral scientists believed that social bonds emerged from an animal's experience of reinforcement contingencies arising from the receipt of conventional rewards. The idea was that young children loved their parents simply because they provided food, water, shelter, and warmth. There was no evidence that the brain contained emotional systems to directly mediate social bonds and social feelings. This behaviorist view began to change when it was shown that human babies fail to thrive if they do not receive physical affection. The classic studies of René Spitz in the 1940s demonstrated that babies in orphanages needed types of sustenance other than simply food and water to thrive.[1] Without caring human contact, many died prematurely, and the lesson is being learned once again in the orphanages of Rumania and other former eastern block countries. It is now widely accepted that all mammals inherit psychobehavioral systems to mediate social bonding as well as various other social emotions, ranging from intense attraction to separation-induced despair.

This same phenomenon has now been seen in many other creatures, ranging from primates to birds, but the details vary considerably from one species to another. The diversity of behavioral and physiological changes that accompany social isolation have been most completely studied in rats and primates, and the responses are quite similar. For instance, although young rats exhibit a very short period after separation when they emit separation calls (see Figure 2.1), they show many other long-lasting changes, including decreases in body temperature, sleep, and growth-hormone secretion, along with increases in brain arousal, behavioral reactivity, sucking tendencies, and corticosterone secretion.[2] The patterning of these responses is influenced by complex physiological controls, but an understanding of brain emotional changes also will be essential to explain this symptom complex.

We are beginning to understand the neural nature of separation distress and closely intermeshed social attachment systems. Not surprisingly, they are closely related evolutionarily and neurochemically to the emotional systems discussed in the last two chapters. My premise here is that a detailed analysis of the brain mechanisms that generate separation distress—as indexed by separation calls and the physiological consequences of social isolation—provides a significant way for us to understand the neurobiological nature of social bonds. Here I will focus on the primal brain system that mediates the emotional anguish of losing someone you love.

There are good reasons to believe that neurochemistries that specifically inhibit the separation-distress or PANIC system also contribute substantially to the processes that create social attachments and dependencies—processes that tonically sustain emotional equilibrium and promote mental and physical health throughout the lifetime of all mammals.

The mammalian brain contains at least one integrated emotional system that mediates the formation of social attachments. The affective components of this system are dichotomous—behaviors and feelings of separation distress on one hand, and those of social reward or contact comfort on the other (Figure 14.1). The existing data suggest that arousability in this system is controlled by multiple sensory and perceptual inputs, and that the evolutionary roots of the system may go back to more primitive control mechanisms such as those elaborating place attachments in reptiles, the basic affective mechanisms of pain, and fundamental creature comforts such as thermoregulation.[3]

One of the key issues for future research will be whether social reward processes exist independently of the neurochemistries that can inhibit separation distress. It is remotely possible that there is no distinct social reward process, since the candidate systems—the opioids, oxytocin, and prolactin—all inhibit separation distress quite well. Perhaps the rewards obtained from interactions such as rough-and-tumble play (see Chapter 15) may eventually yield such a unique reward system, but there is insufficient neural evidence to allow us to reach any definitive conclusions. At present, the most workable approach to understanding the nature of social attachments is through the brain mechanisms that control feelings of separation distress.

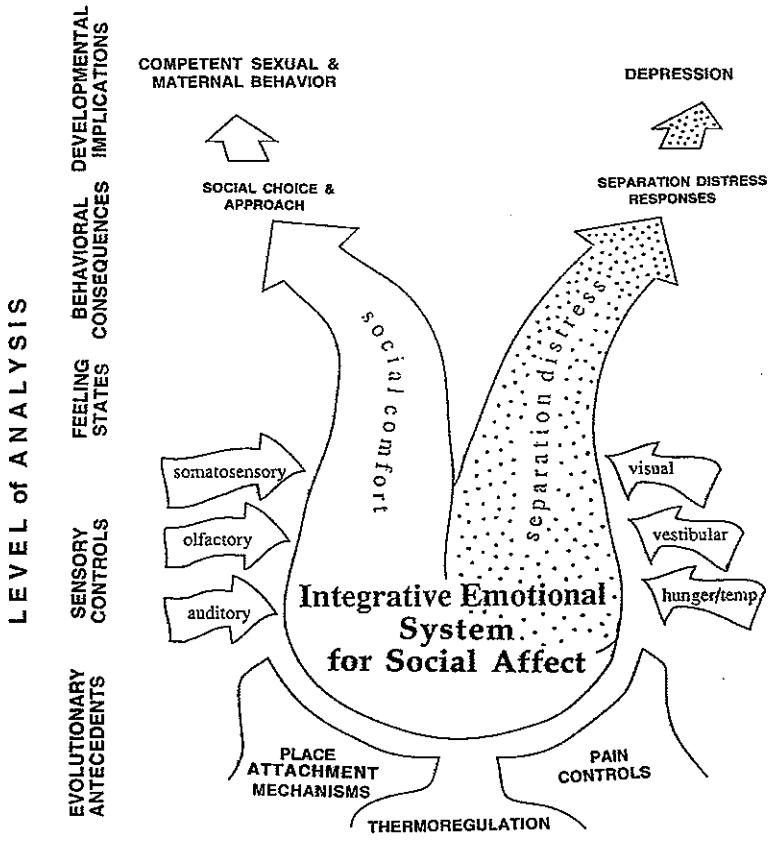

Figure 14.1. Schematic summary of the various influences and levels of analysis that are important in analyzing the potential nature of an integrative emotional system for social affect. (Adapted from Panksepp et al., 1997; see n. 3.)

The Experience of Loneliness and Nonsexual Love

Social bonding in the mammalian brain probably goes hand in hand with the experience of loneliness, grief, and other feelings of social loss. To be alone and lonely, to be without nurturance or a consistent source of erotic gratification, are among the worst and most commonplace emotional pains humans must endure. Indeed, as noted in Figures 13.5 and 14.1, the brain mechanisms of separation distress probably evolved from more ancient pain mechanisms of the brain. Love is, in part, the neurochemically based positive feeling that negates those negative feelings.

Social attachments are probably promoted by the ability of certain interactions (and their attending neurochemistries) to alleviate that mild form of separation distress that we call loneliness. Brain opioids were the first neurochemistries discovered to powerfully reduce separation distress. As predicted by the opiate theory of social attachment (see Figure 13.5), drugs such as morphine that powerfully reduce crying in animals (Figure 14.2) are also powerful alleviators of grief and loneliness in humans.[4] Indeed, as mentioned in Chapter 13, opiate addiction may emerge largely because we have brain systems that were designed by evolution to mediate various pleasures, including those that arise from friendly social relationships; individuals who cannot find those satisfactions in their personal lives will be tempted to succeed by pharmacological means, and this can lead to social isolation. For instance, the French artist Jean Cocteau recollected in his diary how opium liberated him "from visits and people sitting round in circles."[5]

Indeed, the fact that such molecules can alleviate sadness was documented many millennia ago: In Homer's *Odyssey,* we share in a reunion of warriors who had participated in the Trojan War, to rescue Helen of Troy. Although Helen was returned to Greece, many warriors, including Odysseus, did not return home across the wine-dark sea. At a memorial gathering, to Helen's dismay, the thoughts and feelings of the celebrants turn darkly to their lost compatriots, and

> A twinging ache of grief rose up in everyone . . .
> But now it entered Helen's mind
> to drop into the wine that they were drinking
> an anodyne, mild magic of forgetfulness.

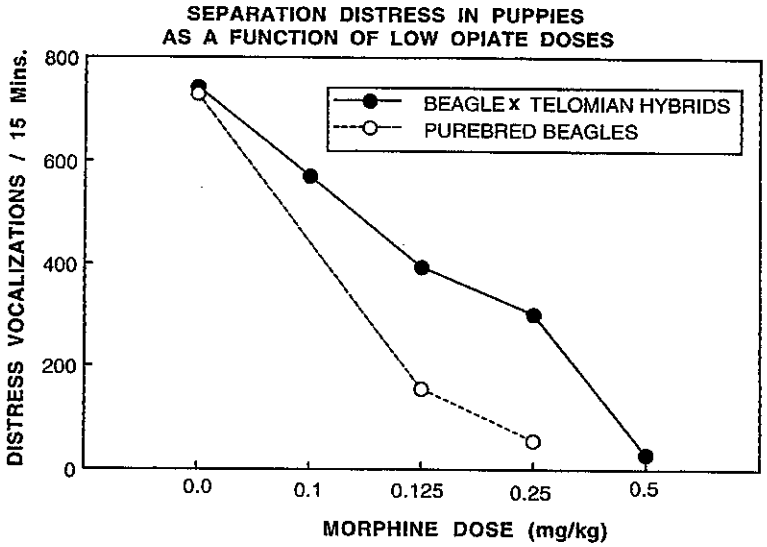

Figure 14.2. Dose-response analysis of the ability of very low doses of morphine to reduce separation distress in 6–8-week-old puppies of a hybrid beagle × Telomian hybrid cross and purebred beagles. (Adapted from Panksepp et al., 1978; see n. 4.)

> Whoever drank this mixture in the wine bowl
> would be incapable of tears that day—
> though he should lose mother and father both,
> or see, with his own eyes, a son or brother
> mauled by weapons of bronze at his own gate.[6]

It is likely that the anodyne Helen used was either tincture of opium or cannabis. Most believe it was the former, and modern pharmacological evidence clearly supports that conclusion.[7] With the limited pharmacopoeia of the times, Helen could only have sustained the convivial spirits of the celebrants with a substance that activates the large synaptic membrane protein that we now know to be the *mu* and *delta* opiate receptors (for distribution, see Figure 6.8). These receptors are among the brain's most powerful modulators of pain, as well as the very source of opiate addiction in humans. In fact, three major varieties of opiate receptors and opiate transmitters have been identified in the brain: The endorphins interact primarily with *mu* receptors, the enkephalins with *delta* receptors, and the dynorphins with *kappa* receptors. Separation distress is most powerfully inhibited by brain opioids that interact with *mu* receptors, which also mediate opiate addiction. The most powerful endogenous opiate-like molecule that interacts with the *mu* receptor is ß-endorphin, which also has the most powerful ability to alleviate separation distress.[8]

There is good reason to believe that several endogenous opioids are important in the control of social emotions, the elaboration of social attachments, and various forms of human love, both nurturant and erotic.[9] Nurturant love emerges between parents and children and seems different in obvious respects from sexual love. But are they really so vastly different in the deeper recesses of the brain? We simply do not know, for love is a difficult concept to biologize, unless we are willing to take some conceptual risks. There has been some theoretical speculation, although no hard data, suggesting that emotional infatuation and erotic love may be promoted by brain dopamine systems and mild dopamine-type psychostimulants such as phenethylamine, which occurs in fairly high levels in chocolate (which many of us "love"). The same type of argument could be made for *anandamide*, the endogenous cannabinoid-type molecule, also present in chocolate.[10] The database for such assertions remains nonexistent, and the argument that such molecules may reduce feelings of social isolation is further weakened by the fact that these molecules are not very effective in quelling separation distress in animals. Perhaps chocolate and other tasty foods help lonely people to cope better psychologically because pleasurable tastes activate endogenous opioid systems (see Chapter 9).

As we saw in the previous two chapters, one plausible way of thinking is that nurturant love emerges from brain systems that promote parental attachments, while erotic love may emerge from brain systems that generate sexual seeking. If so, the first might be more opiate- and oxytocin-based, while the latter is more dopamine- and vasopressin-based. But even if such hypotheses are on the right track, the two could not be completely distinct in the tangled neurochemical skein of the brain. Dopamine and opioid systems interact in several interesting ways, including through the arousal of brain

dopamine by opiate receptors within the ventral tegmental area (VTA) and opiate inhibition of dopamine activity in the terminal fields of the striatum. Likewise, oxytocin has a diversity of neural interactions, including complex interactions with opiate and psychostimulant effects in the brain.[11]

If credible experimental approaches to disentangling such questions are ever developed, it will be remarkable to behold how erotic love and nurturant love are dynamically intertwined within subcortical neural circuits, and we may begin to understand why they are often tangled in the higher cognitive reaches of our minds. Fortunately, there are some more basic questions that can be answered definitively at the present time.

Attachment Styles and an Overview of the PANIC System

During the past several decades, developmental psychologists have constructed a coherent theoretical view of the nature of social attachment. They have observed that children exhibit a variety of attachment "styles," or temperaments, that have strong genetic and environmental antecedents.[12] Some are securely attached, while others are not. Securely attached children are confident of receiving social support from their parents or other caretakers. They are generally outgoing and tend to confront life with optimism and enthusiasm. By comparison, insecurely attached children are timid and do not readily become engaged with new situations. In fact, children who are insecure about their social support exhibit two major emotional and behavioral patterns of "neediness." Some are excessively clingy and seem to need more than the usual amount of attention from their caretakers. Others choose to distance themselves from social contacts, avoiding social situations presumably because they are not confident of receiving the positive support and feedback they crave. Perhaps they have felt rebuffed so often that they no longer reach out to others. In order to subsist comfortably, they have become cognitively detached from their emotional desires.[13]

How these attachment tendencies emerge from the fabric of the brain has remained a mystery until recently. Now, work on animal emotionality is beginning to reveal the neuromotivational forces that may mediate such social feelings. An especially promising line of work is emerging from the detailed analysis of one behavioral measure—the vocal "crying" aroused by social isolation in young animals. Some label these "isolation calls," others refer to them as "distress vocalizations," and others simply call it "crying" (a label that many behavioristically oriented investigators deem too anthropomorphic). The label is less important than the fact that there is an intrinsic neural system in the brain, here labeled the PANIC system, that mediates this strong emotional response.

As we will see, the PANIC circuits have been mapped out with localized electrical stimulation. To the best of our modest knowledge, such circuits help create the emotions organisms experience as a result of social isolation and loss of social comfort. Presumably, social attachments emerge, in part, from environmental events activating brain chemistries that can reduce arousal in these distress circuits.

The Separation-Distress System and Social Attachments

Since the infants of all mammalian species remain quite helpless for a variable period of time following birth, they must have strong distress signaling mechanisms to solicit and sustain parental care. Isolation calls, or distress vocalizations (DVs), as they will be called here, are one of the most primitive forms of audiovocal communication (Figure 14.2); the underlying brain mechanisms are probably shared homologously in all mammals, even though there is bound to be substantial variation among different species depending on their socioecological circumstances. For instance, socially deprived young rats do not vocalize in response to separation as much as many other species (see Figure 2.1), presumably because their underlying affective response system is comparatively rudimentary. This is true for most animals that are born very altricial (i.e., developmentally immature), since the probability that they will stray from the nest is remote. Young rats also are not strongly attached to their mother (i.e., any mother will do as heater and "feed bag"). Only when they become mobile do they exhibit a period of clear social bonding, but their responses still do not compare with the vigor seen in other species, ranging from birds to primates, that exhibit powerful, unambiguous, and long-lasting social bonds.

Human infants are also born very immature, and they do not begin to exhibit true separation distress and specific social attachments until their motor system has matured sufficiently for them to wander off and get lost. At about half a year of age, human babies begin to make sad and sometimes angry sounds of protest in order to attract the attention of caregivers when they are left alone for too long. This emotional response is a robust feature of childhood for many years, but it persists for only a few months in most other mammals because, in relative terms, their "childhood" is much shorter than ours.

In any event, DVs emerge quite promptly whenever young animals are left alone in strange new places. The proximity of a caretaker is typically sufficient to totally inhibit the calls in both humans and other species (Figure 14.3).[14] The home location can also inhibit separation distress to a modest extent, suggesting that separation-distress systems may be evolutionarily related to ancient mechanisms of place attachment. In most species, the mother is more effective in quelling distress than the father, but there are exceptions: As mentioned in the last chapter, among the titi monkeys of South

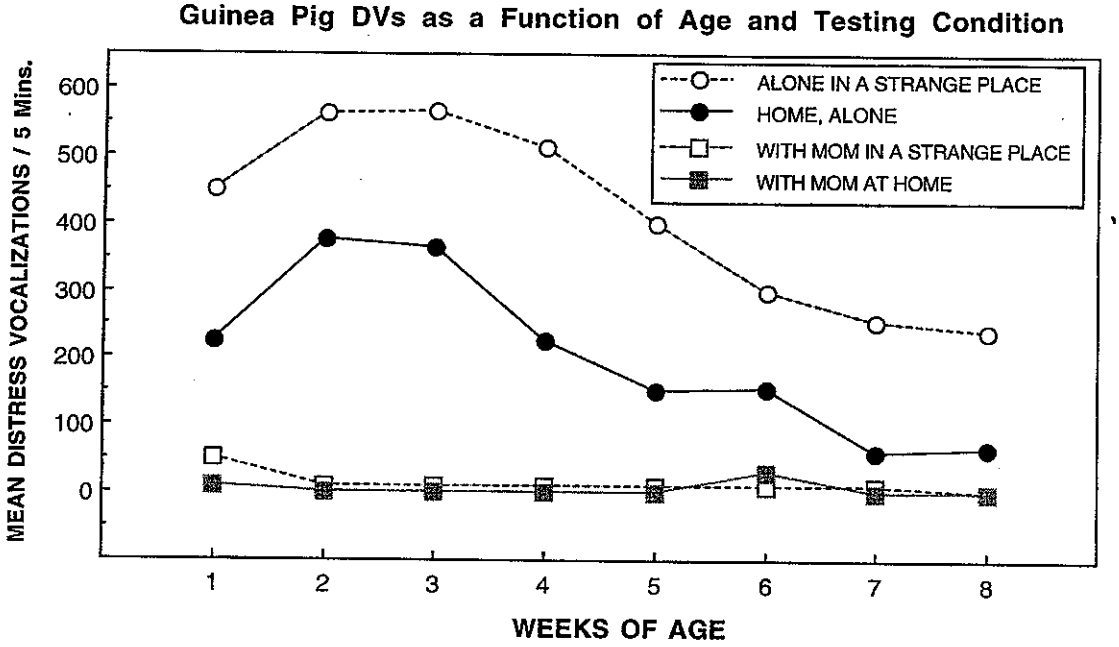

Figure 14.3. Distress vocalizations of young guinea pigs as a function of age, tested either alone or with mother in familiar and unfamiliar environments. (Adapted from Pettijohn, 1979; see n. 14.)

America, the young are more attached to fathers, even though mothers provide most of the food. Indeed, in this rare species, mothers tend to become agitated if left alone with infants, apparently because they are more strongly bonded to their mates than to their own infants.[15] These mothers just don't seem to like being alone with their young.

The fact that the neural systems for separation-induced crying emerged from more primitive distress mechanisms, such as those that mediate pain and feelings of coldness (Figure 14.1), raises a major methodological issue: How shall we discriminate the various types of cries? Even before they fully recognize their social circumstances, infants of most species respond to pain, hunger, and irritation by crying. In animals, there is evidence to suggest that separation-induced DVs can be distinguished from cries of pain on neuroanatomical and neurochemical bases, as well as via an analysis of sound spectrum characteristics.[16] However, because of the evolutionary relations between separation and pain mechanisms, they also share many controls—such as opioid-induced inhibition, as already mentioned.

In the presence of adults who have bonded with the young, DVs have the common effect of arousing the attention and typically the caregiving motivations of caretakers. Many experiments have now shown that the infant's call of distress is highly arousing and a powerful attractant to the parents. They investigate locations from which such sounds emanate, even if they are only tape-recorded, with mothers typically exhibiting stronger responses than fathers.[17] Is it because the cries of infants arouse resonant feelings of distress more readily in mothers than in fathers? Since no one has made the appropriate brain measurements, we do not yet know. However, we do know that specific locations in the auditory system, in both the inferior colliculi and the medial geniculate nuclei, are highly tuned to receive and process these primal communications.[18]

Even though there are many species differences in the detailed expression of bonding and distress mechanisms in the brain, it is assumed that the arousal of PANIC circuits is one of the major forces that guides the construction of social bonds. When these circuits are aroused, animals seek reunion with individuals who help create the feeling of a "secure neurochemical base" within the brain. Presumably, the young animals that exhibit the most intense separation responses will be the ones that exhibit the strongest social dependencies and are the most susceptible to psychiatric disorders that emerge from feelings of social loss.

It is reasonable to assume that the underlying neural dynamics within the PANIC system are especially important in allowing organisms to care for each other. Exactly how a concerned attitude is promoted within caretakers' brains by hearing distress calls from their infants remains unknown, but I would suggest that the sounds of crying arouse distress circuits in parents that

parallel the distress of the children. If so, associated learning systems may rapidly establish the knowledge that an optimal way to reduce distress in both is for the parents to provide care and attention to their offspring. One of the most powerful sensory signals of care is direct contact, and touch appears to activate endogenous opioid systems, thereby reinforcing the social bond.[19]

If no bonds exist, the sound of distress calls may simply be perceived as an irritation, which in humans could easily lead to child abuse. Through a poorly understood reciprocity of social emotional systems, pro-social activities are initiated and sustained between parents and their infants. Pro-social acts are the instantiation of social bonds, and at present they are the only way we can monitor the underlying feelings. Obviously, in humans the role of cognitive factors, for better and worse, can often override emotional concerns. As we saw in the example of Netsilik behavior in the previous chapter, humans sometimes must make very difficult choices in caring for their offspring. In any event, when care is provided, emotionally distressed children rapidly exhibit responses of comfort and satisfaction, even though, if the care has taken too long to arrive, they may also harbor some resentments, as indicated by a transient phase of social detachment upon reunion. Adults often do the same. Apparently, through such social reciprocities, the social bond between related animals is first established and periodically strengthened.

Thanks to the clarity of separation-distress patterns, a study of this emotional processes in animals provides one of the most powerful lines of evidence for guiding our thinking about the deep neural sources of loneliness and social attachments in humans. These lines of thought also have the potential to highlight the primal biological nature of certain forms of love and friendship.[20]

Brain Circuits for DVs and PANIC

One of the best ways to identify the general locations of PANIC circuitry is by administration of localized electrical stimulation of the brain (ESB) into specific areas. This type of work has now been conducted in a large number of species, including primates, cats, and chickens,[21] and has yielded a remarkably similar picture. As depicted in Figure 14.4 from work with guinea pigs, the PANIC system appears to arise from the midbrain PAG, very close to where one can generate physical pain responses. Anatomically, it almost seems that separation has emerged from more basic pain systems during brain evolution (as is also highlighted in Figure 14.1). This affirms that separation distress is related to perceptions of pain, and this relationship remains codified in our language (i.e., to lose someone is a "painful experience").

The PANIC system is also well represented in the medial diencephalon, especially the dorsomedial thalamus. Even farther forward, one finds a high density of active DV sites in the ventral septal area, the preoptic area, and many sites in the bed nucleus of the stria terminalis (areas that figure heavily in sexual and maternal behaviors). In some higher species, one can also obtain separation calls from the very anterior part of the cingulate

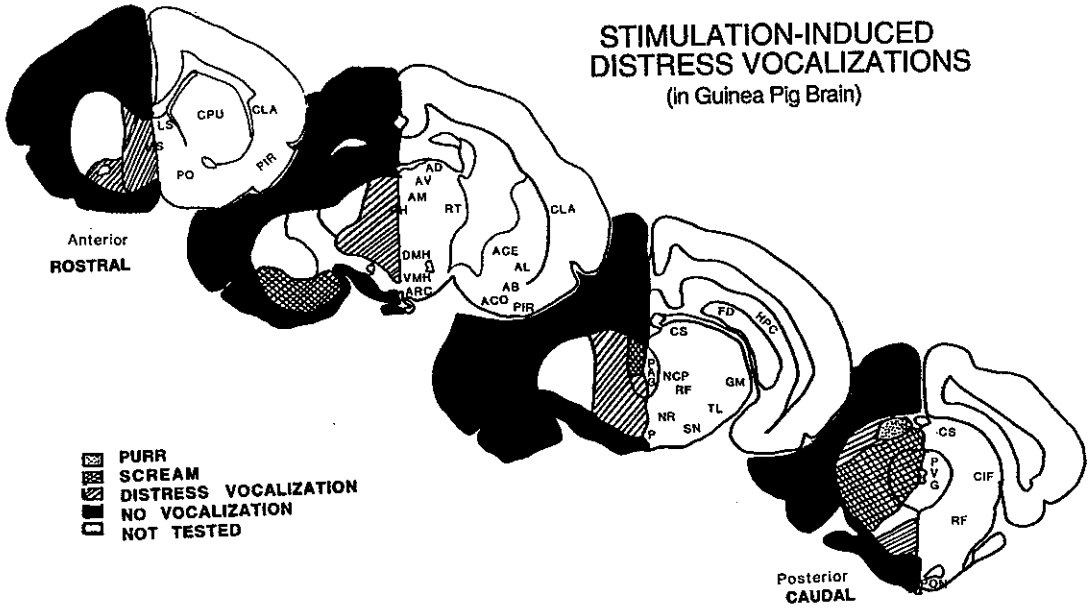

Figure 14.4. Schematic representation of electrically induced separation-distress vocalization sites in the guinea pig brain. (Adapted from Panksepp et al., 1988; see n. 27.)

gyrus, as well as some sites in the amygdala and scattered ones in other areas, including the hypothalamus.[22]

There is a remarkable resemblance between the neuroanatomy of this behavioral control system and those for the corticotrophin releasing factor (CRF) and ß-endorphin systems (see Figure 6.7). Endogenous opioids clearly suppress arousal of this system, not only as measured by natural DVs but also as measured by ESB techniques, and at least in some species CRF increases DVs.[23] Such neural systems extend branches to many other brain areas, suggesting how a variety of psychological processes are affected by the experience of separation and reunion.

It is a common assertion that human females are prone to cry more than males. There may be some neurobiological truth to this stereotype. Work on the isolation cries of guinea pigs and chickens indicates that administration of testosterone diminishes crying in young animals. This appears to be due to a change in the underlying sensitivity of the PANIC system. We have evaluated this possibility using ESB techniques in guinea pigs and have found that as animals get older, the sensitivity of the DV system diminishes; this effect is larger in males than in females.[24]

The age-related decline in males appears to be partly due to the maturation of the pituitary-gonadal axis. Male and female guinea pigs that have had their sexual glands removed exhibit smaller declines than animals with intact testes and ovaries, with the effects varying as a function of the brain region being studied. There are bound to be many other factors that contribute to the decline of separation-induced crying with age, but this natural decline clearly is not simply caused by the gradual degeneration of DV circuits: Strong crying can still be induced in mature animals, which no longer exhibit spontaneous DVs, by applying ESB directly into the trajectory of the crying circuits. The decline is largely the result of reduced sensitivity of the system. This appears to be more precipitous in males than in females, at least partly because of the powerful neural influences of testosterone on DV circuitry.[25] Likewise, young chicks that receive daily testosterone injections begin to vocalize less than controls, an effect that is especially prominent in the presence of social stimuli such as mirrors (Figure 14.5). From this perspective, it is not surprising that crying and panic attacks are more common among women than among men.[26] Such gender differences in emotionality may not simply be learned or culturally created phenomena.

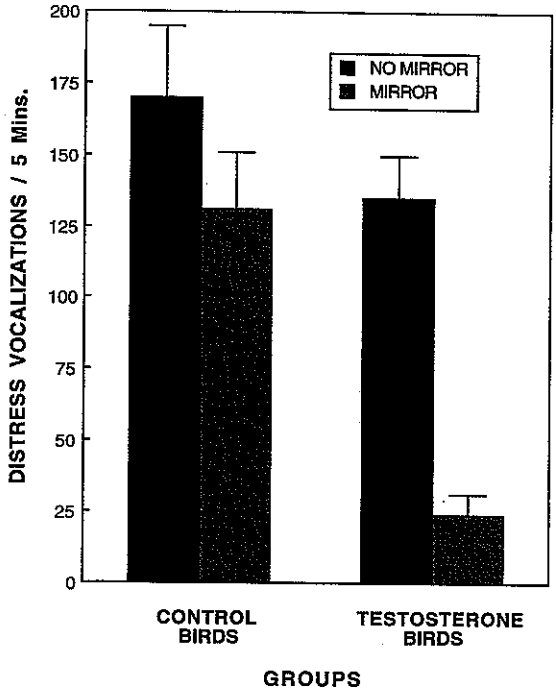

Figure 14.5. Summary of mean (±SEM) distress vocalizations in 14-day-old male chickens treated with testosterone (2 mg) or peanut oil vehicle for the previous eight days when they had been individually housed to reduce aggression. Animals were tested as in Figure 14.8 except for five-minute periods of no mirrors, mirrors, no mirrors, and mirrors. It is noteworthy how high the vocalization rates are considering that the animals are being moved from their isolated housing conditions to new isolation chambers. This may reflect the fact that animals had established place attachments and that separation from those conditions was sufficient to evoke emotional distress. In any event, the testosterone reliably reduced vocalization rates ($p < .001$), and the mirror effect was somewhat larger in them also ($p < .05$). It is noteworthy that usually one sees a larger mirror effect in control birds that are socially housed. (Unpublished data, Panksepp, 1995.)

The Neurochemistry of the PANIC System

We know approximately where in the brain DV circuits are situated, which neurochemistries provoke arousal of these distress systems, and also which chemistries soothe and calm the overarousal.[27] In addition to opioids, other neuropeptides that can greatly relieve the process are oxytocin and prolactin (Figure 14.6). Presumably, there are distinct chemistries for the many sensory and perceptual modulators of this emotional response, such as hearing, smell, and especially touch (see Figure 14.1). Nonpeptide neurochemistries that are effective include such drugs as *clonidine*, a norepinephrine (NE) receptor agonist, which both facilitates (postsynaptically) and suppresses (presynaptically) NE activity in the brain. Nicotine and various glutamate receptor antagonists also relieve DVs effectively. Many other chemistries have weaker, but statistically significant effects, such as some antidepressants, minor

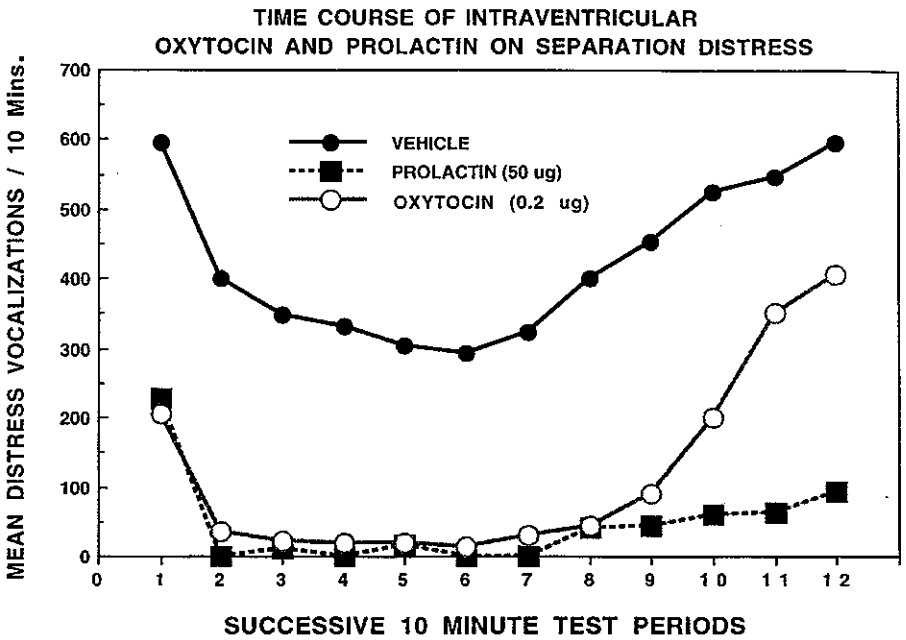

Figure 14.6. Effects of intraventricular oxytocin and prolactin on the separation distress calls of 5–6-day-old chicks socially isolated from their flock for a two-hour period. (Adapted from Panksepp, 1996; see n. 30.)

tranquilizers, and other sedatives. However, the vast majority of neuroactive drugs have minimal effects on this emotional response, including such powerful sedating drugs as the antipsychotics (i.e., the major tranquilizers).[28]

The major chemistries that have been found to activate crying in young animals are CRF, certain types of glutamate receptor stimulants (especially those that act on NMDA and kainate receptors), and also central administration of curare, a drug that normally blocks the nicotinic cholinergic system in the periphery, leading to paralysis, although in the brain it appears to do something else, perhaps activating glutamate receptors. All three of these agents can turn on the crying response, even if animals are housed with social companions.[29] At present, the best estimate is that the neuronal "command transmitter" for the PANIC system, as for so many other basic emotional systems, is glutamate. This is the only system (except for CRF) in which receptor activation can dramatically increase DVs, even in the presence of other animals, and receptor blockade can dramatically decrease DVs (Figure 14.7), even those induced by electrical brain stimulation.[30]

Many other drugs can promote crying that has already been initiated, including reductions in acetylcholine, serotonin, and opioid activity, but these are clearly modulatory, since they cannot evoke crying all by themselves. Hence, they do not directly arouse the primary pathways mediating the neural impulse to cry. Unfortunately, we presently know next to nothing about the specific types of environmental and internal information related to social loss that these various neurochemistries help mediate.

Before proceeding, let me share a methodological point. The aforementioned elevations of crying have been most extensively studied in newborn domestic chicks,[31] and it is easiest to see increases when baseline levels of crying have been reduced by providing social stimuli. One of the easiest ways to reduce the crying is to put mirrors on the wall of the test chamber. The chicks appear to behave as if they are in the company of others and cry less (see Figure 14.5).[32] Similar reductions can be induced with music (see Figure 14.8), which may simulate the comfort derived from audiovocal contact with other animals. This may be one of the reasons people love music—it keeps them company. Both of these comforting effects can be almost completely eliminated by stimulating the glutamate receptor system with intraventricular injections of kainic acid and NMDA, which, as mentioned earlier, can also increase vocalizations in the absence of mirrors. Comparable effects are produced with curare and CRF.

Although most of the early pharmacological work was done in young chicks, there is now considerable corroboratory work with mammals, including primates. This work provides confidence that many of the pharmacological effects reported here may be generalizable to most mammals; it also highlights nature's conserva-

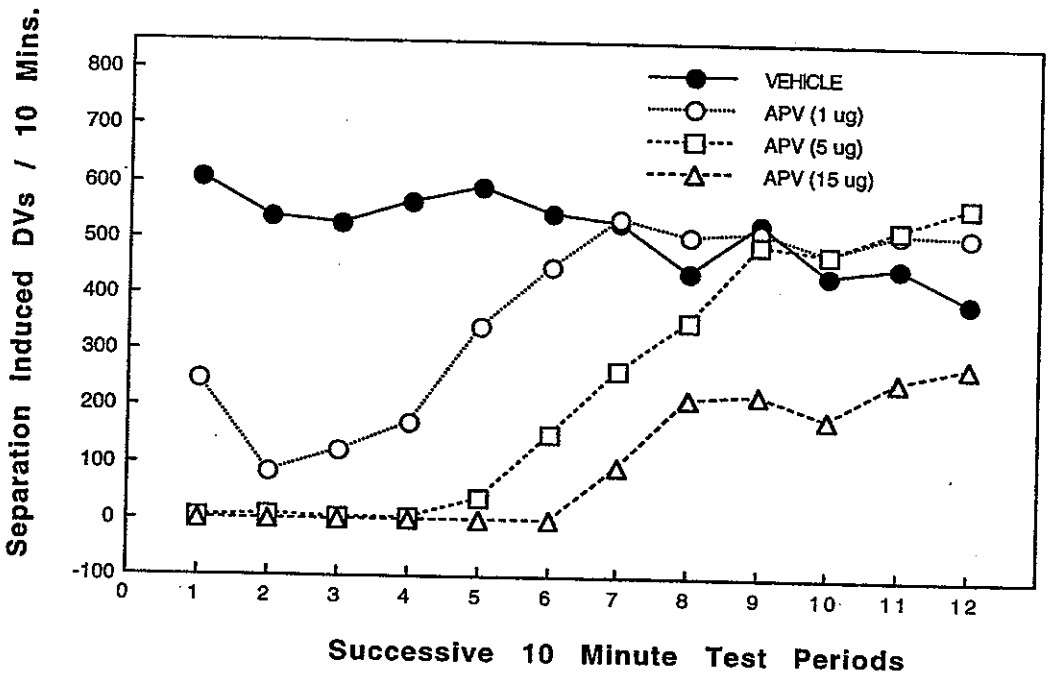

Figure 14.7. The glutamate receptor antagonist 5-amino-2-phosphonovalerate (APV) specifically blocks the NMDA receptor, which appears to be a key transmitter in the production of separation DVs. The animals tested here were 12-day-old domestic chicks that received APV injections into the 4th ventricle region just prior to being separated from their companions (a flock of 20 birds). The magnitude and duration of DV inhibition were directly related to the amount of APV injected. (Adapted from Panksepp, 1996; see n. 30.)

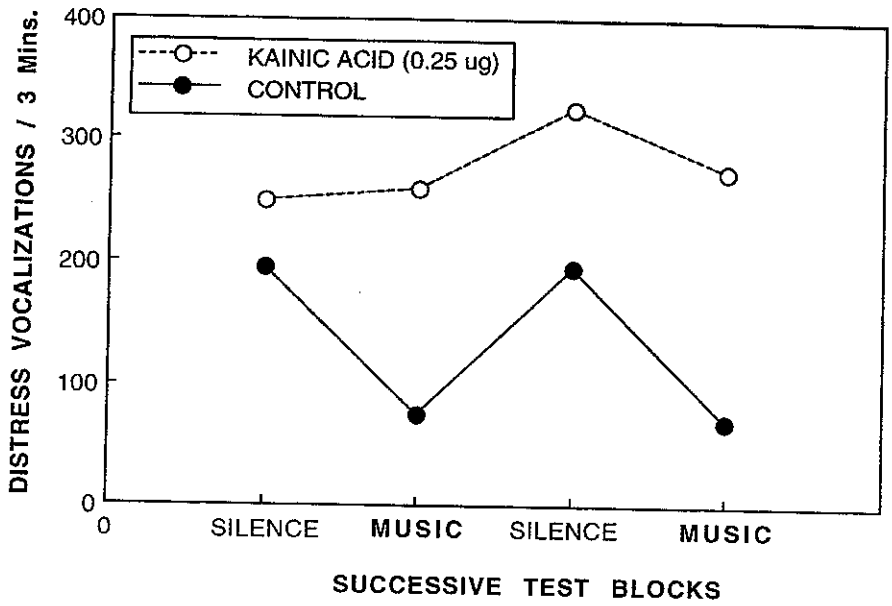

Figure 14.8. Mean number of vocalizations in 4–5-day-old chicks during successive three-minute testing blocks either in ambient silence or during exposure to music. Half of the animals were administered 0.25 μg of kainic acid (KA) into their ventricular systems just before testing. Not only did the KA markedly increase vocalizations, but the "comforting" effects of music were totally eliminated. The same pattern of results is obtained if one uses mirrored environments to reduce the vocalization. (Adapted from Normansell, 1988; see n. 30.)

tism when it comes to the organization of ancient emotional systems. However, there are certain exceptions to these patterns. Perhaps the most problematic ones come from the infant rat, which, as discussed earlier and highlighted in Figure 2.1, is not an ideal subject for separation-distress studies.[33]

On the Nature of Gregariousness

Programmatic research into the neural nature of gregariousness and social investigation has been sporadic, except for the study of social choices motivated by sexual urges. A great deal of work has focused on how gonadal hormones modulate social interest. The results have been fairly straightforward: Males and females seek out each other's company primarily as a function of hormonally primed states. Young intact males generally prefer the company of estrus females, but gonadectomized ones or elderly ones do not.[34] As mentioned in Chapter 12, the social preferences of estrus females are not as well studied, but we do know they seek out the companionship of sexually active males.

Little is known about the brain systems that motivate gregariousness independently of sexual motivation, even though it is recognized that certain interesting social patterns emerge from animals' tendency to congregate. For instance, mountain sheep (and many other herding animals) exhibit defensive group patterns in which the young animals keep to the center of a circle while adults line the periphery. Although it is attractive to see this as an ecologically important cognitive strategy, it may simply be a by-product of gregarious tendencies at different stages of development. For instance, the pattern could emerge simply from the fact that young animals are more gregarious than older ones, which would lead them to form a tighter nucleus, leaving adults to patrol the periphery because they do not prefer to be as close to each other.[35] This is a neat explanation for a factor that promotes defensive tactics in herding species, but it is only a distal explanation because the proximal neural and psychological dynamics are controlled by emotional circuits within the brains of these animals.

To experimentally analyze gregariousness requires systematic laboratory measurements that are relatively straightforward. The most common approach has been to measure the amount of time animals voluntarily spend in proximity to each other. In the 1960s and 1970s, social psychologist Bib Latane and colleagues extensively characterized gregarious tendencies in rats,[36] but they failed to extend their analysis to the brain. This was partly remedied by later investigators who demonstrated that gregariousness increases following septal damage and declines following amygdala damage,[37] and that these effects cancel each other out when both types of brain damage are inflicted.[38] Although these findings indicate that the limbic system is important in motivating animals to spend friendly time together, the underlying neurochemical mechanisms remain to be clarified.

One attractive hypothesis is that neurochemistries modulating separation distress will be important in motivating gregariousness and social reward (Figure 14.1). Thus, manipulations that increase distress should increase social motivation, and vice versa. For instance, reductions in opioid activity should increase desire for social companionship, and increases in this system should reduce the need for gregariousness.[39] Observations consistent with this interpretation have been collected from a large variety of species using several distinct behavioral measures. Animals treated with moderate doses of opiates tend to socially isolate themselves. Rodents reduce the amount of time they spend in proximity to each other,[40] dogs exhibit reduced tail wagging,[41] primates exhibit decreased social grooming, and humans have also reported a decreased need to socialize.[42] In other words, high opiate activity diminishes the underlying emotional need for companionship. Less work has been done with oxytocin, and at present the pattern of results is a bit more confusing, with oxytocin reducing gregariousness in short-term tests but increasing it in long-term conditioning tests.[43]

Conversely, opiate antagonists increase social motivation. Rodents have been observed to exhibit increased social proximity, dogs exhibit increased solicitous tail wagging, and primates groom each other more.[44] It is especially noteworthy that young primates exhibit more social clinging to their mothers and also make more social solicitations to other members of their troops when their opioid systems are blocked with drugs such as naloxone.[45] On the other hand, when mothers are given the same drug treatment, they often exhibit a strong decrease in social affiliation, possibly because they are not able to obtain the proper emotional feedback from their caregiving efforts.[46] In general, though, when animals cannot experience opioid activity in the brain, they are more likely to socialize, if prevailing conditions are nonthreatening. As I will elaborate later, this effect may also be present in humans, since opiate antagonists can induce moderate increases of social responsivity in autistic children.

On the Nature of Contact Comfort

As mentioned earlier, there is little clear-cut evidence for a unique social reward system independent of separation-distress and sexual urges (Figure 14.1). However, it is reasonable to believe that a substantial amount of social motivation emerges from the pleasures of touch, and the pleasure of play is strongly dependent on the sensation of touch. Indeed, it is possible that the mammalian skin contains specialized receptors, such as in "tickle-skin," for detecting social contact (see Chapter 15).

However, the ability of petting to comfort domestic animals and to produce powerful physiological effects is both obvious and poorly studied.[47] One easy way to study such effects objectively is to monitor crying in young animals that are held or not held. The effects are, of course, dramatic. Animals stop crying rapidly when gently touched. There is some evidence that this contact comfort is mediated, in part, by activation of brain opioid systems. For instance, one can also measure the latency of eye closure in response to holding, and opiate receptor antagonists reduce the ability of animals to settle down (Figure 14.9).[48] However, even with complete blockade of the opioid systems by naloxone or naltrexone, birds held gently in this way do eventually settle down and cry much less than unheld control birds. Clearly, neurochemistries other than opioids contribute to the feelings of contact-comfort.

The fact that touch can release opioids in the brain has also been confirmed in primates.[49] Indeed, administration of naloxone tends to increase grooming in primates, while administration of opiates reduces the desire to be touched.

The likelihood is high that prolactin and oxytocin participate in aspects of contact comfort, simply from the perspective that these hormones mediate milk production and the efficacy of the suckling reflex, but empirical data are scarce. However, in this context it is worth noting that the brains of mice with different social temperaments exhibit dramatically different oxytocin receptor distributions, which also change as a function of age.[50] The developmental changes in brain oxytocin receptor distributions are so striking that they suggest this chemical system may mediate different social affective processes at different times in the animal's life cycle (Figure 14.10). With respect to strain differences, the highly social prairie vole exhibits more "infantile" distribution of oxytocin receptors than does the montane vole, which prefers a solitary lifestyle.

Thus, different species, and even substrains of a single species, exhibit differential constitutional levels of arousability of different emotional systems, and it appears that one of these may function as a social reward system. Such differences also exist in humans and reflect intrinsic genetic variability in temperaments, as well as the differential impact of early experiences on the emergence of various personality dimensions.[51] Unfortunately, substantive knowledge at this level remains meager. Nonetheless, the search for a unique social reward system should yield future dividends in understanding social attachment processes.

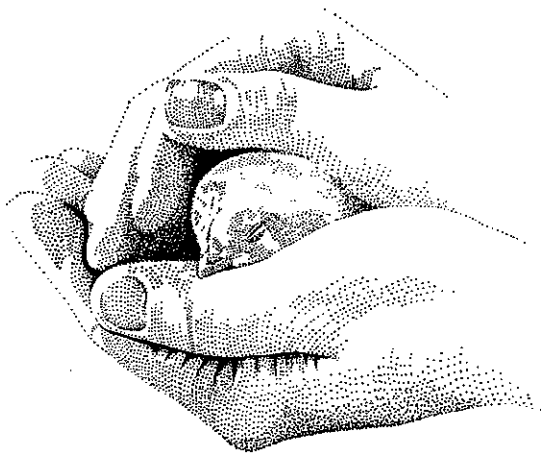

Figure 14.9. When held gently in human hands, newborn chicks exhibit a comfort response consisting of the cessation of vocalizations and eye closure. These effects are attenuated by opiate receptor blockade with naltrexone and amplified by low doses of opioids. (Adapted from Panksepp et al., 1980; see n. 32.)

Social Attachments and Imprinting: A Role for Opioids and Oxytocin

As we saw in the previous chapter, the most important work on the underlying nature of the social bond is emerging from empirical investigations based on two premises: the likelihood that the peripheral physiological processes that accompany birth may also control attachment processes in the brain, and that there are neurochemical similarities between opiate dependence and social dependence. Here I will amplify on these premises and also introduce a third, namely, that all neurochemistries that normally inhibit separation distress may also promote bonding. Obviously, all these factors are intermeshed, perhaps inextricably, within the brain.

The amount of evidence for neurochemical control of attachment processes in mammals is remarkably limited. As noted in the previous chapter, oxytocin clearly promotes bonding, and in unpublished data, we have also found evidence that vasopressin may be equally important.[52] How opiates participate in this process remains ambiguous,[53] but they probably provide a mechanism for making fine discriminations among the available bonding objects—for instance, whether a youngster develops strongest ties with mom, dad, or one of the aunts or uncles at the perimeter of the clan. However, it is clear that when animals have exogenous opiates in their bodies, they exhibit less social activity in general, except at very low doses.[54]

At present we know very little about the brain areas that mediate social bonding, even though we can anticipate that the cingulate cortex, septal area, bed nucleus of the stria terminalis, preoptic area, dorsomedial thalamus, and periaqueductal gray (PAG) will be important—namely, all of the areas that mediate feelings of separation distress. Also, in animals that utilize olfactory cues in the establishment of social attachments,

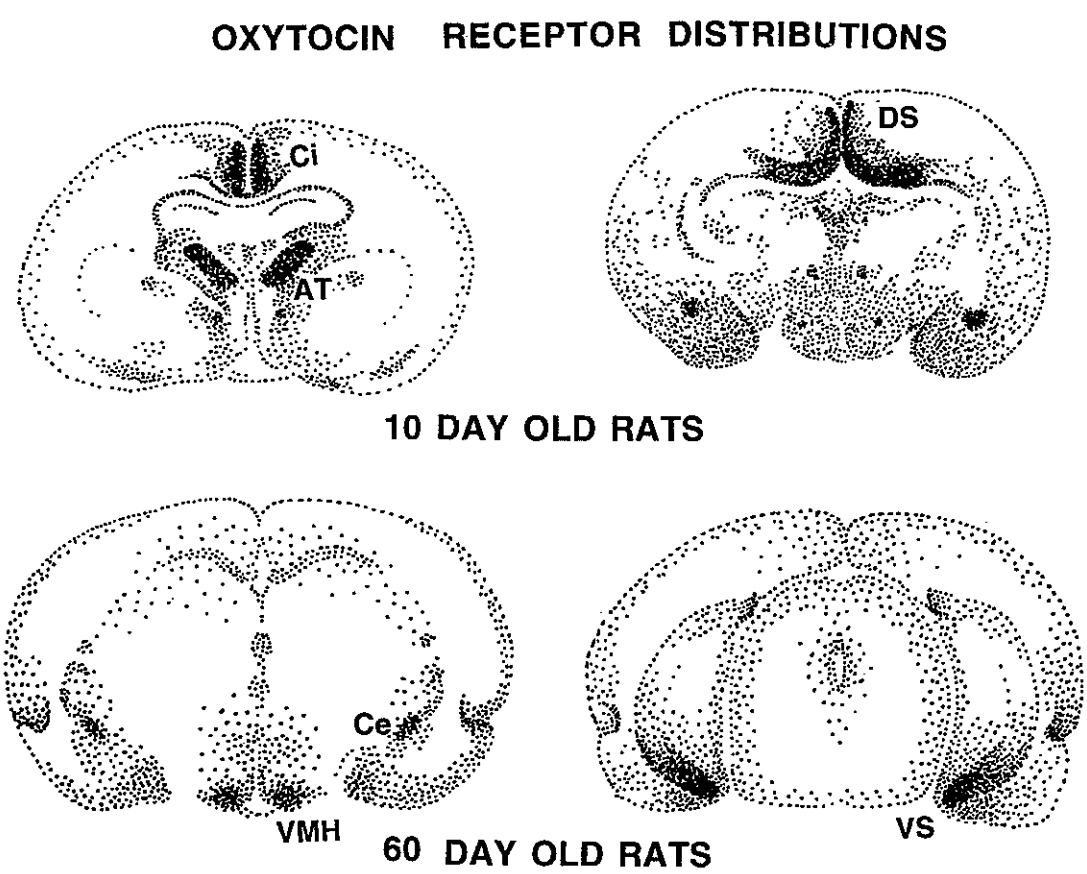

Figure 14.10. Artist's rendition of the redistribution in the density of oxytocin receptors in the rat brain during infancy (top two figures) and maturity (bottom two). It is evident that in the infant, very high receptor densities are present in the cingulate cortex, the anterior thalamus, and the dorsal hippocampal/subicular region. These areas of the brain probably control infantile emotions such as separation distress and primary social bonding. On the other hand, in adult female rats, the densities are highest in the ventromedial hypothalamus and the ventral hippocampal/subicular region. These areas probably mediate female sexual receptivity and memory processes related to sociosexual issues. (Adapted from Shapiro & Insel, 1989; see n. 50.)

including sheep and rodents, the olfactory bulbs play a role. Indeed, the release of norepinephrine in the bulbs is an essential component for solidifying social memories in such creatures.[55]

During the past decade, there has been considerable progress in identifying the brain mechanisms of imprinting in birds. Key areas, such as the intermediate part of the hyperstriatum ventrale (IMHV) and lateral forebrain, are rich in opioid receptors. Lesions of the IMHV have been most extensively studied and found to reduce both the acquisition and retention of imprinting.[56] Likewise, the IMHV exhibits a variety of changes as a function of imprinting, including increases in synaptic density and elevated glutamate binding.[57] It is not clear what is the mammalian homolog of the IMHV, but it may well be the cingulate cortex.

Brain opioids do not appear to be essential for the development of simple imprinting responses (the mere act of following objects). When young domestic chicks are given high doses of naltrexone, an opiate receptor antagonist, during formal imprinting trials, they do not exhibit a diminution of subsequent following responses. Indeed, such animals appear to be more eager than usual to follow the imprinting stimulus, even though they vocalize more, as if they are not getting as much satisfaction from the interaction.[58] In other words, although the birds appear to become cognitively imprinted in the absence of opioids, their sense of security is not as great as one would normally expect. Thus, it is noteworthy that the fine discriminative aspects of imprinting are impaired by opioid blockade.[59] In other words, opioid activity may be important in the establishment of so-

cial choices in the same way that it appears important for gustatory choices (see Figure 9.4). However, if we give moderate doses of opiates to animals that have been imprinted, they no longer exhibit a vigorous following response, affirming once more that low opioid activity increases social motivation.[60]

From the mammalian data on oxytocin and social bonding, one might anticipate that the avian homolog, vasotocin, would be important for bonding. Unfortunately, support for such a hypothesis has remained elusive.[61]

In sum, the most reasonable supposition at present is that social bonding ultimately involves the ability of young organisms to experience separation distress when isolated from social support systems and to experience neurochemically mediated comfort when social contacts are reestablished. In addition to answering basic science questions of considerable importance, the analysis of the biological substrates of social processes in animals has important ramifications for our understanding and treatment of various psychiatric disorders. Although all such disorders are strongly influenced by social variables, some, such as panic attacks, depression, and early childhood autism, seem especially closely connected to the brain dynamics that underlie social emotions. Each of these will be briefly discussed in the next three sections, but first I will explain why we need to distinguish the PANIC system from that which mediates FEAR.

Neurochemical Distinctions between Separation-Distress and Fear Processes in the Brain

An issue raised in Chapter 11 deserves to be reemphasized here—namely, how we can objectively distinguish between the PANIC and FEAR systems of the brain. As indicated by brain stimulation studies, the systems have different neuroanatomies, even though there is considerable overlap and probably interaction in certain parts of the brain, especially lower areas such as the PAG of the mesencephalon. We may even be able to intuit some of the functional interactions from introspective experiences—for instance, we can easily develop anticipatory anxiety in response to situations that will provoke intense feelings of separation. Likewise, some parents find it anxiety-provoking to visit the graves of children who have died. Some children find it extremely anxiety-provoking to be separated from their parents, in situations as simple as going to school for the first time, a reaction that goes by the designation *school phobia*.[62]

Thus, separation distress may promote activity in fear circuits, but behavioral data suggest that the converse does not occur. For instance, the presentation of fearful stimuli tends to reduce the frequency of separation calls,[63] presumably because it would be maladaptive for young animals to reveal their locations when predators are nearby. Also, as we will see later, anticipatory anxiety and panic attacks appear to be generated by distinct neural systems; the assumption here is that much of the former emerges from the FEAR system and much of the latter from the separation-distress or PANIC system.

Some puzzling neurochemical effects may also be clarified by distinguishing between the two systems. For instance, the neuropeptide CRF appears to participate in both FEAR and PANIC processes. Thus, while CRF placed into the brain increases DVs dramatically in young chicks and modestly in young primates, the same manipulation reduces DVs in guinea pigs.[64] This difference could be explained by the fact that CRF in the first two species has stronger effects on the PANIC system, while in the latter it has stronger effects on the FEAR system.

Pharmacologically, we can also distinguish these systems by noting that opiates are very effective in reducing separation distress but not fearful behaviors.[65] Conversely, benzodiazepines are quite effective in reducing fear behaviors but not as effective in reducing separation calls.[66] As we will see at the end of this chapter, similar patterns of results have been observed with the different drugs used to treat generalized anxiety disorders and panic attacks.

Separation Systems and the Origin of Panic Attacks

The selection of the term PANIC for the brain system that mediates separation distress was originally premised on the hypothesis that the emotional problem known as panic attacks may emerge from precipitous arousal of the separation-distress system. This hypothesis was based on several relationships between the two responses: People who suffer from repeated panic attacks typically have had childhood histories characterized by separation anxiety problems.[67] During separation distress as well as during panic attacks, the victims feel as if their center of comfort and stability has been abruptly removed, leading to active solicitation of help and social support. Both are commonly accompanied by such autonomic symptoms as a feeling of weakness, difficulty in getting one's breath, and a feeling of having a lump in the throat.[68] Perhaps most strikingly, the type of medication that was first found to be beneficial for panic attacks,[69] the tricyclic antidepressant imipramine, was also the first drug that was found to exert a substantial ameliorative effect on separation-distress vocalizations in a variety of species, including primates and dogs.[70] Although this by no means proves that these two types of emotional expression emerge from the same system, the pharmacological analysis of panic attacks clearly indicates that the disorder is not simply a variant of fearful, anticipatory anxiety.

Careful work by the psychiatrist Donald Klein in the early 1960s indicated that the newly discovered benzodiazepine-type antianxiety agents such as chlordiazepoxide (Librium®) and diazepam (Valium®) had little beneficial effect on the incidence of panic attacks. Since the tricyclic antidepressant imipramine had just been discovered, Klein proceeded to evaluate it as well. Even though patients first claimed that imipramine had no beneficial effect, in fact they complained of panic attacks much less often than they had prior to taking the drug.[71] When the incidence of panic attacks was actually counted, it was clear that they had markedly diminished during medication. Apparently the patients had not noticed their improvement because the drug did not diminish the anticipatory anxiety associated with the disorder—namely, the fear that an attack might be forthcoming. While the antianxiety agents tested had diminished anticipatory anxiety, they did not diminish the frequency or intensity of the panic attacks themselves.

Subsequent work has found that children who suffered from "school phobias" could also be helped with tricyclics.[72] Such children seem to be seriously disturbed by the prospect of separation when they first have to leave home to enter the school system, but when given low doses of imipramine they feel more confident, presumably in part because the underlying arousal of the PANIC system is diminished through the facilitation of brain serotonin activity at synapses that modulate separation-distress responses. Of course, it remains to be clearly demonstrated that this, in fact, is the case in humans, but facilitation of serotonin activity is quite effective in reducing DVs in animals.[73] More recent work has indicated that the new generation of selective serotonin reuptake inhibitor (SSRI) antidepressants are also quite effective in controlling panic, as are some of the more potent modern benzodiazepines such as alprazolam.[74] In general, these lines of evidence suggest that the arousal of separation-distress circuitry may promote the incidence of panic attacks.

Alternative views are, of course, possible. For instance, Klein has recently suggested that panic attacks arise from precipitous arousal of a suffocation alarm mechanism in the brain stem.[75] It may well be that this primitive self-defense system is, in fact, functionally coupled to arousal of the PANIC system. A common denominator of both is that they are closely linked to respiratory and audiovocal dynamics, and under both emotional states one feels in desperate need of immediate aid.

There are also milder forms of separation distress that can lead to social phobias, such as a chronic feeling of insecurity when one is interacting with others. Phenelzine, a monoamine oxidase (MOA) inhibitor, has been found to have remarkable efficacy in reducing such symptoms.[76] Recently other serotonin-facilitating drugs that reduce separation distress, such as fluoxetine (i.e., better known as Prozac®), have been touted to increase social confidence.[77]

Psychiatric Implications: On the Nature of Social Loss and Depression

Chronic arousal of the PANIC system may have long-term psychiatric consequences. The persistent stress of social isolation, as indicated by overresponsiveness of the pituitary adrenal system (see Figure 6.9),[78] may eventually contribute to the despair and depression that commonly follow social loss and long-term separation.[79] As Harry Harlow's well-known research demonstrated,[80] isolated rhesus monkey babies will seek out any comfort they can find, including inanimate "terry-cloth mothers," in preference to hard wire ones that provide only nourishment. When this type of social isolation was sustained for an excessive period, the animals exhibited lifelong problems in social adjustment.[81] Females that had been reared in isolation were poor and abusive mothers, especially in response to their firstborn infants. Subsequent offspring typically received better treatment, apparently because of the beneficial effects of previous learning. In general these motherless mothers were rather timid and emotionally overexcitable, exhibiting behavior patterns resembling a severe form of insecure attachment in human children.

No type of conventional "therapy" administered to such animals provided any substantive long-lasting assistance in restoring normal social functions. The most effective treatment was exposure to much younger monkeys, apparently because they provoked safe and playful social interactions that drew the isolates out of their self-centered misery.[82] In this context, it is noteworthy that dogs made excellent surrogate mothers for isolated monkeys, which fared much better than those that did not have a cross-species pet-mom. This highlights why pets can be so important in promoting mental health and emotional equilibrium in humans; it is much better to have a warm furry or feathered friend to interact with than no one at all.[83] Clearly, practically all mammals need important others in their lives to maintain emotional equilibrium.

It is well documented that the major life factor in humans that precipitates depression is social loss.[84] The genesis of many forms of depression can be linked to the neurobiological nature of the primal-loss experience—the despair of children who have been irreparably separated from their parents. Many believe that we will be able to understand the sources of depression when we understand the cascade of central neurological changes that arise from the successive emotions aroused by social separation—from active protest (crying) to the eventual despair response (depression).[85] Although animal models for evaluating such processes have been perfected, few neurochemical analyses of the associated brain changes have been conducted.[86]

It is generally thought that there may be some evolutionary use for young organisms to exhibit a depres-

sive response to separation after the initial protest response. After a period of intense vocalization, which could help parents find their lost offspring, it might be energetically adaptive to regress into a behaviorally inhibited despair phase in order to conserve bodily resources. Such a depressive state would help conserve limited energy resources and discourage the helpless organism from wandering even farther from safety. Silence would, of course, also minimize detection by predators. In other words, if initial protest did not achieve reunion, a silent despair response might still optimize the likelihood that parents would eventually find their lost offspring alive. No doubt the separation call returns in a periodic manner during the circadian cycle, but this issue remains unanalyzed.

In any case, the cascade of events during the initial protest phase of separation appears to establish the brain conditions for the subsequent despair phase. This includes activation of the brain CRF system along with the pituitary adrenal stress response,[87] followed by a depletion of brain norepinephrine, serotonin, and certain dopamine reserves.[88] Indeed, depressive symptoms in animals and humans can be evoked experimentally by establishing these types of physiological changes in the body.[89] For instance, prolonged administration of CRF, along with depletion of the biogenic amines, can promote depressive responses.[90] We do not yet know precisely how this ultimately leads to the persistent psychological changes that characterize clinical depression, but medications that counteract these changes tend to have antidepressant effects. For instance, all antidepressants facilitate synaptic activity of biogenic amine systems,[91] whether it is by blockade of synaptic reuptake of the transmitters, as achieved by the tricyclic antidepressants and SSRIs, or by inhibition of degradation, as produced by MAO inhibitors.[92]

In the early days of psychopharmacology, even morphine was used as an antidepressant,[93] but this practice diminished with the advent of more effective medications. Presumably, future drugs that inhibit brain CRF and promote oxytocin activity should have new and useful profiles of antidepressant activity. Of course, environmental and cognitive therapies can also help, perhaps partly by providing the social support that depressed individuals need. In fact, perhaps the most effective nonphysiological maneuver for alleviation of depression is to provide increased social support. After young animals exhibit depressive responses to isolation, social contact is sometimes sufficient to cure them.[94]

In sum, even though early investigators did not believe in the existence of intrinsic social processes within the brain, it now seems likely that a great deal of higher brain organization evolved in the service of promoting social behaviors and sustaining feelings of social homeostasis.[95] Much more work along these lines needs to be conducted before the puzzle of the social brain is solved, but progress will have profound implications for the development of new treatments for various psychiatric disorders, including the most devastating ones, such as early childhood autism.

Additional Psychiatric Implications: Autism and Brain Socioemotional Systems

Early childhood autism is characterized by severe failures in socialization, communication, and imagination. As Leo Kanner said in his seminal 1943 paper, autistic children "have come into the world with an innate inability to form the usual, biologically provided affective contact with people."[96] A current theoretical perspective is that these children do not develop a "theory of mind," which refers to the ability of most children past the age of 2 to begin recognizing the types of thoughts and feelings that go on in the minds of others.[97] Obviously, the appreciation of these thoughts can become highly complex, and often delusional, in adults.

The existence of this syndrome affords investigators a unique opportunity to study the workings of social emotional systems in human beings. After a long period in which many claimed that the disorder arose from faulty parenting, virtually all investigators now agree that autism is a neurobiological disorder,[98] which probably reflects some type of dysfunction in normal neural development originating in the second trimester of pregnancy, when primitive brain stem and limbic circuits are laid down in the developing brain.[99] Exactly what goes wrong during the development of an autistic brain is not yet known precisely, but a large number of brain changes have been documented in these children.[100]

In addition to a variety of gross brain abnormalities, such as an undersized cerebellum and brain stem, and a larger than normal cerebrum, significant abnormalities have recently been described at the fine structural level. Autistic children have too many densely packed small neurons within parts of the limbic system,[101] suggesting that selective cell death, a natural process of the developing brain called *apoptosis*, has not progressed normally.[102] This also means that the neurons do not interconnect with the rest of the brain as well as in normal children, which all goes to suggest that a biochemical program for neuronal development has malfunctioned. It is presently impossible to correct such a wiring problem of the brain.

Without prenatal detection of autism, it will be impossible to correct such deficits even with new maneuvers such as the administration of appropriate neural growth factors (see Chapter 6). At the time most children are diagnosed, at around 2 years of age, neuronal development has progressed to an irreversible point. Still, many affected children do exhibit some functional improvements following the readjustment of brain chemical imbalances.[103] Since there are so many abnormalities in autism, related to deficits in communication, socialization, and imagination (known as the "autistic

triad"), no single medication is likely to help all children. Indeed, no drug is yet medically approved for the treatment of autistic disorders, and much research work remains at a hit-or-miss level. However, some lines of work are emerging from a careful consideration of the many potential underlying causes.[104]

For instance, numerous similarities have been noted between the behavior of young animals with medial temporal lobe damage as well as those treated with opiates and the symptoms of children diagnosed with autism.[105] Both are characterized by pain insensitivity and deficits in communication, play, and curiosity. For instance, opiate-treated animals, like autistic children, do not exhibit a high desire for social companionship; rather, they exhibit a pervasive reduction in social responsivity, with the exception of rough-and-tumble play, which, as we will see in the next chapter, can be increased by low doses of opiates at least in rats. Indeed, the motivation for rough-and-tumble activity is practically the only social desire that autistic kids exhibit at a relatively high level, but not with the reciprocating give-and-take and fantasy structures of normal childhood play.

Young animals chronically treated with opiates also exhibit a pervasive stunting of development in all realms, from growth and bodily maturation to the onset of various behavioral abilities.[106] It is now generally agreed that opiates given during early development can regulate growth.[107] This raises the possibility that autistic children may have been exposed to excessive levels of endogenous opioids, or related molecules, during early development. Moreover, they may continue to experience excessive opioid activity within certain circuits of their brains as they mature. This could explain their pain insensitivity and consequent tendency to exhibit self-injurious behavior, as well as many other symptoms ranging from stereotypies to social aloofness.[108] Because of these considerations, it has been suggested that some benefits may be brought to these children by the administration of opiate receptor blocking agents such as naltrexone.[109]

Although tests of this hypothesis have yielded mixed clinical results, the lives of about half of all autistic children can be improved with the judicious use of this medication. Moderate doses of naltrexone can reduce some of the active symptoms of autism such as overactivity, stereotypies, and self-injurious behaviors, and in low infrequent doses, it can promote social activities. Many investigators have reported positive signs such as increased social initiative and interaction, heightened desires to communicate and cooperate with others, and increases in attention, curiosity, and social interchange, often accompanied by a better mood.[110] Most of these benefits reflect a general normalization of day-to-day living. Although naltrexone does not produce improvements in all children, nor can it be deemed anything close to a cure, the benefits are often substantial enough that parents choose to keep their children on the medication for the long term. Family life is generally less stressful and more cheerful. Although there is presently no way to predict which children will be helped, presumably it will be those who have high circulating levels of opioids in the brain, a condition that has been demonstrated in about half of all autistic children who have been tested.[111]

Although naltrexone is only a marginally beneficial medicine, it highlights a coherent theoretical strategy for developing new and better agents: Substances that increase social motivation in animal studies, as indicated by increased vocalizations and gregariousness, may be beneficial in these children. One could also focus on other symptoms, such as the highly irregular sleep patterns found in many autistic children, suggesting that natural sleep-promoting agents such as melatonin might be beneficial (see Chapter 7). Indeed, melatonin has recently proved to be an effective treatment for developmentally delayed children, with improvements seeming to extend to domains other than sleep.[112] However, this could be an indirect effect of the medication. Perhaps the stabilization of sleep rhythms allows the restorative effects of sleep to provide widespread benefits in many realms of brain functioning. Investigators are presently also looking into the potential roles of oxytocin and serotonin in the genesis of the disorder.

It should also be noted that there is a related genetic disorder, Williams syndrome, whose symptoms are just the opposite of those of autism.[113] Children with this syndrome tend to have a characteristically elfish facial appearance and a sweet social disposition. They are extremely friendly, socially outgoing, and can chatter on smoothly as if at a stimulating cocktail party, but there is comparatively modest propositional content in their speech. Nothing substantive is known about this syndrome at the neural level, but it almost appears to be the mirror image of autism. They love to socialize. We might surmise that children with Williams syndrome have highly responsive social interaction systems that are poorly connected to cognitive analyzers. Clearly, we will need to know more about the social circuits of the mammalian brain before we can understand these perplexing disorders. Indeed, the manifestations of these emotional systems in real life are remarkably diverse.

Conclusions and Future Prospects

Although many psychologists study and speak of the importance of attachment processes for human personality development, the critical information about these mechanisms has come from brain research on animal models. Once we understand the underlying brain processes in other animals, we may be able to intervene in such processes in humans. We may be able to help mothers who are having difficulty bonding to their children, perhaps because of postpartum depressions or psycho-

ses, or simply for the lack of neural resilience within their bonding systems. It is possible that certain manipulations of brain opioid or oxytocin systems would facilitate bonding even among relative strangers, such as occurs during the social reconstruction that typically transpires in broken families following divorce.[114] Of course, these are far-fetched possibilities, and they may be unrealistic options within our current social milieu. As a society, we still have great difficulty in coming to terms with the neurochemical nature of the human mind. However, this type of transformation in thinking has already transpired in biological psychiatry.

The emotional distress that accompanies major psychiatric disorders is probably more closely linked to the changing dynamics of underlying emotional systems than to the cognitive systems in which we most commonly see the symptoms. However, the separation-distress system poses a new challenge for psychiatry. It seems evident that depression and panic attacks are most common in individuals who have had a history of separation anxiety, while autistic children appear to have a primary deficit in the ability to experience social emotions and to perceive the meaning of such emotional dynamics in others. This suggests that all these disorders are at least partly modulated by separation-distress mechanisms of the brain.

Although many investigators now accept that the primary deficits in these disorders must be sought in neurobiological imbalances rather than simply in social dynamics, the recognition of separation-distress systems in the creation of affective turmoil is not yet well recognized. An understanding of this emotional system takes us to the very heart of what it means to be a socially sensitive and deeply caring human being. Also, this type of knowledge may eventually help clarify the most noble human aspirations, namely, the desire to help others—in a word, what it means to be altruistic as opposed to selfish.[115]

AFTERTHOUGHT: Music and Chills

Might transient arousals of our ancient separation-distress response systems be felt during certain aesthetic experiences? I believe one of the most intriguing manifestations of separation distress in the human brain may reflect a powerful response many of us have to certain types of music. It is widely recognized that music is the language of emotions. It is one of the few ways that humans can allow the external world *voluntary* access to their emotional systems on a very regular basis. Most of us listen to music for the emotional richness it adds to our lives. We even love to hear sad songs—especially bittersweet songs of unrequited love and loss. A common physical experience that people report when listening to such moving music, especially melancholy songs of lost love and longing, as well as patriotic pride from music that commemorates lost warriors, is a shiver up and down the spine, which often spreads down the arms and legs, and, indeed, all over the body.[116] To the best of our knowledge, this response reflects a mixture of vasoconstriction, local skin contractions caused by piloerection, and perhaps changes in evaporative cooling at the skin surface. Such effects can be objectively measured as a galvanic skin response (GSR), which is a general yardstick of skin resistance. Of course, there is great variability in the incidence of this response. Some people rarely recognize such feelings in their lives, while others, probably the more social ones, delight in them frequently. For many years, I have sought to understand this intriguing phenomenon. Here I will summarize the insights I've obtained, as described in detail elsewhere.[117]

I will refer to this shivery-tingly experience by the term *chills*, although many, especially males, tend to use the term *thrills*. I prefer the label *chills* because females use it predominantly, and it is clear that females, as a population, exhibit this response more frequently than males. There are many exceptions, of course. I, for one, am so sensitized that I can have the experience on a regular basis just thinking about events. Females typically recognize that sad music is more likely to produce this chill phenomenon than happy pieces, while males more commonly suggest that happy music is the cause. However, when one actually conducts an experimental analysis, it is clear that sad music does in fact produce more chills than does happy music, even in males. Conversely, those pieces of music that produce more chills are typically rated as sad rather than happy by listeners. People tend to have many more chills to pieces they themselves have selected, which may reflect the rich networks of associations people have to music they have enjoyed often. What is the underlying meaning of this emotional phenomenon?

An intriguing possibility is that a major component of the poignant feelings that accompany sad music are sounds that may acoustically resemble separation DVs—the primal cry of being lost or in despair. In other words, a high-pitched, sustained crescendo capable of piercing the "soul" seems to be an ideal stimulus for evoking chills. A single instrument, like a cello or trumpet, emerging from a soft orchestral background is equally provocative. Thus, the chills we experience during music may represent the natural tendency of our brain emotional systems, especially those that are tuned to the perception of social loss, to react with an appropriate homeostatic thermal response. When we are lost, we feel cold—not only physically but also as a neurosymbolic response to social separation. As mentioned earlier, the roots of the social motivational system may be strongly linked to thermoregulatory systems of the brain (Figure 14.1). Thus, when we hear the sound of someone who is lost, especially if it is our child, we also feel cold. This may be nature's way of promoting reunion. In other words, the experience of separation establishes an internal feeling of thermoregulatory discomfort that can be alleviated by the warmth of reunion.

In music that provokes chills, the wistful sense of loss and the possibility of reunion are profoundly blended in the dynamics of sound. Thus, there may be no better stimulus for chills than a sustained note of grief sung by a soprano or played on a violin. This audiovocal experience speaks to us of our humanness and our profound relatedness to other people and the rest of nature. Since naloxone can reduce the incidence of chills, we can conclude that the chill response to music is partly controlled by endogenous opioids.[118] Avram Goldstein, the pharmacologist who originally discovered the opiate receptor and the powerful opioids ß-endorphin and dynorphin, interpreted this finding to reflect the fact that release of brain opioids may produce chills (or "thrills," as he referred to them). From the present perspective, it seems more likely that opioid blockade reduces chills because one no longer experiences the rapid decline in opioid activity that is produced during the perceptually induced affective experience of social loss, an experience that, in the human mind, is always combined with the possibility of redemption—being found and cared for when one is lost. The study of music will have profound consequences for understanding the psychology and neurobiology of human emotions.[119]

Suggested Readings

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