Searching for the Mark of Cain

Hampered by political, ethical, and methodological problems, a small group of researchers is trying to understand the biological roots of violence—with the ultimate hope of finding a treatment

MEDFORD, MASSACHUSETTS—There's a cocktail lounge in this Boston suburb where the customers are encouraged to overindulge. It's a place where mice get tipsy. A thirsty mouse pokes its nose through a hole, where a sensor takes its order, then it scampers over to a spout a few centimeters away, which immediately dispenses a few drops of an alcohol solution roughly the strength of beer. Mice don't know when to stop. Invariably they scoot back to trip the sensor for another round, and so on, until a computer program decides the bar is closed—by which time the rodent has ingested the equivalent of one or two human drinks.

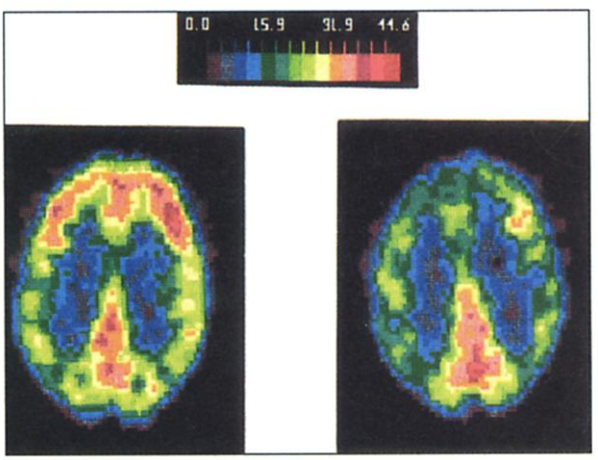
Klaus Miczek, a psychopharmacologist at Tufts University here, wants to know why this binge drinking turns about one in four mice extremely nasty. Miczek has just put a sober male mouse into a cage with one such inebriated male. The drinker starts chasing the newcomer and attacks it within seconds. The sober mouse raises its front paws to ward off the teeth of its attacker and to signal its submissiveness. But the defensive postures and peace overtures are snubbed: By the time the two are separated 5 minutes later, the drunk has inflicted more than 20 bites on its cowering victim. Miczek is studying what neurochemical factors set the aggressive mouse apart. To do so he can plug a set of tubes into its brain, to decant minute fluid samples during a confrontation.

Miczek thinks studies like this are highly relevant to a society in which alcohol figures in two out of every three violent crimes. Yet he and other researchers who study the biology of aggression find themselves struggling to make headway. Part of the problem is lukewarm support for their work. In 1992, a proposed conference on the genetics of aggression exploded into a major political row after Frederick Goodwin, then director of the Alcohol, Drug Abuse, and Mental Health Administration, likened inner city violence to a "jungle"; since then, the National Institutes of Health has quietly de-emphasized studies on the biology of violence (see p. 570). "It used to be a thriving area of research," says Miczek. "But the whole field has been dismissed as irrelevant because of those remarks."

Baring its teeth. A rhesus macaque vents its rage.

Further undermining their efforts are attacks from animal rights activists. Opposition from activists dried up funding for what had been a flourishing violence research school in the United Kingdom in the 1980s (see p. 572). As a result, the research community is tiny, amounting to a few hundred researchers worldwide, and it's hard to entice good young scientists, says Miczek. "Why keep banging your head against a brick wall, when there are much easier areas of research?" adds Adrian Raine, a neuropsychologist at the University of Southern California (USC) in Los Angeles.

Despite these handicaps, the field has generated some interesting findings and hypotheses about how hormones, genes, and the brain control aggressive behavior. Researchers refer to these sets of discoveries as "stories": There's the serotonin story, the Y chromosome story, the hypothalamus story, and many others. But it's still hard to see how these single, and sometimes controversial, pieces of the puzzle fit together, says behavioral geneticist Stephen Maxson of the University of Connecticut, Storrs, and progress is slow. And some are wary that if the field matures and starts producing new, specific anti-aggression drugs, they could be abused by governments or doctors as a "quick fix" for violence in society, rather than addressing the social and economic problems that often underlie it.



Murderous mind? A PET scan reveals less activity in the prefrontal cortex of a convicted killer (right) than in that of a nonviolent control.

CREDITS: (TOP TO BOTTOM) DEE HIGLEY; ADRIAN RAINE

Tainted past

That difficult position today stems in part from the field's checkered past. In the late 18th century, Viennese anatomist Franz Joseph Gall developed a theory called phrenology, which held that most human traits—including antisocial behavior—were regulated by specific brain regions. The larger a region's size—which could be determined from bumps on the skull overlying that area—the better developed the corresponding faculty. His theory was later discredited, as was a doctrine by the Italian criminal anthropologist Cesare Lombroso, almost a century later, who claimed that certain body features he called "stigmata"—such as a sloping forehead or asymmetrical facial bones—could give away criminal types. These and other notions brought the field into such disrepute that, even today, the mere whisper that one's constitution might predispose an individual to violence or crime is enough to raise hackles. In the first half of the 20th century, the widespread use of lobotomy (a procedure in which the frontal or temporal lobe is cleaved from the rest of

the brain) to make people less aggressive and impulsive cast a cloud over clinical research on aggression as well, despite having won the Nobel Prize in medicine for its inventor, Portuguese neurosurgeon António Egas Moniz, in 1949.

In part because of this tainted legacy, modern-day violence researchers take pains to emphasize that one's genetic heritage isn't everything—rather, behavior is shaped by a subtle interplay among genes, environmental conditions, and life experiences. "That's the beauty of this work," says Dee Higley, who studies aggression in rhesus macaques at the National Institute on Alcohol Abuse and Alcoholism in Poolesville, Maryland. "It shows you that genes matter, but they're not destiny."

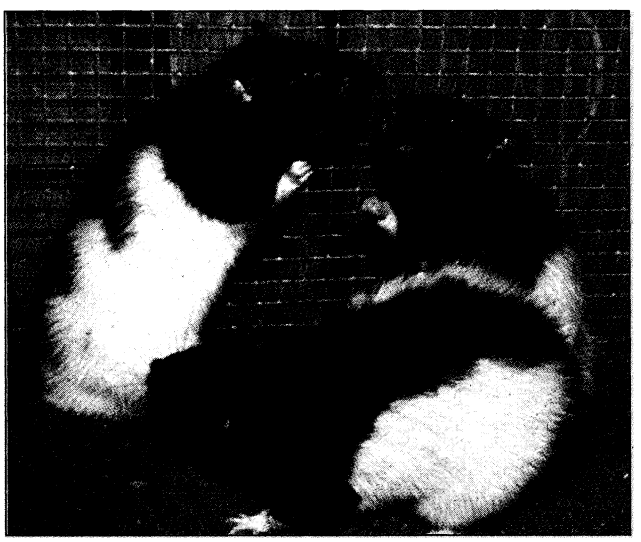
Teasing apart the contributions of nature versus nurture, however, is a daunting task. One problem is finding animal models that mimic human violence yet are ethically acceptable. Popular techniques in the '60s and '70s included giving rats electrical shocks or applying heat to their footpads to elicit aggressive behavior—a model that many researchers now concede was cruel and, because it was so unnatural, hardly meaningful.

The Snarls and Sneers That Keep Violence at Bay

A bull elephant gores a rival in a duel over a female. A rat attacks and eats his mate's pups. In a fight for supremacy, one chimpanzee mauls another to death. Scenes like these may suggest that the ability to mete out violence is linked to survival in the animal kingdom. But a handful of researchers is now making a persuasive case that scores are settled far more often by subtle, nonviolent signals—a curled lip, a snarl, a swivel toward an opponent. Their provocative idea is that inflicting violence on a member of one's own species is a pathological condition that arises when these signals are missed or misinterpreted.

Scientists are now unearthing clues to the behaviors that keep violent impulses at bay. Their findings suggest that personality, social status, life experience, and anxiety levels all factor into whether chance encounters end in peace or, more rarely, in carnage. "For many animals, a lot of social behavior is probing or testing a relationship, always testing with a little aggression and a little friendliness," says Sergio Pellis, an ethologist at the University of Lethbridge in Alberta, Canada.

"Humans also have a tendency to restore relationships and resolve conflict," says Frans de Waal, a primatologist at the Yerkes Regional Primate Research Center in Atlanta, Georgia. Laying bare the roots of violence in people, says Jaap Koolhaas, a behavioral physiologist at the University of Groningen in the Netherlands, may lie in understanding how we—like many other animals—rely on instinctual behaviors that keep violence in check.



A bully in the cage. A male rat strikes an offensive sideways position while two others rear up to defend themselves.

Coping strategies

In the 1960s, the great German ethologist, Konrad Lorenz, made a case, extrapolating from his studies of birds and fish, that humans are an aggressive species and that a penchant for violence leads to clan and tribal warfare. But that dogma is beginning to fade, largely thanks to studies suggesting that aggressiveness is part of a repertoire of behaviors that has arisen to balance the need of the individual to look out for himself and still maintain good standing within the group.

By the time Koolhaas delved into this area about a decade ago, researchers had shown that in many species, individuals are mainly polarized into aggressive or passive personality types. "There's a bimodal distribution," he notes. Searching for cognitive differences that set these two personality profiles apart, Koolhaas's team found in 1993 that highly aggressive rodents are more likely than calmer peers to act quickly when thrust into a potentially life-threatening situation. He proposed the existence of an inborn tendency toward either a "proactive" or "reactive" coping strategy, which has since been discerned in organisms as diverse as birds, cattle, pigs, fish, and octopi. A typically reactive rat, for example, will sniff an electric probe introduced into its cage and get zapped just once, thereafter steering clear of the pain-giving intruder. A proactive rat, on the other hand, will actively try to cover it with the bedding of its cage. That type of reaction may seem wasteful, but proactive coping strategies can boost the odds of survival: Put in a chilly cage, proactive rats build nests to stay warm, while reactive rats sit in a corner and shiver.

Proactive animals also tend to be less easily deflected once they learn a behavior, Koolhaas and his colleagues have found. "The highly aggressive animal tends to develop routines," he says. "With repeated experience, these animals don't pay any attention to environmental stimuli." At the XIV World Meeting of the International Society for Research on Aggression in Valencia, Spain, earlier this month, Koolhaas detailed experiments on rodents in mazes and in social situations. His group has found that proactive mice and rats that have learned to navigate a maze to get to a food reward are unperturbed when the maze is slightly altered—such as when tape is placed at a spot on the floor. They keep going as if the tape weren't there. Reactive individuals, on the other hand, stop and check out the new landmark. Then, as if confused by the tape, they often lose their way to the food, even though the course is otherwise the same.

This tendency shows up in social interactions, too. Even rodents that have never seen a member of the opposite sex can quickly tell a male from a female. Males tend to be nasty toward other males when first introduced, whereas they usually nuzzle new females. But if a solitary, proactive male is presented with another male several times in a row, then is introduced to a female, he will fail to notice the gender switch and will attack the female. "It first does and then thinks," says Koolhaas, whereas a reactive individual "first thinks and then does. It's a crucial difference, and it leads ultimately to violence."

Once a highly proactive animal for the first time wins a series of aggressive encounters and repels an intruder, it acquires a fighting habit, and "its behavior does not depend anymore on what the opponent is doing," Koolhaas says. It ignores peace overtures, such as baring the belly. But such highly proactive animals are rare: Most aggressive encounters between a solitary rodent and a newcomer end up

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"That was nutty stuff," says Craig Ferris of the University of Massachusetts (UMass), Worcester. Instead, most researchers now use so-called ethological models in which they draw out more natural forms of aggression displayed by animals defending territory or establishing a dominance hierarchy. Ferris, for instance, pairs up male Syrian golden hamsters and monitors their aggressive confrontations. In monkey models, researchers are limited to studying "display behavior" where animals snarl and growl, but very rarely actually hurt each other (see sidebar below); eliciting more injurious forms of aggression is considered by most to be unethical. Although such dustups may seem only a distant echo of, say, a wife-beater or a bloodthirsty psychopath, researchers think some of the same neural pathways may be involved.

Clinical researchers face formidable hurdles, too. For one, many studies involve unpleasant or time-consuming experimental procedures, such as spinal taps or brain scans. In addition, it's notoriously difficult to quantify a person's aggressiveness. "You could have a confederate frustrate a subject and see how they respond," says University

with the guest showing the proper deference followed by détente or even playfulness. In observing the highly proactive animal's failure to take into account what the opponent is doing, Koolhaas says, "we have hit upon one of the causes of the development of violence."

Personality and rank

"Type A" behavior is not limited to rodents, says Robert Sapolsky, a neuroendocrinologist at Stanford University in California. He has observed several troops of baboons in their native habitats for almost 20 years. "Personality can be at least as important as social rank" in determining how well an individual fits in, and consequently, the likelihood of getting into fights, he says. Like Type A humans, who tend to perceive a hostile world around them, Type A baboons have higher levels of stress hormones. And if a male Type A baboon can't tell the difference between a minor provocation and a major power struggle—inferring a threat, for instance, from a subordinate that happens to be napping too close to his turf—he's "less likely to remain dominant," Sapolsky says.

Although baboons are considered quite aggressive primates by nature, violence tends to be much more prevalent when the troop's structure is unstable, such as when baboons are kept in captivity. If the troop members don't know one another, or if the hierarchy is disturbed, say, by the loss of the top male, the rush to establish rank results in scuffles that only subside when everyone knows his or her place. "Aggression has something to do with attaining a high rank, but far less to do with retaining it," Sapolsky says. Once dominance is established, violent actions subside, replaced by subtle signals—a sideways glance, for example, or a slight but perceptible tensing of the body.

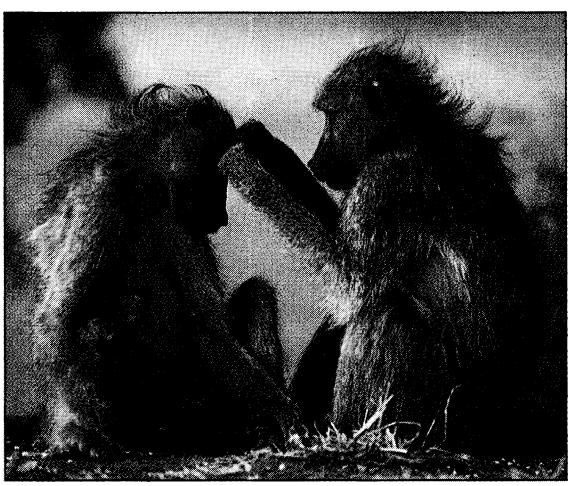
Should a squabble occur, animals know how to make amends. In a new book, *Natural Conflict Resolution*, de Waal and Filippo Aurelli chronicle peacemaking in animals and in people: After an aggressive encounter over food, for example, animal combatants often offer each other friendly overtures, such as grooming or licking one another. Children, too, kiss and make up. Such conciliatory gestures are "extremely widespread," de Waal reports, as they help preserve relationships that may be necessary to survival and can be particularly key when animals (or people) live in crowded conditions. (See de Waal's Review on p. 586.)

These gestures acquire meaning, it seems, during critical developmental windows. By play fighting, young rats, for example, learn how to interact with one another. Both proactive and reactive coping strategies are moderated by these experiences. As Koolhaas's team reported in the March 1999 issue of *Developmental Psychology*, depriving adolescent rats of just 2 weeks of contact—and, consequently, play fighting—transformed them into maladapted individuals who had serious problems dealing with their peers. Isolation, he argues, prevents an individual from "learning to play the game according to the rules."

Those results are in line with what Pellis has found in 20 years of observing play fighting among rats. His team has gleaned the subtle changes in posture and movements that distinguish "play" from something more serious. A rat lacking play experiences is likely to be overly friendly when he first encounters another animal, sniffing it with gusto. "But when the other animal reciprocates, it exhibits hyperdefensiveness," backing off or trying to nip the face, Pellis says. Such behavior seems odd to a rat that has had a normal rough-and-tumble youth, and the miscommunication can result in escalated aggression as both animals get excited and drawn into a fight. This, says Pellis, suggests that "social skills are especially sensitive to what happens in juveniles."

Studies on nonhuman primates support the idea that play fighting is not so much a way to learn combat skills as a way to develop social intuition. According to Pellis, adults in species with irregular contact are more playful than adults of species that live in close-knit groups. Play fighting involves a lot of sniffing and touching, and animals that spend much time together have substituted more sophisticated signals that are often visual or vocal.

Even so, Pellis says, grooming among nonhuman primates suggests that touching still plays an important role in defusing tensions. For example, when primates are fed on a regular schedule, they develop a habit of grooming one another before the food arrives, possibly to ease tensions that might escalate over access to the upcoming meal.



Chacma tai chi. By grooming each other, these chacma baboons and other nonhuman primates may diffuse tension over daily tribulations such as getting enough to eat.

The thought of schoolchildren combing each other's hair to calm down before lunch may seem odd. But animal studies are relevant to people, says Pellis. Children have a biological need to play, he points out, and perhaps even to get into minor scuffles with their peers. That may be how they learn subtle social cues. "Preventing kids from doing it may be causing them harm," he says. "They may be less able to deal with subtle interactions."

Neither Pellis nor others studying aggression in animals think their work will fully explain why people on occasion turn violent. Nevertheless, "the distance between us and animals may be smaller than we like," says Menno Kruk, a behavioral neurobiologist at Leiden University in the Netherlands. "Actually too close for comfort sometimes."

—ELIZABETH PENNISI

CREDIT: D. ALLEN/ANIMALS, ANIMALS

of Chicago psychiatrist Emile Coccaro. "But that's kind of dangerous. What if the guy hurts your confederate?" Instead, researchers query subjects on violent acts they committed in the past or seat them behind a computer and make them believe they're playing a game against an invisible opponent whom they can jolt with mild electrical shocks. The higher they are willing to crank up the voltage, the more aggressive they are presumed to be.

The complex serotonin story

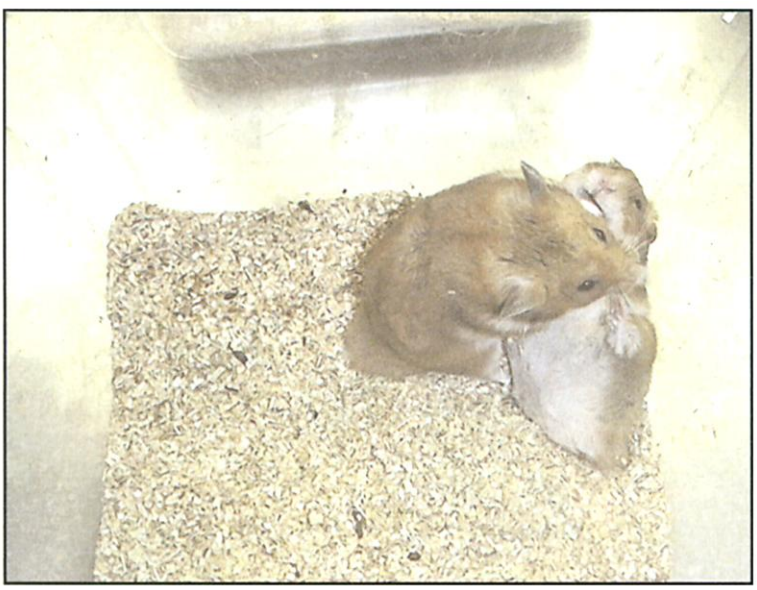
Using such approaches, many research teams are focusing on neurotransmitters, the chemicals that ferry messages between neighboring brain cells. Without doubt the hottest one around is serotonin, which besides aggression has been blamed for a panoply of problems including depression and eating disorders. Numerous studies have found that aggressive animals, including humans, on average have lower levels of a serotonin metabolite—which is thought to reflect lower serotonin levels in the brain—in their cerebrospinal fluid (CSF). To demonstrate a causal relationship, researchers have given animals drugs that lower serotonin levels, which sometimes makes them more impulsive and aggressive, or increase levels, which has the opposite effect. "It's stronger than most stories in neuroscience," says Coccaro.

Even so, the serotonin story is complicated, says Miczek. Researchers know there are at least 14 receptors for serotonin in the brain, and they're currently studying what each of them does. Miczek, for instance, is working on a receptor subtype called 1B. Activating that with a drug seems to quell aggression in mice, rats, and monkeys, he says, and the receptor seems to be an interesting target for new drugs to treat violent behavior in humans. But strangely, the drug lowers serotonin levels in the brain rather than increasing them, presumably because 1B is a so-called presynaptic receptor, which decreases the amount of serotonin a brain cell churns out. That means although serotonin is involved in aggression, its role is far from clear-cut—a fact most researchers overlook. "Complexity never sells," says Miczek. "A simple line is easier."

Nor do researchers know how many other neurotransmitters may be involved. Ferris, for instance, has found that aggression in his golden hamsters rises with increasing levels of another messenger, vasopressin, in a part of the hypothalamus. A study of 26 people with antisocial disorder that Ferris published with Coccaro in 1998 also found that higher levels of a vasopressin metabolite in their CSF correlated with a more aggressive past.

Findings have led to similar confusion on the genetic front. Twin and adoption studies strongly suggest that violent behavior does have at least some genetic component; one dramatic example is a 1993 study of a Dutch family, some of whose male members engaged in all kinds of violence, from arson to attempted rape. Researchers traced their rages back to a very rare defect in the gene encoding an enzyme called MAOA, which breaks down neurotransmitters.

In mice, researchers have pinpointed at least 15 genes (including the mouse version of MAOA) that seem to either heighten or reduce aggression. Some of their findings were published in high-profile journals and were hailed by the press as "aggression genes"—yet most researchers warn not to make too much of them. Several of the genes were identified after they had been knocked out in a popular lab mouse strain called 129, says Miczek. But that strain is known to be unusually pacific, he says, so any increase in aggression looks quite dramatic. However, the knockouts are sweethearts compared to some other lab strains or wild mice, he says, which begs the question of how relevant these genes are. Moreover, knockout studies can be misleading, warns Maxson; if, for example, a researcher disrupted a mouse's sense of smell, they'd also wreck its ability to communicate through pheromones, making it prone to end up in fights. That, however, wouldn't mean the researcher had found an "aggression gene."



No trespassing. A male Syrian golden hamster attacks an intruder.

CREDIT: CRAIG FERRIS

Yet the mouse knockouts tantalize some researchers studying humans. In 1995, Randy Nelson of Johns Hopkins University in Baltimore reported in *Nature* that mice lacking the gene for nitrous oxide synthase (NOS), an enzyme that produces the gaseous neurotransmitter NO, are more aggressive than wild-type mice. Recently, he says, he was approached by researchers who want to check whether violent prison inmates have low levels of NOS, too. "It's an easy experiment," says Nelson. But he says he's leery of doing the study, because he's not sure how NOS deficiency causes aggression and whether this happens in nature, too. Besides, the transgenic mice attack other mice from the back, says Nelson, reminiscent of how they catch a grasshopper; he wonders whether their aggression is a predatory behavior gone awry, which may have no human equivalent at all. "It's a very charged kind of thing," says Nelson. "You want to have a decent intellectual fabric behind it before you go to humans."

The prefrontal cortex story

Some researchers, meanwhile, wonder whether further animal studies are useful at all to understand human violence. "Animals don't rob banks, they don't rape people. They don't create the problems in society," says USC's Raine. "What's really holding us back is research in humans." Raine, who moved from Britain to Southern California in 1987—because, as he once wrote, "in addition to the good weather, there were plenty of murderers"—has another reason for sticking to humans: He believes violence is regulated in part by the prefrontal cortex, a brain area that's large in humans, but small in monkeys and minuscule in rodents. Researchers have suspected that this area plays an important role in controlling impulsive and violent behavior ever since the famous 19th century case of Phineas Gage, who changed from a kind, thoughtful man into a reckless brute after a horrible accident with an iron bar destroyed a large part of his prefrontal cortex.

In a 1997 positron emission tomography (PET) scan study of 41 incarcerated murderers and 41 controls, Raine found that glucose metabolism in the prefrontal cortex was diminished in the murderers—suggesting that the area didn't work properly. A few months ago, he published a study in the

Archives of General Psychiatry showing that in people with so-called antisocial personality disorder, of whom many had committed violent acts, the amount of gray matter was 11% less than in controls. But Raine has no idea how his results fit in with, say, the serotonin data. "We don't know," he says, "because nobody has looked at low serotonin and frontal functioning in the same study."

Coccaro, too, has found evidence that violent and impulsive people are not as good at several tasks thought to involve the frontal cortex. For instance, when given the option of choosing from different card decks, some of which promise higher returns but in the end cause losses, they keep picking from the dangerous decks, whereas normal people learn to avoid them. They also tend to fail to recognize certain facial expressions, such as anger or disgust. Coccaro now wants to have them perform the same tasks while observing their brain activity using functional magnetic resonance imaging. "The hypothesis would be that the activity is less in the orbitofrontal areas," he says. "But of course you never know what's going to light up until you put them in the scanner."

The promise and perils of treatment

The ultimate goal of much of this work—besides satisfying intellectual curiosity—is to develop treatments for violent people. For instance, if the prefrontal cortex is at fault, says Raine, one future way to intervene may be to implant chips that somehow make up for its reduced function. Already, he notes, some biomedical engineers have predicted that the first electronic brain implants will become a reality within the next decade. "Forty years ago, we were chopping off the frontal cortex in violent people. In 50 years' time, we'll be doing the opposite," Raine says. "We'll be doing reparative surgery." But others dismiss the idea out of hand. "At this point, I would call that science fiction," says Miczek. "We're dealing with very high-level processing, with circuits involved in making moral judgments. It's not a machine."

Instead, most researchers are thinking of specific drugs to treat aggression. Right now, such therapies don't exist; violent mental patients are usually treated with high doses of antipsychotics that act on a neurotransmitter called dopamine. Those drugs quell aggression but also cause what Ferris of UMass calls the "potted-plant syndrome"—they are heavily sedative and make patients lose interest in life. Ideally, a drug would inhibit aggression only, leaving other mental processes intact. Building on the serotonin evidence, several researchers have tried using so-called selective serotonin reuptake inhibitors, such as Prozac, which block serotonin's removal from the synapse. And although they did reduce aggression in human patients, they're still not as selective as researchers would like them to be. The new compounds acting on the 1B receptor are promising new candidates, says Miczek—although they too may turn out to have side effects.

But even if such selective aggression drugs were developed, there are difficult regulatory and ethical issues looming on the horizon. At the moment, aggressive or violent behavior is not a separate entry in the *Diagnostic and Statistic Manual IV*, the bible of psychiatry; rather, it's considered a symptom that can occur in several mental illnesses. As a rule, the U.S. Food and Drug Administration (FDA) approves drugs only for clearly specified disorders, not symptoms. There are exceptions, such as pain or fever, but those are well defined, says Thomas Laughren, team leader at FDA's Psychiatric Drug Products Group. How aggression should be defined is a matter of debate. "We need some kind of consensus in the clinical and academic community that it's a real thing," says Laughren, "and they have to define a reasonably homogeneous group of patients."

Indeed, this obstacle helped kill the only commercial program so far aimed at developing a class of aggression-reducing drugs, or "serenics." In the 1970s, a Dutch company called Duphar (now part of Solvay) started a program to develop a drug that would be used to treat aggression in various mentally ill patients, such as manic-depressives, schizophrenics, and Alzheimer's patients. After screening thousands of compounds in animals, a team led by Berend Olivier identified one promising candidate called eltoprazine that seemed to have few side effects. (They later discovered it mimicked serotonin's action on two receptors.)

The fur flies. Studying violence in rodents may yield clues to preventing human aggression.

CREDIT: J. M. KOOLHAAS/DEPT. OF ANIMAL PHYSIOLOGY

In a trial among retarded people, eltoprazine reduced aggression better than a placebo. "It was really quite a nice compound," says Olivier, now at a Connecticut company called Psychogenics, "and it would have been a good basis for further research." All along, the company was aware that the drug would be politically sensitive—Olivier even received PR training to deal with the media—but when it became clear that the FDA would not allow it onto the U.S. market, Solvay halted the entire program in the early '90s, says Olivier.

Another question is who would be treated with such drugs. Unlike most diseases, it's usually not the perpetrator who defines aggression as a problem, notes Laughren; it's the environment. Violent people may feel they are functioning normally, and some may even enjoy their occasional outbursts and resist treatment. Thus, the question would become who decides who needs the new drugs. "We would have to have a serious ethical debate about that," says Laughren.

Most researchers emphasize that they're not advocating drugging everybody who has ever committed a violent crime—or is deemed prone to do so. The most obvious patients, they say, are extremely violent people who are currently locked up in psychiatric wards and heavily sedated, or incarcerated in solitary confinement. But all agree that there will be a gray zone, and there may be a push to treat more and more people. Indeed, some have warned that violent incidents might be latched onto as a pretext for using drugs to pacify minorities. "The problem is that the public is going to say, 'Why don't you give this to the disenfranchised part of society that's more violent because of their environment?' " says Ferris. "But we're not here to solve our social problems. That's a quagmire."

—MARTIN ENSERINK