

Nature Red in Tooth and Claw

The Neurobiological Sources of Rage and Anger

Our ferocity is blind, and can only be explained from below. Could we trace it back through our line of descent, we should see it taking more and more the form of a fatal reflex response. . . . In childhood it takes this form. The boys who pull out grasshoppers' legs and butterflies' wings, and disembowel every frog they catch, have no thought at all about the matter. The creatures tempt their hands to a fascinating occupation, to which they have to yield . . . and . . . we, the lineal representatives of the successful enactors of one scene of slaughter after another, must, whatever more pacific virtues we may also possess, still carry about with us, ready at any moment to burst into flame, the smoldering and sinister traits of character by means of which they lived through so many massacres.

William James, *Essays on Faith and Morals* (1910)

CENTRAL THEME

Although aggression has multiple causes, in psychiatric practice the most problematic forms arise from anger. Many stimuli can provoke anger, but the most common are the irritations and frustrations that arise from events that restrict freedom of action or access to resources. Although psychologists have documented numerous environmental precipitants of anger and aggression, they have yet to clarify the difficult question: What is anger? One reason this topic has been avoided is that anger is a primitive state of the nervous system that cannot be explained by mere words or environmental events. It must be clarified through a study of the underlying neuroevolutionary processes. As most observers have agreed throughout history, the emotion of anger is a human birthright, arising from our ancestral heritage. During this century, we have finally come to understand, at least in part, the nature of brain circuits that generate these powerful and often dangerous feelings, which yield behaviors that moral philosophers of the previous century said "deserved reprehension" and which emerge from our potential for "evil." Modern evidence suggests that anger emerges from the neurodynamics of subcortical circuits we share homologously with other mammals. The general locations of these circuits have been identified by localized electrical stimulation of the brain. The RAGE circuits

run from medial areas of the amygdala, through discrete zones of the hypothalamus and down into the periaqueductal gray of the midbrain. These areas are hierarchically arranged so that higher functions are dependent on the integrity of lower ones. The more we understand about these circuits, the more we will understand the fundamental nature of anger itself. A knowledge of the brain areas where rage is evoked now allows us to work out the neurochemistries of this basic emotion. Such knowledge should eventually permit development of new medications to control pathological rage, as well as other impulse-control disorders that promote aggression. Unfortunately, most forms of human aggression may be instrumental or predatory in nature, and an understanding of anger will not help us solve the prevalent social problems that arise from such sociopathological motivations. In sum, aggression is a broader phenomenon than anger itself. Aggression is not always accompanied by anger, and anger does not necessarily lead to aggression, especially in mature humans who can control such base impulses. Because the two do not always go together, a tradition has evolved in animal brain research of overlooking the concept of anger, which cannot be observed directly. Thus, we rarely find terms such as *rage* and *anger* in the modern brain research literature. Indeed, students are commonly discouraged from using such concepts in relation to animal behavior. Even

though we have abundant data on the deep neurobiological nature of ragelike aggression (or "affective attack," as it is called by behavioral neuroscientists), few bridges have been built between this database and the nature of anger and rage in human experience. These connections will be cultivated in this chapter. Of course, the primitive neural circuits of RAGE also interact with higher cognitive processes. However, before we can understand how appraisals and other acquired symbolic processes can trigger or inhibit anger, we must first fathom the lower reaches of RAGE circuits and the affective experiences that emerge therefrom. In sum, to understand anger, we must come to terms with that powerful brain force we experience as an internal pressure to reach out and strike someone.

On Aggression

At times animals threaten, bite, and kill each other.¹ Such behavior is known as aggression. Its manifestations range from a threatening baring of teeth to the tearing of flesh, from the graceful dive of a hunting hawk to the spitting spectacle of a cornered cat, from the display of pompous sexual plumage to the catastrophes of well-oiled guns and hidden bombs. Aggression is neither a universal nor a unidimensional phenomenon. Many invertebrates, like mollusks, exhibit no apparent aggression during their life cycles. However, nearly all vertebrates exhibit aggression from time to time, and such behavior can have several distinct environmental and brain causes.

Three distinct aggressive circuits have been provisionally identified in the mammalian brain: predatory, intermale, and affective attack or RAGE circuits. Only the last one provokes enraged behaviors, and presumably the experience of anger. For instance, males that fight each other for access to sexual resources do not appear to be enraged but instead present themselves as potential champions on the field of competition. Of course, they may eventually become angry at each other as they lock horns. Likewise, predators kill other animals not out of anger but because they need food to live. We must assume that the hunt and the kill is as positive a psychological experience for the predator as it is a fearful one for the prey. Predatory attack is a distinct type of aggression that arises from different circuits than anger or the seasonal competition for dominance among males of "tournament species." However, as we will see, it is not fully distinct from the SEEKING circuits discussed in Chapter 8.

Are there other aggression circuits? Perhaps, but we do not have sufficient evidence to discuss them as distinct entities. For instance, killing and injury of the young (infanticide and child abuse) are common behaviors in nature and human societies, but these tendencies may emerge from some combination of the three brain systems already mentioned, as well as others. Also, does

defensive aggression arise from a distinct system in the brain? We simply do not know, but here we will assume it emerges largely from a dynamic intermixture of RAGE and FEAR systems.

In addition to distinctions we can make among different forms of aggression, all forms share certain features, such as the potential for bodily injury and individual concerns about the distribution of resources. In humans, such resources may even be psychological ones. Because aggression entails many destructive potentials, intrinsic biological restrictions are placed upon it within all species (i.e., few animals, besides humans, kill other adult members of their own kind), and there are numerous societal sanctions against it in most human cultures. In general, there is much less aggression when animals have known each other for a long time than when they are strangers.

Animals in stable societies usually develop an acceptance of their social status, and hence their "rightful" priority in the line for resources, yielding dominance hierarchies.² Among those that know each other, competition is often resolved by glances and gestures rather than blows. However, when organisms do not know each other, they are more likely to take the path toward physical confrontation and, if neither side backs down, bloodshed. At the cultural level, our laws attempt to ensure that humans do not impose their will on others; those who fail to comply with societal expectations are commonly recipients of various forms of societal retribution, which, with a modest stretch of the imagination, may also be defined as aggression.

At the outset, I wish to make one disclaimer: The most broadly destructive kinds of human aggression—wars between nations and competing cultural groups, as well as many violent crimes—do not arise directly from brain circuits of the type discussed here. These are instrumental acts that arise as willful activities of humans. Only weak precedents have been described in our kindred species, the chimpanzees, who occasionally exhibit group aggressive activities that resemble human tribal skirmishes, or miniwars, against others of their kind.³ Very little of what we have to say here can highlight the causes of similar instrumental political phenomena in human societies, except that aggression may seem like a reasonable strategy among those who have little to lose or much to gain.⁴ Of course, warlike tendencies in humans are ultimately accompanied by many hateful emotions, including avarice, spite, and triumph, but to the best of our meager knowledge, most of these complex feelings are not instinctual potentials of the old mammalian brain. They probably arise from higher brain areas through social learning. Without the neocortical sophistication that we humans possess, other animals simply are not able to have the complex thoughts and feelings about such matters that humans have. Still, elemental emotions like fear and anger occur on every battlefield, and the subcortical nature of these brain states can be understood through animal brain research.

Evolutionary Sources of Aggression and Rage

Some individuals are more prone to aggression than others, partly because of the quality of their neural circuits and partly because of the constrictive, irritating, and impoverished environments in which they live. As James continued in the passage from *Essays on Faith and Morals*: "Our ancestors have bred pugnacity into our bone and marrow, and thousands of years of peace won't breed it out of us." Perhaps the proper kind of education may. In any event, genetic selection experiments in both male and female rodents indicate that one can markedly potentiate aggressiveness through selective breeding within a half dozen generations, and that breeding for aggression is as effective in females as in males.⁵

Tendencies for sociopathy also appear to be genetically transmitted in humans,⁶ and certain families with very high levels of aggression have been found to be characterized by neurochemical traits such as high plasma monoamine oxidase-A (MAO-A) activity,⁷ the enzyme that breaks down several biogenic amines, including serotonin, within the brain. Likewise, animals and humans that have constitutionally low brain serotonin activity are more prone to aggression and the impulsive acting out of other emotions than those with higher levels.⁸ In addition, males are generally more aggressive than females partly because of fetal organizational and adolescent activational effects of testosterone on their brains (see Chapter 12).⁹ However, when it comes to defending their young, females of most species develop a propensity to become more defensive and assertive soon after giving birth. This may be partly due to a shift in brain chemistries within certain aggression circuits toward patterns that are more typical of males (see Chapter 13 for more on this topic).

In many species, males are disproportionately larger than females (e.g., "tournament species," such as elk and walrus, which seek to captivate many females in "harems"); especially high levels of intermale aggression are evident among such creatures. However, the fighting is typically restricted to the breeding season, when testosterone levels are particularly high. In species where males and females are closer in size, pair-bonding is more common, and sex differences in aggression are less evident; but often, as in wolf packs, only a single dominant female in a group reproduces. In a few avian species, females are bigger and more pugnacious than males, and similar patterns are evident in some mammals, most notably the spotted hyena.¹⁰

Female hyenas have unusually high levels of circulating testosterone, and, quite remarkably, the appearance of their external genitalia resembles that of males; one cannot tell the sexes apart with a casual peek, for the female's enlarged clitoris is as large as a male penis, and as capable of erectile activity. Female hyenas are also more aggressive than males, and it is suspected that

they exhibit increased development of the underlying emotional systems that are typically more robust in the males of most species. Newborn hyenas, commonly twins, begin life with rather aggressive temperaments and remarkably high levels of circulating testosterone. They seem to be born in a fighting mood, and because of their sharp teeth, one of the two commonly dies before they enter the gentler phase of youth that is characterized by friendly play-fighting (see Chapter 15). However, there is no reason to believe that this form of aggression emerges from anger, although it might. It is more likely to reflect an early expression of dominance urges. This is not to say that anger cannot occur during such vigorous antagonistic interactions.

Although anger appears to have several obvious precipitating stimuli in the environment, the emotion is not created out of environmental events but represents the ability of certain types of stimuli to access the neural circuitry of RAGE within the brain. For instance, a human baby typically becomes enraged if its freedom of action is restricted simply by holding its arms to its sides.¹¹ This highlights a general and lifelong principle. Anything that restricts our freedom will be viewed as an irritant deserving our anger, contempt, and revolutionary intent. Of course, restriction of freedom is not the only precipitant of our anger and scorn. The same response emerges when one's body surface is repeatedly irritated or when one does not receive expected rewards, namely, when one is frustrated. To take a trivial example: Who has not experienced a brief flash of frustration-induced anger when a vending machine takes one's money without dispensing any goods? Most can shrug off the feeling rapidly with cognitive intervention, especially if one is not too hungry and still has sufficient coins available to try again elsewhere. This simple observation suggests that unfulfilled expectancies within the SEEKING system activate the neural patterns of frustration, probably in frontal cortical areas, which compute reward contingencies. As will be explained in detail later, reward and expectation mismatches may promote anger by downward neural influences that arouse RAGE circuits.

Such cognitive precipitants of anger would, of course, require prior learning. By contrast, a young baby who becomes enraged because it is prevented from moving may not initially conceptualize the external source of its anger, but with social development and insights into the nature of social dynamics, it rapidly learns to appraise the sources of the irritations and frustrations in its world. And then the neural paths have been prepared for retributions.

Indeed, human brains are evolutionarily "prepared" to externalize the causes of anger and to "blame" others for the evoked feelings rather than the evolutionary heritage that created the potential for anger in the first place. Of course, this makes adaptive sense. The aim of anger is to increase the probability of success in the pursuit of one's ongoing desires and competition for

resources. But this is also the dilemma that therapists commonly highlight when they exhort their clients "to take responsibility for their feelings."¹² Other people do not cause our anger; they merely trigger certain emotional circuits into action. Ultimately, our feelings come from within, and perhaps only humans have a substantive opportunity, through emotional education or willpower, to choose which stimuli they allow to trigger their emotional circuits into full-blown arousal.¹³ Animals, because of their limited ability to conceptualize the nature of emotions and intentions, do not appear to have such options.

Although we cannot go back in evolution to explore the origins of anger circuitry (since the brain does not fossilize well), we can at least provide reasonable scenarios concerning those sources. Perhaps one of the earliest evolutionary vectors was the adaptive advantage of having invigorated psychobehavioral responses to physical constraint, as commonly occurs in predator-prey encounters. Once a predator has captured its prey, there are two behavioral strategies that might benefit the diminishing behavioral options of the prey. The "victim" may become totally still, feigning death, which might fool the predator into releasing its grip. Indeed, this type of "tonic immobility" is a common response of several prey species (e.g., rabbits, guinea pigs, and chickens), and it is referred to by the rather sensational label "animal hypnosis."¹⁴ The other strategy is for the animal's behavior to become vigorous very rapidly, which might startle or otherwise dissuade the predator from pursuing its course of action, thereby giving the prey a chance to flee and escape. I assume it was this latter response, initially an adaptive reflex of invigorated movement, that guided the evolution of the full-fledged emotional system that now mediates anger.

That a complex form of psychological constraint such as frustration would eventually provoke the same type of psychobehavioral activity highlights the evolution of emotional systems. New controls, including layers of learning, have been gradually added to ancient emotional integrative systems, thereby enhancing and expanding the range of behavioral control. In other words, circuit openness (see Figure 4.2) has been promoted in emotional systems by the addition of hierarchical layers of new control (see Figure 2.2). With multiple inputs and control functions, the degree to which animals can exhibit emotional regulation has been expanded. However, the more recently evolved controls continue to depend critically on the nature of preexisting emotional circuit functions. In adult humans, higher cortical controls can be refined to the point that we can, to some extent, choose to be angry or not. But also, because of such higher cognitive functions, we can become angry merely in response to symbolic gestures (reflecting how past learning and current appraisals can come to arouse emotional systems).

Appraisals, Higher Cognitive Functions, and Aggression

Since the study of violence and aggression has become a sensitive societal and academic topic (see note 4), many investigators hesitate to discuss the potential insights that a psychobiological analysis of aggression circuits could provide. It is not generally accepted that the potentials for aggression are inborn. Rather, the prevailing view is that most impulses for aggression emerge from the appraisal of events. Here I will advocate the idea that the subcortical neural systems that generate anger are inborn, although it cannot be emphasized enough that a great deal of learning comes to modulate these underlying emotional forces, perhaps in all mammalian species,¹⁵ but most certainly in humans. Conversely, it is also likely that the neuropsychic force we call anger promotes certain types of cognitive activities in humans, such as thoughts of vengeance and the pursuit of retribution.¹⁶ Higher cerebral abilities must be taken into account in any comprehensive explanation of angry behavior, and it is incorrect to believe that a study of animals will fully explain why humans exhibit and inhibit aggression. Many cognitive aspects of anger are undoubtedly unique to the human species. What animal research can provide is lasting insight into the fundamental sources of primal feelings of rage within the brain.

Even limited claims such as this are not especially popular in the present intellectual zeitgeist, where ideas are commonly constructed and deconstructed without recourse to the evidence. Nonetheless, there are abundant reasons to believe that the subcortical anatomies and major neurochemistries for the feeling of anger are remarkably similar in all mammals. For instance, one can evoke angry behaviors and feelings by electrically stimulating the same brain areas in humans as in other species. Angry behaviors can also be modulated by manipulating the same neurochemistries in all mammalian species that have been studied.¹⁷ Thus, the major differences between species probably lie in the cognitive subtleties that incite and channel the internal emotional force we commonly call anger. The material values upon which cognitive appraisals are premised are bound to differ substantially among species, depending on the resources they value and how much competition is needed to obtain them.

Although the cognitive activities that accompany anger will be harder to analyze across species, it remains possible that some cross-species analyses will be informative. For instance, anger may provoke certain types of primitive thoughts and perceptual changes in all animals. During anger, rapid movement on the part of other animals may be viewed as provocations, as opposed to irrelevant pieces of information. Certain cues from other animals that have been repeatedly associated with the provocation of anger may also develop the ability to sustain angry moods for extended periods through clas-

sical conditioning. This type of learning, once it becomes cognitively represented, may be called "hatred." Is the feeling of hatred, then, little more than the emotion of anger, conditioned to specific cues, that has been cognitively extended in time? This may well be the case, and it would explain why hatred should not be called a basic emotion, even though it has certain features that differentiate it from anger. Hatred is obviously more calculated, behaviorally constrained, and affectively "colder" than the passionate "heat" of rage.

In fact, anger does not always provoke explicit threat or aggression in humans. Mature humans can voluntarily inhibit the expression of their primitive impulses and, with a great deal of social learning, can express their anger with the cool detachment of barbed words. However, when we humans experience anger, even at times when we are unwilling to express the underlying urges to others, our mental dialogues overflow with statements of blame and scorn for the individual(s) or institution(s) that provoked (or seemed to provoke) the anger. These internal dialogues deserve more study by psychologists, but there are other aspects of anger that cannot be studied through the analysis of words or human actions. To be angry is to have a specific kind of internal pressure or force controlling one's actions and views of the world. This affective "force" within the human brain can be reasonably well understood, if one is willing to consider that it emerges from the neuro-psychic energies aroused by RAGE circuits shared by all mammalian brains. A similar analysis can be done for brain systems that can reduce anger.

Both psychologically and behaviorally, certain attitudes and gestures are especially efficacious in reducing anger.¹⁸ Among many types of animals, appeasement signals—for instance, lying on one's back, exposing vulnerable parts like the belly and neck—commonly reduce aggression by others of the same species. Defeated rats often emit long 22 Khz vocalizations. Do these submissive gestures release specific neurochemicals that counteract angry urges, or is the reaction purely cognitive? Although it is next to impossible to probe the thoughts of emotional animals, we will here assume that there are certain neurochemical profiles that can promote peaceful relations among animals, including chemistries that emerge from circuits mediating sexuality (see Chapter 12), nurturance (see Chapter 13), and social bonding (see Chapter 14). But before we can understand the influence of these factors, we will first have to understand the nature of anger within the mammalian brain.

The General Neurocognitive Substrates of Anger and the Frustration-Aggression Hypothesis

In the body, anger is accompanied by an invigoration of the musculature, with corresponding increases in

autonomic indices such as heart rate, blood pressure, and muscular blood flow. As is so well conveyed by idiomatic descriptions of anger (e.g., "getting hot under the collar"), body temperature also increases during anger. In the brain, there emerges an intense and well-focused tendency to strike out at the offending agent. The emotional state aroused in the brain is a fiery mental storm, capable of being defined in neurophysiological and neurochemical terms, that rapidly persuades us that the offending agent is below contempt and deserves harm. Previous memories related to the anger episode are easily remembered and potential plans for vengeance are automatically promoted.¹⁹ This indicates powerful interactions of RAGE systems with memory encoding systems of the brain, although, as already indicated, we know little neurophysiologically about such matters.

The study of such internal experiences of humans could provide some testable hypotheses concerning the properties of anger systems. Since anger is most easily aroused when the availability of desired resources diminishes, it should have close anatomical and neurophysiological linkages to the SEEKING system. Indeed, arousal of the self-stimulation system entails an increased possibility of frustration, since this system establishes neural conditions for an affective state of high expectations and hence their failure to be met (Figure 10.1).

To the best of our knowledge, positive expectations, and the possibility of frustration, arise from neurodynamic activities of higher brain areas that compute reward contingencies—psychological processes that are linked intimately to the cognitive functions of the frontal cortex.²⁰ A rapid suppression of activity within the SEEKING system, in the absence of homeostatic pleasures, which would normally index that a reward has been obtained, should unconditionally promote the arousal of anger circuitry. Indeed, such effects have been observed in animals' elevated tendency to bite when rewarding brain stimulation is terminated.²¹ In comparable circumstances, humans tend to clench their jaws and swear epithets. In other words, the RAGE and SEEKING circuits may normally have mutually inhibitory interactions (see Figure 3.5), even though both may be comparably sensitized by other processes such as the feelings of hunger aroused by the body's energy needs. This makes psychological sense, since such need states would heighten the value of positive expectations, and hence the feelings associated with those expectations not being met.

The frustration-aggression hypothesis has been one of the most well-developed theories in the psychological literature (as highlighted in the famous book by Dollard and colleagues, cited in the Suggested Readings). Frustrating experiences have traditionally been linked to anger through the hypothesis that if a goal response is interrupted, aggression follows. A basic postulate of this view is that aggression will increase in proportion to the level of frustration—namely, in

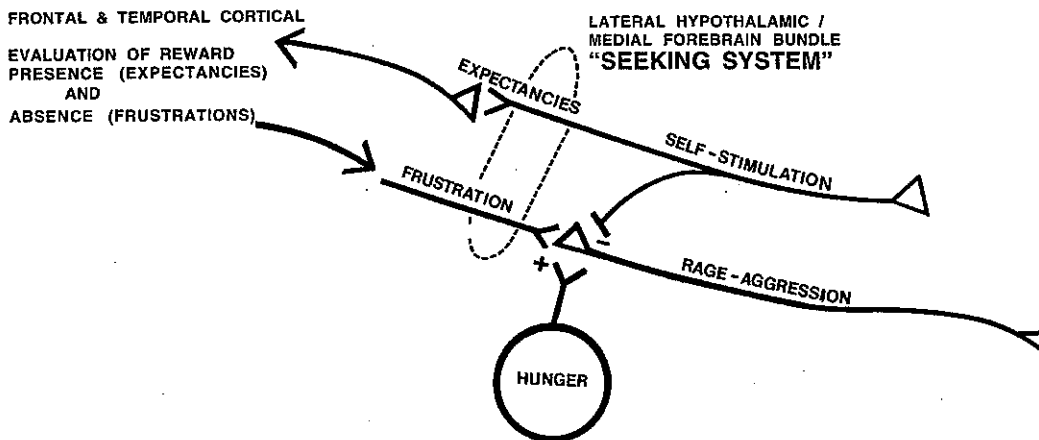


Figure 10.1. Schematic suggestion of likely interactions between neural systems that mediate the anticipatory behaviors of SEEKING and arousal of the RAGE system. (Adapted from Panksepp, 1981; see chap. 3, n. 25.)

direct relation to the intensity of the desire that is thwarted and the number of times the thwarting occurs. Such predictions are supported by a large amount of human data. For instance, children who have not been allowed to participate in a favorite activity will subsequently tend to exhibit higher levels of aggression, and such frustrations bring other dark thoughts to the surface such as prejudice toward minority groups.²²

From both neural and affective perspectives, we must also ask some deeper questions. Is the feeling of frustration really substantially different than that of anger? Psychobiological evidence certainly allows us to conclude that they are intimately linked, since manipulations that reduce the effects of frustration, such as antianxiety agents and temporal lobe damage or more restricted amygdaloid lesions, also tend to reduce emotional aggression.²³ Thus, the emotional feeling of frustration may largely reflect the mild arousal of RAGE circuitry, in the same way that anxiety may reflect weak arousal of the FEAR circuitry (see Chapter 11). In other words, the outputs of cognitive brain systems that evaluate reward contingencies may simply have special access to RAGE circuitry. Even though there is little evidence on this, it also remains possible that feelings of frustration arise directly from higher brain activities, such as of the frontal cortex, that evaluate reward contingencies. Certainly, the fact that patients with frontal cortical damage can become angry rapidly, but can also lose their anger rapidly,²⁴ suggests that frontal cortical influences are important in sustaining instinctual anger responses that are elaborated by lower regions of the brain.

Although it remains to be empirically demonstrated which brain systems are essential for generating feelings of frustration, such feelings may very well arise from mild arousal of RAGE circuitry. Since the frontal cortex elaborates reward expectancies, presumably a

neural representation of those perceptions feeds back onto the subcortical components of the anger system. However, in this context it is important to remember that there are many other facilitators of aggression beside frustration—including hunger, pain, and perhaps some of the neural effects of testosterone. Conversely, it is also worth considering that such intense feelings may also sensitize the higher neural substrates that instigate frustration through the computation of positive expectancies. How this might operate for specific commodities that alleviate hunger and pain is more straightforward than it is for testosterone, unless we consider that the hormone may generate greater expectations by promoting feelings of social strength and dominance. Such strong feelings may help set the stage for stronger feelings of frustration when things do not go as well as anticipated, especially during intermale competition. Because of the likelihood of multiple layers of neural interactions among the various aggression systems, as well as the other basic emotions, it is important to consider all the various forms of aggression that have been documented by animal behaviorists.

Taxonomies: Environmentally Induced Varieties of Aggression

Although the frustration-aggression hypothesis has been of great value in promoting coherent psychological analysis of aggression, we must remember that behavioral manifestations of aggression are quite diverse. There are several distinct brain systems that can precipitate aggressive acts and an even greater number of external stimuli that can trigger such systems into action. As we saw in Chapters 2 and 8, all emotional circuits appear to be designed to permit a great deal of

behavioral flexibility, which helps explain the variability of behavior patterns seen during a single emotional state, within as well as between species. Thus, it is understandable why there would still be considerable confusion about how aggression should be subcategorized and studied. Taxonomies of aggression can be based on (1) the possible psychological causes of aggression (as in the previous section), (2) the varieties of behavioral expressions, as well as (3) the basis of the types of underlying neural systems. Let us now move to the second level of analysis.

The types of aggression that have been distinguished on the basis of eliciting conditions are more numerous than those based on the behavioral manifestations and the types of aggression-organizing systems that have been discovered in the brain. Even though many distinct circumstances lead to aggression, several forms, distinguished on the basis of eliciting conditions, probably do emerge from the same neural operating systems. For instance, the aggression that a mother exhibits to defend her offspring may not be fundamentally different from the aggression a male exhibits when an intruder infringes on his territorial "rights." In both situations, aggression may be evoked by essentially one and the same brain circuit, even though the two can be distinguished taxonomically by the different psychosocial/cognitive precipitating conditions. Thus, a single brain process can be activated by several different inputs.

The most widely cited behavioral taxonomy based on the eliciting conditions for aggression was developed by Kenneth Moyer.²⁵ His list includes seven distinct forms of aggression: (1) *Fear-induced aggression* occurs when an animal cannot escape from an aversive situation; (2) a female often displays *maternal aggression* when an intruder is perceived to threaten the safety of her offspring; (3) *irritable aggression* results from annoying occurrences in the environment that are not strong enough to provoke flight; (4) *sex-related aggression* occurs in the presence of sexual stimuli; (5) *territorial aggression* occurs when a strange animal enters the living space claimed by a resident animal; (6) *intermale aggression* reflects the fact that two males placed together are much more likely to begin fighting than two females placed together; and (7) *predatory aggression* is a food-seeking mechanism in certain omnivorous and carnivorous species. One could even suggest others, such as *play-fighting*, *defensive aggression*, and perhaps even *lovers' spats*, but these types of distinctions are presently not very useful at the neuroscience level of analysis.

As will be highlighted later, all these forms of aggression are certainly not distinct at the subcortical level. Environmentally based taxonomies such as Moyer's do not reflect the distinct types of brain operating systems that can mediate aggression. Several items in his taxonomy share underlying controls, while others do not. For example, most investigators consider predatory

aggression to be motivationally and neurologically distinct from other forms. Indeed, William James, in his famous *Essays on Faith and Morals*, may have been conflating distinct forms, such as predatory aggression (little boys' pulling of butterfly wings) and those aggressive passions that can lead to intermale conflict and warfare. Unlike most of the other forms, predatory aggression is largely endogenously generated and accompanied by positive affect (even though the concurrent energizing contributions of hunger may be aversive), and I will argue, contrary to traditional wisdom, that hunting largely emerges from the SEEKING system discussed in the previous chapter. Of course, this does not mean that the whole predatory attack sequence or any other real-life emotional pattern ever remains under the control of a single emotional system. A predator surely experiences irritability or frustration if the prey struggles so vigorously that it seems liable to escape. Thus, in real life, there are sudden shifts in emotions depending upon the success or failure of specific behavioral acts, as well as in the changing cognitive expectations and appraisals of each situation.

Let us now shift to the third level of analysis and focus on the distinct circuitries for aggression that actually exist in the brain. The final word on this is not in, but it is certain that there are fewer aggression systems than are highlighted in Moyer's taxonomy. How might we empirically winnow the list and then empirically distinguish among them? One problem is that many environmental, neuroanatomical, and neurochemical influences act similarly on each and every type of aggression listed. For instance, prolonged social isolation or hunger may increase all forms of aggression, while high brain serotonin activity may reduce them all.²⁶ Such important shared variables do not allow us to make useful distinctions. At present, the most effective way to distinguish among the various neural systems is via the analysis of "stimulus-bound" aggressive tendencies evoked by localized electrical stimulation of specific circuits in the brain, and via the analysis of which variables modify the sensitivities of these circuits.

Varieties of ESB-Induced Aggression and Their Affective Consequences

Distinctions among neural pathways for aggression have been effectively made by the careful psychobehavioral analysis of aggressive sequences evoked by direct electrical stimulation of the brain (ESB). The fact that coherent patterns of aggression can be produced in this way is remarkable in itself. If, as many scientists used to believe, aggression is largely a learned response rather than an intrinsic potential of the nervous system (e.g., see the contribution by John Paul Scott in the Suggested Readings), it would be unlikely that localized ESB could evoke attack behaviors. However, since Walter Hess's work in the 1930s (see "Afterthought," Chap-

ter 4), it has been clear that rage can be precipitously provoked by ESB administered to specific brain areas.

My own initial experience with this technique was revealing. When I first applied ESB to a cat that had been surgically prepared with an indwelling electrode in the medial hypothalamus, within the first few seconds of ESB the peaceful animal was emotionally transformed. It leaped viciously toward me with claws unsheathed, fangs bared, hissing and spitting.²⁷ It could have pounced in many different directions, but its arousal was directed right at my head. Fortunately, a Plexiglas wall separated me from the enraged beast. Within a fraction of a minute after terminating the stimulation, the cat was again relaxed and peaceful, and could be petted without further retribution.

As mentioned at the outset of this chapter, at present three distinct kinds of aggression can be aroused by applying ESB to slightly different brain zones: predatory aggression, angry, ragelike aggression, and perhaps intermale aggression, even though the last may also have strong components of the other two. It is the second of these systems that will be the center of attention in the remainder of this chapter, even though I will summarize selected issues related to the other two.²⁸

Several early investigators called aggressive displays induced by ESB "sham rage," based on the assumption that the animals were not experiencing true affect. This seemed plausible because some of the subjects could be petted even while they were hissing and snarling.²⁹ However, such sites appear to be quite low in the brain stem and in the minority. Now it seems more likely that most electrode placements above the mesencephalon do evoke a central state indistinguishable from normal anger (except perhaps for the fact that stimulation-induced rage is not sustained for a long time after ESB offset, perhaps because of the sudden release of an opponent neural process). Perhaps the most compelling evidence that the ESB evokes a true affective feeling is that humans stimulated at such brain sites have reported experiencing a feeling of intense rage.³⁰

At a logical level, it is by no means clear whether the experience of anger should be deemed an unambiguously aversive emotion. It could easily become positive if it succeeds in changing the world in desired ways. However, we can conclude that most animals do have unpleasant affective experiences during such stimulation, since they readily learn to turn off ESB that generates affective attack.³¹ Although some electrode sites, especially those low in the brain stem, may only activate motor-pattern generators with no accompanying affective experience, most animals are truly enraged by the ESB. They readily direct their anger to the most salient potential threat in their environment. However, other forms of aggression evoked by ESB do not appear to be accompanied by anger.

The early distinction between *affective* or *defensive attack* and *quiet-biting* or *predatory attack* has been most extensively analyzed. During affective attack (see

Figure 10.2), animals exhibit piloerection, autonomic arousal, hissing, and growling during their attack pattern, while during quiet-biting attack they exhibit only methodical stalking and well-directed pouncing.³² Subsequent studies in rats established a similar taxonomy.³³ Additional work with rats has provided evidence for a third form: intermale aggression.³⁴

The fact that only these three forms can be provoked with ESB suggests that the many environmental influences outlined by Moyer probably converge on a limited set of aggressive operating systems in the brain. For instance, maternal and fear-induced aggression may reflect a convergence of inputs onto an affective attack or RAGE system. On the other hand, intermale, territorial, and sex-related aggression may have some common influence on the system that elaborates *intermale fighting*, whereas instrumental and predatory aggression may largely arise from the quiet-biting attack systems. Of course, as already mentioned, it must be emphasized that in real-world encounters, several emotive systems are bound to be recruited concurrently or successively in the excitement of ongoing events.

Although the so-called quiet-biting attack or predatory attack system described in cats is surely distinct from the one that mediates rage, the notion that it is separate from the SEEKING system is probably a misinterpretation. A great deal of evidence suggests that both emerge from a homologous brain system on the basis of anatomical, neurochemical, and functional grounds. The two behaviors are obtained from essentially the same brain areas, and in rats the most effective quiet-biting attack electrodes always evoke self-stimulation.³⁵ Self-stimulation is facilitated by anti-anxiety agents,³⁶ as is ESB-induced quiet-biting attack,³⁷ and both behaviors are reduced by dopamine-blocking agents.³⁸ It is evident that the segregation of these two lines of research (i.e., work on the lateral hypothalamic self-stimulation system in rats and the quiet-biting attack system in cats) has overlooked this remarkable commonality in the underlying brain substrates. To the best of our knowledge, the two response patterns are simply two distinct behavioral expressions of SEEKING tendencies that arise from homologous systems in the brains of different species. The species-typical expressions of this system lead to foraging in some species and predatory stalking in others.

But how about the distinction between affective attack and quiet-biting attack systems? Can that distinction be defended on the basis of hard empirical evidence, as opposed to mere differences in outward appearance? Might it not be that these seemingly distinct forms of aggression emerge from a single system, and the apparent differences are due to activation of extraneous influences, such as other emotional systems located nearby—for example, those that elaborate FEAR or PANIC? The answer appears to be no. A substantial amount of evidence now shows that affective attack and quiet-biting attack systems are quite distinct



Figure 10.2. Artist's rendition of a cat in the midst of a stimulus-bound affective attack episode (electrodes to cat not depicted). Although the behavior of the animal is well directed and apparently intentional, there is substantial autonomic arousal and an anger type of behavioral presentation. (Adapted from a photograph by John Flynn, 1967; see n. 28.)

in the brain. In addition to the observable behavioral differences and neuroanatomical divergencies to be discussed in the next section, quiet-biting attack is typically evoked during ESB of the dorsolateral hypothalamus, while affective attack sites are more concentrated in the ventrolateral and medial hypothalamus.³⁹ The approximate neuroanatomy of the RAGE system is summarized in Figure 10.3.

The two forms of aggression can also be distinguished in rats by several other criteria. First, with re-

spect to affective correlates, brain sites that yield quiet-biting attack invariably also support self-stimulation, while affective attack sites yield escape behaviors.⁴⁰ This same trend is apparent in the periaqueductal gray (PAG), where affective attack and aversive responses can generally be aroused from the dorsal half of the PAG, while quiet-biting attack and self-stimulation are more readily obtained from the ventral half.⁴¹ This does not mean that anger must necessarily be considered a wholly negative emotion. As mentioned, if the ener-

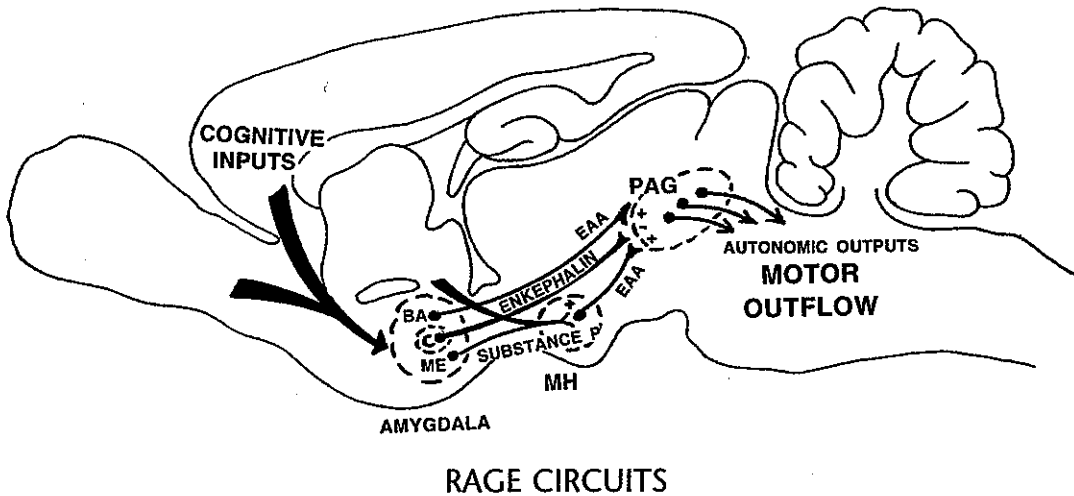


Figure 10.3. Summary of the localization of RAGE circuitry in the brain. (Adapted from data in Siegel & Brutus, 1990; see n. 39; and Siegel & Schubert, 1995; see n. 81.)

gized behavior of rage produces the desired changes in the environment, then it is rapidly mixed or associated with positive emotional feelings.

The differentiation of predatory and affective attack can also be made in terms of the higher brain areas that control these tendencies, as can be evaluated by stimulating two brain areas concurrently. For instance, stimulation of the bed nucleus of the stria terminalis facilitates affective attack while suppressing quiet-biting attack.⁴²

The two types of attack can also be distinguished with respect to eliciting conditions. Rats exhibiting quiet-biting attack will, in addition to attacking live prey, also bite dead mice, while stimulation of affective attack sites does not support the latter behavior. On the other hand, when confronted by conspecifics (members of the same species), no attack is generated from quiet-biting attack sites, while intense attack is still evoked from affective attack sites. Apparently, during anger, the type of available target is not as important as the fact that there is a living target upon which to vent one's rage. Yet as one does these types of ESB manipulations in more complex creatures such as monkeys, the aroused animals tend to vent their rage on more submissive animals and avoid confronting more dominant ones. With repeated stimulation within a colony-living situation, however, it has been found that animals can actually ascend in rank within their dominance hierarchies.⁴³

Affective and predatory attack sites can also be distinguished pharmacologically. While minor tranquilizers such as chlordiazepoxide (Librium®) reduce affective attack and increase quiet-biting attack, psychostimulants

such as amphetamine can increase affective attack without clearly affecting quiet-biting attack.⁴⁴ In sum, quiet-biting and affective attack circuits are clearly distinct. Also, as mentioned earlier, there is preliminary evidence that one can activate aggressive intermale fighting independently of these two systems. Let us now focus on the details of each of these "aggression" systems.

Brain Circuits for Affective Attack (RAGE)

It seems highly probable that the emotion we commonly call *anger* or *rage* derives much of its motivating energy and affective impact from the neural circuits that orchestrate affective attack. The most compelling evidence, of course, comes from subjective reports that have been obtained from humans. The core of the RAGE system runs from medial amygdaloid areas downward, largely via the stria terminalis to the medial hypothalamus, and from there to specific locations within the PAG of the midbrain. This system is organized hierarchically (Figure 10.4), meaning that aggression evoked from the highest areas in the amygdala is critically dependent on the lower regions, while aggression from lower sites does not depend critically on the integrity of the higher areas.⁴⁵ In other words, lesions of both medial hypothalamic and PAG zones dramatically diminish rage evoked from the amygdala, but not vice versa. Thus, from diencephalic zones, around the medial hypothalamus, the aggressive tendency is critically dependent on the integrity of the PAG but not of the medial amygdala. This probably indicates that the higher areas provide

HIERARCHICAL CONTROL OF BRAIN STIMULATION-EVOKED ANGER RESPONSE

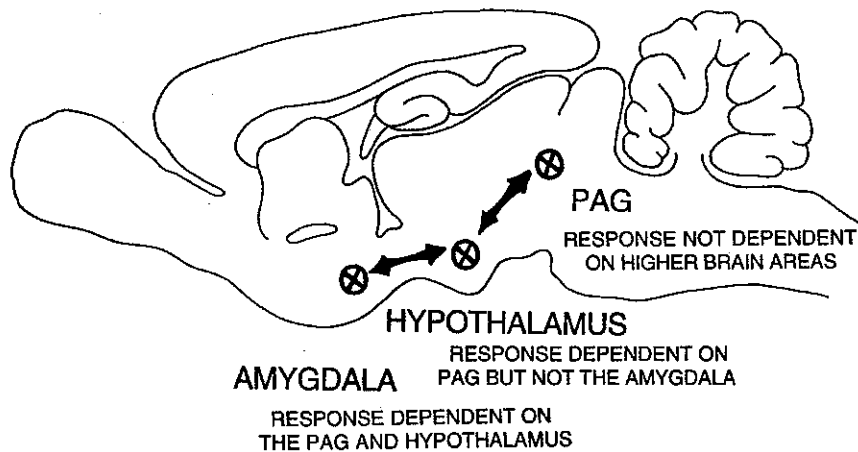


Figure 10.4. Hierarchical control of RAGE in the brain. Lesions of higher areas do not diminish responses from lower areas, while damage of lower areas compromises the functions of higher ones.

subtle refinements to the orchestration that is elaborated in the PAG of the mesencephalon. For instance, various irritating perceptions probably get transmitted into the system via thalamic and cortical inputs to the medial amygdala, while more basic physiological "irritations," such as hunger and basic hormonal/sexual influences, enter the system via medial preoptic and hypothalamic inputs.

Since the primary evolved function of anger is to motivate individuals to compete effectively for environmental resources, we would anticipate that reciprocal relations would exist between the SEEKING and RAGE systems (see Figures 3.5 and 10.1). Indeed, as mentioned earlier, animals are less likely to bite during "rewarding" lateral hypothalamic stimulation, but they tend to bite more at the offset of such stimulation. In addition, frustration, a major precipitant of anger, seems to be elaborated largely within frontal cortical areas, where neurons register conditional stimuli that predict forthcoming rewards.⁴⁶ These neurons can track reward-relevant stimuli, so that when CS+ and CS- (i.e., the conditional stimuli predicting reward presence or absence) are reversed, the neurons reverse their firing patterns to follow the new reward relationships. Neurons within the temporal lobes, which also exhibit similar initial discrimination of conditional reward associations, do not readily exhibit response patterning reversals when the valences of the conditional stimuli are reversed.⁴⁷ It is not clear which type of brain tissue is more important for the generation of frustration, but presumably frustration emerges from the ability of such cognitive systems to monitor the probability of forthcoming rewards. If an expected reward is not registered, the higher cell assemblies send out *opponent process*

messages that invigorate activity within the RAGE system. Does the relevant neuroanatomy support such a scenario?

Detailed maps have now been constructed of the brain interconnectivities of the executive system for RAGE which ultimately terminate in the PAG. Both the retrograde and anterograde maps of these brain sites yield a provocative set of connections.⁴⁸ PAG sites that support rage behaviors receive inputs primarily from six areas of the brain (Figure 10.5), including several areas of the cortex, the medial hypothalamus, and several zones of the lower brain stem. The six major areas, with their potential psychobehavioral functions are as follows: (1) The highest brain areas sending direct information to the PAG emerge from the frontal cortex—primarily from medial areas that contain reward-relevance neurons, as well as from a more lateral area called the frontal eye fields, which help direct eye movements to especially prominent objects in the environment. It seems appropriate that the basic anger circuits receive information from brain systems that regulate these important integrative areas. (2) Another set of inputs comes from the orbitoinsular cortex, especially the insular area, where a multitude of senses converge, especially ones related to pain and perhaps hearing. These areas presumably code the affective content of certain irritations, including vocalizations, and may give specific sounds direct access to RAGE circuitry. For instance, it is not an uncommon human experience that an angry tone of voice directed at you activates your own anger in return. (3) Powerful inputs emerge from the medial hypothalamus. Not only is this brain area part of the trajectory of the anger system itself, but it also elaborates energy homeostasis (see

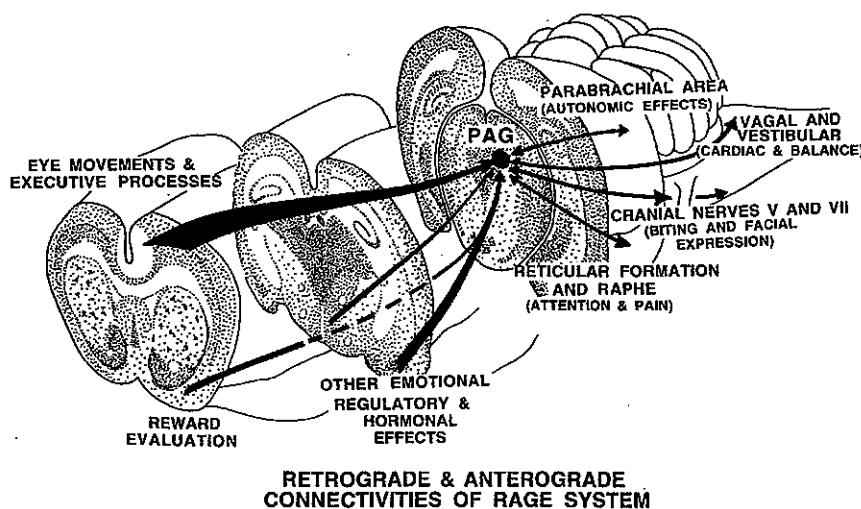


Figure 10.5. The anterograde and retrograde connectivities of mesencephalic RAGE sites in the cat brain. (Adapted from Bandler, 1988; see n. 41.)

Chapter 9) and sexual matters (see Chapter 12); thus it is an ideal area where those influences come to modify anger. For instance, both hunger and testosterone are capable of sensitizing the anger circuit, while satiety and estrogen are able to quell activity within this system. Inputs from lower areas include (4) the vestibular complex, which may help enrage animals when their bodily orientation is disrupted; (5) amine cell groups such as the locus coeruleus and raphe, which are known to exert nonspecific modulatory control over all behaviors (see Chapter 6); and (6) the nucleus of the solitary tract, which collects visceral information via the vagus nerve and probably is important for apprising the anger systems of the tone of peripheral autonomic processes such as heart rate and blood pressure. It is important to emphasize that most of these connections are reciprocating two-way avenues of interdependent control (i.e., they reflect reciprocating feedback mechanisms).

Indeed, it is known that some peripheral inputs can control the sensitivity of rage systems. For instance, increased activity in *baroreceptors* of the carotid arteries monitors levels of blood pressure and can facilitate the sensitivity of RAGE circuitry. When blood pressure goes up, the sensitivity of RAGE systems does, too.⁴⁹ Probably the most important brain area for the actual integration of the overall anger response is in the PAG, an area that also sends reciprocal efferent feedback to most of the systems mentioned previously. This reciprocity indicates that the RAGE system remains informed of its activities at all of the hierarchical levels of the basic control circuitry. This, of course, makes considerable adaptive sense.

Quiet-Biting Attack

As already indicated, the major brain areas that yield predatory aggression during ESB overlap remarkably with brain areas where self-stimulation is obtained, although quiet-biting attack has typically been studied in cats, while rats have been the species of choice for self-stimulation studies. If both self-stimulation and predatory attack actually emerge from a homologous basic brain function, it is understandable why cats are so rarely used in self-stimulation research. Cats do not acquire self-stimulation behavior as readily as rats, and when they do, they do not behave in a rapid, agitated way like rats. Presumably, this is because a cat's typical food-acquisition strategy is stealthy hunting that requires considerable motor inhibition. Rats, on the other hand, acquire the behavior rapidly and behave energetically, probably because their natural foraging style, which is accompanied by vigorous activity and object manipulation, fits nicely with vigorous lever pressing.

Conversely, it is much easier to obtain quiet-biting attack from cats than from rats, probably because rats normally harvest energy by searching and scavenging for their food rather than hunting. In one of the first

studies to map out aggression circuits in the rat brain, it proved remarkably difficult to demonstrate quiet-biting attack until subjects were preselected for the tendency to exhibit predatory intent.⁵⁰ In other words, predatory attack could be obtained easily only in those individual animals that had a preexisting strong tendency to approach and vigorously investigate potential prey objects such as mice. In these animals, brain stimulation at lateral hypothalamic sites would eventually induce systematic pursuit and attack of available mice.⁵¹ However, if mice were not available, the same animals would readily exhibit one of the other stimulus-bound behaviors, such as eating or drinking, that is typically evoked from the lateral hypothalamus (see Chapter 8). There was no reason to suppose that quiet-biting attack was aroused from different circuits than those alternative behaviors (even though the terminal behavioral component obviously requires some different circuitry in the brain stem and spinal cord for the differential patterning of the final behavioral output). In short, ESB-induced quiet-biting attack could be obtained readily only from those animals that already exhibited some predisposition to attack. Accordingly, it seems that quiet-biting attack is simply one behavioral product of the SEEKING system. Even though this behavior has been extensively studied within the context of aggression, from the animal's point of view, there is no apparent anger involved in this food-seeking response. Indeed, it has always been more reasonable to assume that the emotive pattern was, in fact, accompanied by positive affect, since cats, just like rats, readily exhibit feeding during low-intensity stimulation of those lateral hypothalamic sites where higher levels of stimulation provoke predatory attack.⁵²

Moreover, it should be noted that many of the perceptual sensitivity changes that have been obtained in stimulus-bound aggression studies on felines are restricted to quiet-biting attack rather than affective attack circuitry. For instance, during application of this kind of brain stimulation, the perioral regions of cats are sensitized, so that light touch along the lip line is more likely to evoke orientation and biting than it is without the brain stimulation (Figure 10.6).⁵³ The stronger the current, the broader the area of sensitization. A similar phenomenon is obtained in rats with lateral hypothalamic stimulation that sustains stimulus-bound appetitive behavior,⁵⁴ which further affirms the commonality of these systems in the two species. In a similar way, this type of stimulation sensitizes the skin of the cat's paws, so that mild touch is more likely to provoke a vigorous striking reflex.⁵⁵ Again, the more intense the stimulation, the broader the area of sensitivity. In neurological terms, the more intense stimulation recruits more *dermatomes* along the forearm (i.e., dermatomes are skin zones served by the individual spinal sensory nerves).

Another fascinating aspect of brain stimulation is that it provokes a predatory temperament only on the

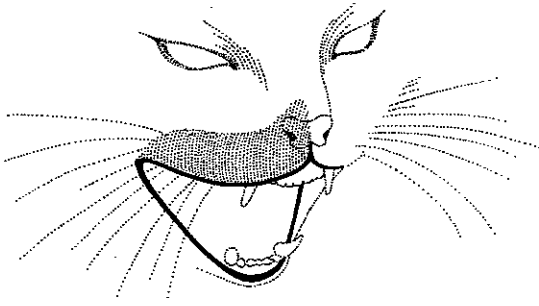


Figure 10.6. Animals stimulated in quiet-biting attack areas exhibit a clear sensitization of various sensory fields, especially that around the lip line and around the muzzle. The area of sensitization increases with increasing stimulation intensity. Similar changes may occur at brain sites that produce affective attack, but that is not clear from the available literature.

side of the brain that is stimulated directly, and this is reflected in the sensitization of the corresponding visual fields. Specifically, ESB applied to the right side of the brain makes an animal exhibit predatory aggression in its left visual field but not in the right (please note that information from the right visual field is transmitted to the left cerebral hemisphere because of the way the optic nerves cross in the optic chiasm). Conversely, stimulation of the left side of the brain leads to attack directed at target animals in the right visual field. In other words, lateral hypothalamic stimulation sensitizes sensory processing within the ipsilateral cerebral hemisphere, which sensitizes the animal's response to information coming in through the contralateral sensory fields.⁵⁶ Accordingly, a prey moving across one half of a subject animal's visual field will provoke attack, but when it reaches the opposite visual field, attack behavior ceases.⁵⁷ A similar unilateral sensitization of higher areas has been demonstrated for self-stimulation circuitry in rats,⁵⁸ again reinforcing the relationship of that circuitry to predatory aggression. Comparable types of brain effects have yet to be demonstrated with electrode placements that generate affective rage, but they may well exist once studies are done.

Intermale Aggression and Dominance

In nearly all mammalian species, males fight more than females. In neural terms, this is the case because males possess more active aggression circuits, at least those types of aggression circuits that were evolutionarily designed to assure reproductive success. Females possess the more precious reproductive resource (the egg and gestational abilities), so it has been left for males to compete for the sexual favors of females. Some have

even speculated that male assertiveness is a selection process driven by the female, whereby the most vigorous males within a breeding population are allowed preferential access to reproductive opportunities.⁵⁹ To put it bluntly, from the female's point of view, a male that can trounce his rivals is more likely to be carrying competitive, winning genes.

In virtually all mammals, male sexuality requires an assertive attitude, so that male sexuality and aggressiveness normally go together. Indeed, these tendencies are intertwined throughout the neuroaxis, and to the best of our limited knowledge, the circuitry for this type of aggression is located near, and probably interacts strongly with, both RAGE and SEEKING circuitries. Our knowledge about the intermale aggression system remains preliminary, but the general neurogeography of the system is highlighted by the high density of testosterone receptors running from the medial amygdala, through the preoptic, anterior hypothalamic area, and down into the PAG of the brain stem (which is really quite distinct from the trajectory of the RAGE system). One can dissociate intermale social aggression from the other types in various ways, including the types of brain damage that affect them. For instance, many forms of brain damage (including lateral septum, nucleus accumbens, medial hypothalamus, and raphe) intensify aggressive responses directed toward experimenters and prey objects but tend to reduce fighting between males.⁶⁰ Thus, brain manipulations that appear to intensify anger and predatory aggression, such as ventromedial hypothalamic damage, do not necessarily intensify social aggression, suggesting that they are independently controlled in the brain.

An especially critical question from both philosophical and empirical points of view is to what extent neurons "irritated" by testosterone in the service of sexual arousal (see Chapter 12) also participate in aggressive arousal. Are these extensively or only mildly overlapping systems? This question is actually more philosophical than practical because testosterone emanating from the testes would affect both systems simultaneously. It would be of practical interest, however, to discover whether the systems are extensively independent and capable of independent modulation. If they are essentially a single system in the human brain, then the only hope for tempering the negative aspects of this neural dilemma would be through education—namely, cognitive specification as to what is acceptable and unacceptable behavior. Although we do not have an answer for humans, the question is partly answered for hamsters. Using *cfos* visualization of neural activity, it is known that many neurons in the amygdala that are aroused by aggressive encounters are also aroused by sexual activity.⁶¹

Although there is no longer much dispute that, in most natural circumstances, males are more aggressive than females (with a few exceptions, such as spotted hyenas), the brain mechanisms for this difference have

only recently been revealed. Testosterone has powerful effects on the expression of several brain neurochemical systems. The most extensively studied is the neuropeptide arginine-vasopressin (AVP). There are extensive AVP-based systems in the brain; major nuclei are situated in the anterior hypothalamus, with projections to the hippocampus, septal areas, and downward through the diencephalon, to the midbrain PAG (see Figure 6.7).⁶²

Testosterone sustains the genetic expression of AVP in a large number of these circuits. Accordingly, males have more extensive vasopressinergic circuits than females.⁶³ When male rats are castrated, AVP is markedly reduced in approximately half of their vasopressinergic circuits. This is paralleled by a decline in both sexuality and aggressiveness.⁶⁴ If one replaces testosterone directly into the brain via microinjections into the appropriate hypothalamic tissues, these behavioral tendencies return. Several experiments have now directly manipulated the AVP systems, revealing that elevating AVP levels by direct central administration increases intermale aggression in rats.⁶⁵ In hamsters, centrally administered AVP markedly increases territorial marking behavior, even in the absence of other males.⁶⁶ If one places an AVP receptor antagonist into the brain, both of these behavioral tendencies are markedly reduced.⁶⁷ Thus, it would seem that AVP is certainly one factor that promotes intermale aggression; as we will see in Chapter 12, it is also a powerful factor in promoting male sexuality and the formation of social memories. Thus, we can speculate that a molecule such as AVP that can facilitate intermale aggression may only do so because it increases a more generalized male tendency such as behavioral persistence—the relentless and single-minded pursuit of a goal. Clearly, we have much more to learn about this aggressive system in the brain that plays a key role in the elaboration of social dominance. At an affective level, we might expect that the initial motivation for intermale aggression is positive, since both combatants readily enter the fray; it is only later, when frustration occurs and defeat is imminent, that more negative emotions begin to intervene. There is a distinct possibility that brain systems that mediate social play (see Chapter 15) are highly interrelated with intermale aggression systems, which would be another reason for seeking linkages to positive affect within intermale aggression circuits.

Although testosterone can clearly increase intermale aggression, we should also briefly consider how those processes relate to RAGE circuits. Although evidence is sparse, the present supposition is that they are largely independent but highly interactive systems. It is possible that testosterone modulates activity in the RAGE system in a way quite comparable to its effects on the intermale aggression systems,⁶⁸ but the evidence is not definitive. There is little reason to believe that testosterone promotes anger independently of its effects on male assertiveness and the potential conflicts and problems

that can lead to. Intermale aggression is an ideal behavioral circumstance where anger could be evoked. Because of such interactions, we cannot be certain that testosterone is directly sensitizing RAGE circuits. For instance, human studies have not provided unambiguous evidence that testosterone increases feelings of irritability. Indeed, some recent human work indicates that testosterone administration does not facilitate such feelings, and human males given supplementary testosterone typically tend to feel better than those who received placebos.⁶⁹

Learning and Aggression

As with any emotional system, a great deal of aggressive behavior is learned. Animals can be trained to be more aggressive or more passive. They can be trained to be winners or losers.⁷⁰ However, it is remarkable how the hormones that promote intermale aggression also provide feedback and reinforce the learning of status. One series of recent findings has shown that victory in a variety of forms leads to increased secretion of testosterone in male animals as well as humans. In humans, such victories as the completion of law or medical school or military training increase plasma testosterone levels.⁷¹ Victory on the tennis court can have the same effect.⁷² To what extent these hormone changes help reinforce future assertive behavior remains to be evaluated, but it would come as no surprise if the neurophysiological solidification of assertiveness was the end result.

Of course, many antiaggressive factors also influence the brain. The “female hormones” estrogen and progesterone have been found to exert antiaggressive effects,⁷³ and it is known that the pleasures of touch and sexuality can inhibit certain types of aggressive tendencies.⁷⁴ Perhaps the most striking example of inhibition has been found with infanticide, a form of sex-related aggression.⁷⁵ Males of many species will harm young animals already present in a new territory to which they wish to lay claim. This is an evolutionarily adaptive strategy. By eliminating lactation-induced infertility, infanticide increases the probability that new males will be able to rapidly fertilize available females, producing offspring of their own. At the same time, males should have natural evolutionarily derived inhibitions against harming their own offspring.

To evaluate this possibility, investigators monitored the pup-killing habits of male rats as a function of copulatory experiences.⁷⁶ It was reasoned that if males were given a chance to mate, they might reveal an inborn system that diminishes the likelihood that they will kill their own offspring at some future point in time. Considering that female rats have a three-week gestational period, it was anticipated that the pup-killing tendencies of males might diminish approximately three weeks after mating, at about the time their own offspring might be born. That, in fact, was what happened (Figure 10.7). While males exhibited about 80% infanticide at the

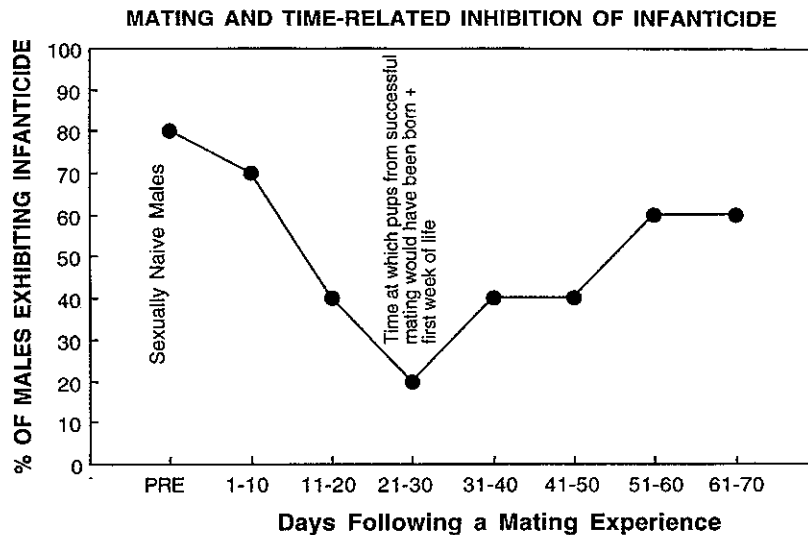


Figure 10.7. The percentage of male rats exhibiting infanticide on a weekly basis following one sexual encounter. (Adapted from Mennella & Holtz, 1988; see n. 76.)

beginning of testing, they gradually diminished to 20% at the three-week time point and then gradually returned to original levels. This points to a specific form of sociosexual memory: Male rats seem to “recognize,” on the basis of their own prior sexual activity, which pups are likely to be their own offspring.

Although it has not been demonstrated which brain changes register this type of memory that promotes peaceful coexistence, a reasonable candidate is the gradual induction of oxytocin in the brain. This hormone, which is more prevalent in females than males (see Chapter 12), promotes nurturant behavior (see Chapter 13). Not only is it known to be an effective antiaggressive agent,⁷⁷ but it can be increased in the brains of male rodents by preceding sexual activity (see Chapter 12). If similar mechanisms exist in humans, the knowledge might have important implications for the discussion of sociosexual policies and politics.

Although females generally exhibit less infanticidal behavior than males, it is certainly not absent, but it often serves a different function. A mother may kill and consume some of her own offspring if food is scarce, even though such killing can also occur for more subtle “political” reasons. Perhaps the most famous perpetrators of such acts were the cruel female chimpanzees, Passion and her daughter Pom, who killed off at least three and probably more of the young infants of other females in the group that Jane Goodall studied for many years.⁷⁸

Although learning controls many forms of aggression, is it important in the mediation of rage? Unfortunately, there is practically no work on the issue since animal models of angry behavior remain poorly devel-

oped—partly because most investigators are not willing to study angry animals and partly because it is somewhat difficult to bring anger under systematic laboratory control. Perhaps the best approach has been to analyze the biting tendencies of organisms that are confronted by frustration induced by reward reductions.⁷⁹

In lieu of critical data, we can only speculate. I would suggest that the classical conditioning of anger should proceed readily. If one pairs certain neutral stimuli with the unconditional response of anger, one would expect that conditioned anger responses would emerge rapidly. Perhaps one of the best ways to do this would be using electrical stimulation of the relevant brain circuits, but to my knowledge, no work along these lines has yet been done. If it were to work, it would be a useful model to analyze how trigger points for anger develop in the nervous system. This would allow us to understand, both pharmacologically and behaviorally, how to reverse or minimize the development of such excessive sensitivities.

Pharmacology and the Neurochemistry of Aggression

One of the most difficult psychiatric problems is aggression. Before the era of psychotropic drugs, it was not unusual for newly admitted patients to arrive at psychiatric hospitals in straitjackets or other restraints to prevent them from hurting themselves and others. Antipsychotic drugs discovered in the early 1950s, such as chlorpromazine, were rapidly found to be quite effective antiaggressive agents, but only at high doses. The

effects were largely due to sedation arising from global reduction of brain catecholamine activity. Although a variety of newer and more specific antipsychotic drugs can now be used to reduce violent behaviors, they are still little more than chemical straitjackets. To this day there is no highly specific way to treat pathological anger pharmacologically.⁸⁰

However, there are now many drugs that can reduce various forms of aggression in animal models,⁸¹ and some of them may be effective against pathological anger. Most prominent among the current generation of antiaggressive drugs are those that promote the activity of the serotonin, gamma-aminobutyric acid (GABA), opioid, and oxytocin systems of the brain. The opiate receptor stimulants exert an especially powerful inhibitory effect on various forms of aggression, which may be partly due to their ability to promote pleasurable feelings of satisfaction and general well-being (see Chapter 9), but it is unlikely that this system can be harnessed for useful medical purposes because of the addictiveness of opiates.

Indeed, opiate addiction gradually strengthens a variety of physiological "opponent processes," which tend to counteract the high levels of opiates in the body. Because of the release of these opponent processes during opiate withdrawal, irritability and impulsive aggression can be dramatically increased. This is one reason that opiate addicts undergoing withdrawal have a heightened tendency to initiate violent acts. Of course, as long as they have opiates in their systems, the tendency to exhibit aggression remains very low. Should society recognized this "Catch-22" when it wages various wars against drug abuse? Whose fault is it if an opiate addict in withdrawal has no legal source of drugs to reduce irritability and becomes aggressive in an effort to obtain such agents? The answer is not obvious.

It is not yet clear which brain neurochemistries promote anger, but one neuropeptide, substance P, may be a key modulator in the RAGE system. Angry displays elicited by brain stimulation can be increased by brain infusions of substance P and they can be reduced with substance P antagonists.⁸² Perhaps an orally administered substance P antagonist, or some other peptide receptor antagonist, can one day be used as an antiaggressive agent in clinical practice. If so, it will be because human anger has been studied through the analysis of RAGE systems in the animal brain.

Which system is most likely to provide a medically useful antiaggressive drug at the present time? Among the biogenic amines, both norepinephrine (NE) and serotonin (5-HT) control anger, the first tending to increase it because of general arousal effects and the second reducing it, just as it controls every other emotional response. Clinically, it has been found that drugs that block the β -NE receptors, such as propranolol, are clinically useful antiaggressive agents. Unfortunately, the overall efficacy of such β -blockers has not been as uniform as desired, and serotonin has been the focus of the

most intense efforts to yield better agents that are desperately needed.

Eltoprazine, a serotonin receptor agonist that acts specifically on the 5-HT-1A receptor, has emerged during the past decade as a very specific antiaggressive agent. It is one of a number of drugs called *serenics*. Eltoprazine and related drugs are effective in reducing virtually every form of aggression that has been studied in the laboratory, but it is no longer on the fast track for general medical use.⁸³ Not only does eltoprazine decrease aggression without any sedation, but it actually increases other friendly and social exploratory behaviors (Figure 10.8). Dissection of the precise mode of action of this drug has indicated that the antiaggressive effects are due to *postsynaptic* 5-HT receptor activity, while the pro-social effects are due to *presynaptic* inhibition of serotonin cell bodies, both being mediated by the same type of 5-HT-1A receptor.⁸⁴ In other words, eltoprazine reduces aggression by facilitating brain serotonin receptor activity in higher limbic circuits, but increases social interactions by reducing serotonin neuronal activity throughout the brain.

However, the increase in social interaction resulting from decreased serotonin is found only in well-socialized animals. Across different strains of rodents, aggressiveness produced by prolonged social isolation is highly correlated to isolation-induced decreases in brain serotonin activity,⁸⁵ and serotonin supplementation can decrease aggression in animals that have become irritable because of long-term social isolation.⁸⁶ In general, reduced brain serotonin activity also tends to increase impulsive and acting-out forms of behavior in humans.⁸⁷ A higher tendency toward delinquency has been observed in human males who have low serotonin activity (as indexed by low cerebrospinal fluid levels of the serotonin metabolite 5-HIAA).⁸⁸ Such evidence suggests that the same neurochemical dynamics known to control animal aggression may also control human criminality and social assertiveness.

Conversely, socially dominant animals, who can control aggression with a glance, have been found to have high brain serotonin activity. Indeed, monkeys tend to climb higher in their dominance hierarchies following long-term treatment with drugs such as the selective serotonin reuptake inhibitors (SSRIs), which increase serotonin availability in the brain.⁸⁹ In sum, many serotonin-promoting drugs, as well as other agents, can provide inhibitory control of aggression.⁹⁰ But specific antianger agents will have to emerge from our understanding of the specific brain modulators that promote RAGE in the brain, in the way that AVP seems to promote intermale aggression.

The neurochemical systems that have been found to promote aggression are less numerous than those that reduce it. In addition to the work on substance P mentioned earlier, the two best candidates for specifically promoting the impulse of anger are glutamate and acetylcholine. One can provoke defensive hissing by ad-

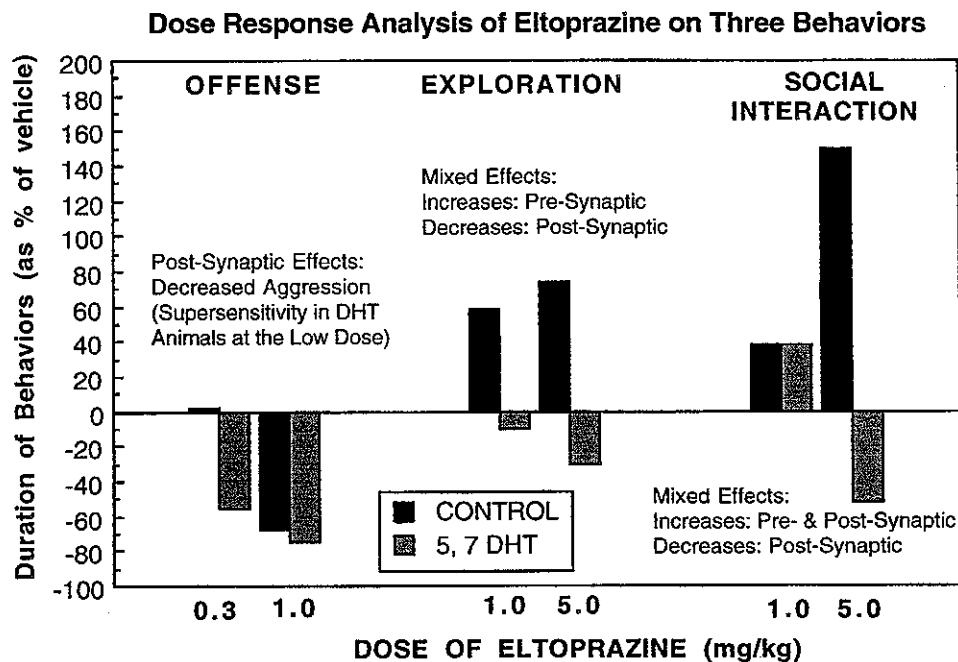


Figure 10.8. Dose-response effects of eltoprazine on offense, exploration, and social interest in normal rats and those whose midbrain serotonin neurons had been destroyed with the selective 5-HT neurotoxin 5,7-dihydroxytryptamine (5,7-DHT). (Adapted from Olivier et al., 1991; see n. 83.)

ministering cholinergic agonists into those regions of the brain where ESB has been found to provoke rage,⁹¹ but it is possible that this hissing response is merely an alarm-fear response rather than an angry one.⁹² A somewhat clearer effect is obtained following localized glutamate administration into specific areas of the brain.⁹³ From this one might conclude that glutamate antagonists or acetylcholine antagonists will prove to be excellent antiaggressive agents. Unfortunately, because of the participation of these transmitters in so many brain processes, there is little hope that their manipulation will ever provide clinically useful antianger/antiaggression agents.⁹⁴ Clearly, the most important neuromodulators for the instigation of rage have not yet been definitively identified.

In any event, existing evidence suggests that mammalian anger emerges from a homologous RAGE circuit that has been remarkably conserved during mammalian brain evolution. Accordingly, a cross-species comparison has a greater potential to reveal neurobiological sources of human anger than any other strategy that is presently available. Of course, this will tell us little about the cognitive sources of anger in humans. It will only tell us how the feeling of anger emerges from specific brain activities. Also, because aggression is such a multidimensional phenomenon, considerable insight will be needed to develop models of anger and aggression that are reasonably pure and distinct from

the multifaceted mixtures of aggression and fear that one normally sees in nature.

In conjunction with data summarized in the next chapter, we now know that circuits for aggression and fear overlap in many areas of the brain, including areas extending from the anterior hypothalamus to the PAG. Thus, one of the easiest aggressive responses that can be elicited with brain stimulation in cats is a hissing-defensive response with no attack (see Figure 10.9). Although this type of response could be interpreted as supporting the existence of a distinct "defense system" within the brain,⁹⁵ at present the most parsimonious conclusion is that such defense responses arise from the concurrent stimulation of two distinct but highly overlapping and interactive emotional systems, namely, those of RAGE and FEAR. This second emotional system will be the focus of the next chapter.

AFTERTHOUGHT: Autonomic and Cerebellar Control of Rage

The outdated James-Lange theory (see "Afterthought," Chapter 3) suggested that peripheral autonomic effects that feed back onto the thinking brain create our experience of emotions. Although the modern view is that emotional circuits within the visceral brain coordinate affective processes, there are certainly many feedback

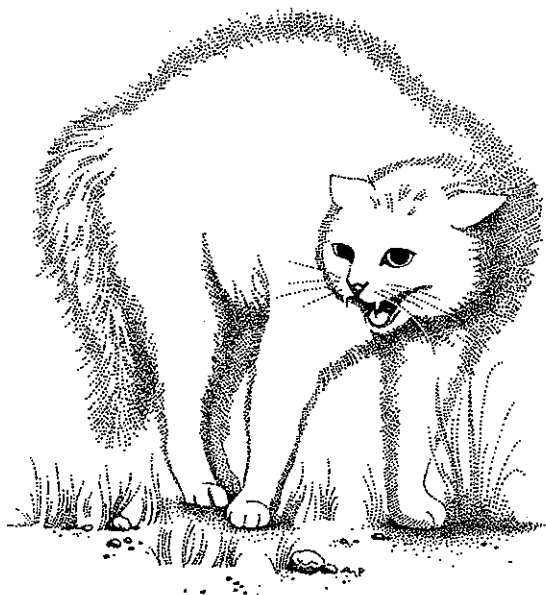


Figure 10.9. Brain stimulation–induced defensive behavior, which may reflect a mixture of simultaneous activation of ANGER and FEAR systems. (Adapted from a photograph by Walter Hess.)

relationships between the relevant peripheral and central processes. For instance, while centrally induced anger increases blood pressure, the arterial detectors for blood pressure changes (i.e., the baroreceptors in the carotid arteries) can modify the sensitivity of the RAGE circuit. As mentioned earlier, if we artificially increase blood pressure, it is easier to evoke angry behavior in cats by hypothalamic stimulation. Thus, we must remember that the actual brain mechanisms that control anger are complex, are under multiple physiological, neuroanatomical, and neurochemical controls, and are only roughly understood. Many details of this emotional system remain to be revealed, and many surprises are bound to emerge from future research.

For instance, one of the most intriguing recent findings is that knockout mice, which are lacking the gene for nitric oxide synthetase (NOS), exhibit high levels of violent behavior and hypersexuality.⁹⁶ However, this psychopathic tendency, presumably caused by reduced brain levels of the gaseous transmitter nitric oxide (NO), is evident only in male rats, and the finding was totally serendipitous. Because of past data implicating NO in learning, the experiment was being conducted to evaluate the role of genetic deletion of the enzymatic machinery needed for NO synthesis on memory. As it turned out, these animals, missing one form of NOS, exhibited normal learning. The tendency of such NOS-deficient animals to be aggressive was discovered only because animal caretakers noted that many of the ani-

mals were dying with injuries on their bodies. It turned out that only the males were killers; they were also hypersexual, with an apparent reduced ability to understand the meaning of “NO.”

Will such knowledge help us deal better with human violence, a most serious social problem? Most think it is unlikely that our society can implement biological interventions for such matters of personal conduct, but new possibilities for biological control are bound to emerge. They will pose enormous ethical problems for future generations, unless we can teach individuals who have aggressive “hair triggers” to voluntarily utilize pharmacological or other aids to control their negativistic urges. Indeed, there are also bound to be nonpharmacological interventions to control aggression, ranging from meditation to the well-established effects of castration and new forms of brain stimulation. Let me focus on the last of these options.

One of the most unusual ways that violent tendencies have ever been controlled in the annals of medicine is by cerebellar stimulation. Although the cerebellum was long believed to simply control motor coordination, it is now known to contribute to attentional and emotional processes as well. This emerging knowledge was utilized by one daring and controversial neurosurgeon, Robert Heath, to control violent pathological aggression. Electrical stimulation was applied to the cerebellum via a plate electrode implanted at the back of the head (over the cerebellum), and the whole contraption was given the provocative name “cerebellar pacemaker.”⁹⁷ Of course, this radical maneuver was attempted only in seriously ill individuals whose aggressive outbursts could not be controlled by any other means, including high doses of heavily sedating antipsychotic drugs.

Heath reported remarkable success in reducing the irritability of such individuals with his “cerebellar pacemaker.” Folks who had been totally incapacitated by their persistent violent thoughts and impulses, could now lead peaceful lives. How this strange therapy works is still unknown, but there are sites in the most ancient part of the cerebellum (in the deep cerebellar nuclei, such as the *fastigial* and *interpositus*) where one can elicit aggressive tendencies with ESB.⁹⁸ Maybe just like the cerebral cortex, which tends to provide chronic inhibition over subcortical processes, the neocerebellar cortex exerts a similar effect on its deep nuclei, and Heath’s “cerebellar pacemaker” facilitates that effect.

Now that new procedures have been developed to activate the brain through the application of intense magnetic fields several inches outside the head (i.e., via rapid transcranial magnetic stimulation [rTMS]; see Chapters 5 and 16), the day may soon arrive when such procedures will become an accepted part of psychiatric practice.⁹⁹ Already, several investigators have had considerable success using this noninvasive rTMS approach to alleviate drug-resistant depressions.¹⁰⁰ It is widely believed that this fairly gentle form of brain stimulation will eventually replace electroconvulsive

therapy (ECT) as a treatment for those depressed individuals who do not respond to the many new medications that have recently become available during this "Age of SSRIs."¹⁰¹ Will someone eventually construct an antiaggression chair, where the back of the headrest contains a magnetic stimulator that is able to change underlying cerebellar activity to such an extent that one's impulsive urges melt away as if by magic? If such a useful device is constructed, it should be used only with a clear recognition that anger, at a cognitive level, may be not only a destructive but a useful force in society.

Although affective neuroscience research can provide us with a substantive knowledge of the experience of anger, it cannot explicate the cultural, environmental, and cognitive causes of aggression. In humans, it is usually the appraisal of events that triggers anger; obviously, many values upon which appraisals are premised are culturally learned in humans. For instance, presently many humans are angry at others for the views they hold about abortion, capital punishment, and innumerable other sociopolitical issues. With sufficient depth of personality, the psychic energy of human anger can be diverted into outrageously creative or constructive efforts. Where would we be today if our ancestors had not had the passion to say: "Give me liberty or give me death." Psychobiology presently has little of importance to say about the many cognitive components of human anger, especially the fiery human energies that help change societies.

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