

Sex and Violence

Using optical and genetic techniques, neuroscientists have identified an “on/off” switch for aggression in the brain

BY CHRISTOF KOCH



RECENTLY DEVELOPED powerful, yet also delicate and refined, genetic tools can invasively probe nervous systems of animals, far surpassing the safer but much cruder techniques that psychologists and cognitive neuroscientists use to observe the human brain. Now in a remarkable series of experiments, researchers have located a trigger for aggression in mice—providing us with fresh insights into the workings of our human consciousness.

You might object that mice and men are not the same and that studying the murine mind is different from studying the human mind. This fact is obviously true. Yet both *Mus musculus* and *Homo sapiens* are nature’s children, sharing much perceptual, cognitive and affective processing. The same process of relentless evolutionary selection has shaped both species—our last common ancestor was a mere 75 million years ago. The structure of their brains, and of their genomes, reflects this similarity. Indeed, only a neuro-anatomist can tell a rice grain–size piece of mouse cortex from the same chunk of human cortex. If you think of a mouse as a mere automaton, Google “world’s smartest mouse.” The top hit will be a YouTube video of Brain Storm, a cute brown mouse, running a complicated obstacle course—crossing an abyss on a rope; jumping through hoops; going up and down a seesaw, over a pencil, up a steep incline and down a ladder; and navigating around obstacles. It hesitates on occasion, sniffs the air but, once started, speedily completes the circuit.

The amazing finesse and utility of contemporary molecular biology techniques are illustrated in recent experiments dealing with sex and power—the twin themes around which much of popular culture, psychoanalysis and art is centered.

Aggression Neurons From Correlation to Causation

Our story starts in the hypothalamus,



an ancient region of the brain, conserved throughout mammalian evolution. In humans, it is about the size of an almond, housing a motley collection of sets of neurons. These cells regulate distinct bodily functions such as temperature, circadian rhythms, sleep, hunger, thirst, sex, anger, aggression and response to stress. Earlier work has showed that electrical stimulation of some of these sites provokes cats and rats to sudden bouts of rage and that the ventromedial hypothalamus (VMH) has some involvement in sexual behaviors. Yet the precise location of attack-promoting neurons, their mode of action, and the interplay between aggression and mating—normally two opposing forms of social interactions—had remained deeply mysterious.

Enter a team from the California Institute of Technology, under the leadership of neurobiologist David Anderson. In four steps, the seven scientists, spearheaded by postdoctoral fellow Dayu Lin (now at New York University’s Smilow Institute), nailed down the critical role of aggression neurons in the VMH. The setting was the home cage of an individually

housed, sexually experienced male mouse. When another mouse, either a male or a sexually receptive female, entered the cage, the resident male mouse usually attacked the former but mated with the latter. The scientists video recorded the behavior so that the detailed time course of interaction of every pair of animals—the cautious sniffing and retreating, the pushing, shoving and biting, the mounting and consummatory activities—in hundreds of encounters could be statistically analyzed and time-aligned using software developed by machine vision engineers Piotr Dollar and Pietro Perona.

The first experiment is a molecular biology version of brain imaging. By detecting the presence of c-fos, a protein that is rapidly synthesized following neuronal activity, researchers can identify nerve cells that are involved in some behavior. Unlike functional MRI, which visualizes “voxels” of active gray matter containing upward of one million neurons, this method homes in on individual cells. A subset of neurons within the VMH, termed the ventrolateral region of the VMH (VMH-*vl*), became active following male-male

CHRISTOF KOCH (Koch); CREDIT (directional)

(The illuminated male **indiscriminately attacked** other mice, sometimes even a blown-up latex glove.)

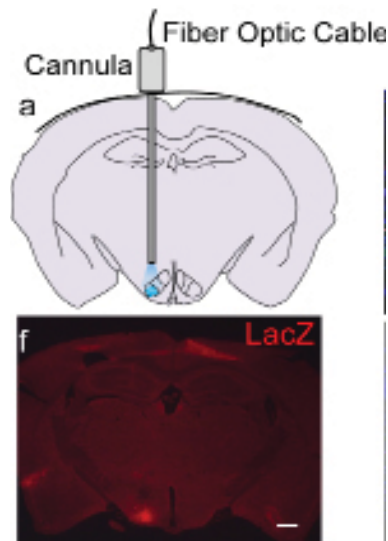
encounters that ended up in fights. Similar results occurred in males mating with females. But were these neurons the same or different cells? With help from collaborators at the Allen Institute for Brain Science in Seattle, the team applied a variant of the *c-fos* method that distinguishes the neurons activated in two different, successive behavioral encounters. These results indicated that, surprisingly, many brain regions surveyed contained separate but intermingled populations of neurons activated during fighting versus mating, with only a small degree (about 20 percent) of overlap.

Now that the biologists had identified one site—out of many—housing neurons that activated selectively for social encounters, they listened in on the goings-on by placing very fine electrodes in proximity. Silent when the mouse is solitary, these cells' activity level progressively increased as a male intruder entered the cage and the resident mouse attacked. More puzzling was the observation that some neurons were also active, albeit only transiently, in the initial exploratory phases of mating with a female. Conversely, many of the cells signaling during fighting were actively suppressed during mating, indicating an inherent opposition between aggression and sex. To paraphrase the 1960s slogan: you either make love or war, but not both.

So far these experiments have revealed interesting correlations between neuronal activity and behavior (fighting). But what role does VMHvl play in aggression? Are its neurons the cause of fighting?

Marrying Light and Genes

Anderson and his team are masters at exploiting a remarkable technique known as optogenetics [see “Playing the Body Electric,” *Consciousness Redux*; March/April 2010] to stimulate hundreds to perhaps thousands of cells in the VMHvl, out of the 40 million cells of the mouse brain. Scientists injected into the VMHvl



Aggression trigger: neurons in the hypothalamus at the bottom of the brain (bright red) are targeted by blue light. The photons trigger excitation in neurons that causes the animal to attack other mice.

on one side of the animal stunted viruses carrying a modified piece of DNA engineered to encode a photosensitive ion channel selective to blue light. Because it is dark in the catacombs of the brain, enlightenment comes from a tiny optical fiber snaking its way through the tissue. Expressed in the membrane separating the cell from the outside, the neuron responded to blue light with excitation. Every pulse of light reliably triggered one or more electrical pulses in the infected neuron. Once the animals recovered, little difference was apparent in their behavior alone or when interacting with another.

Stimulating the VMHvl when the mouse was by itself did not do anything. Yet in the presence of another animal, the mouse initiated a concerted attack, often by biting the back of the intruder. Unusually for this species, the illuminated male indiscriminately attacked female, cas-

trated male or anesthetized mice—and sometimes even a blown-up latex glove. Aggression ceased once the light stopped. The infection and light delivery had to be targeted to the VMHvl nucleus; stimulating a nearby region **S** did not produce such an effect. It is a striking and immediate demonstration of the link between neurons and behavior. Exciting VMHvl neurons causes aggression.

Finally, Anderson and his team turned to the question of whether the VMHvl cells are necessary for aggression to occur. Using a different technique, they genetically “silenced” VMHvl cells, turning them effectively off for days at a time. This silencing significantly reduced the chances of an aggressive encounter and lengthened the time it took to initiate an attack.

Of course, we do not know what the infected rodent experiences in its murine mind when light beams illuminate its hypothalamic attack center. But its behavior is fully compatible with the idea that its sudden violence is accompanied by a bout of petulant anger directed at anything nearby, including helpless victims that pose no threat. Some readers may not be strangers to such “irrational” impulsive feelings welling up. But fortunately, most of us can control our anger, not lashing out at our screaming boss, possibly by inhibiting our hypothalamus via descending fibers from the prefrontal cortex. It is not unreasonable to hope that researchers can investigate the neuronal basis of such anger management in the mouse in the near future.

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(Further Reading)

- ◆ **Functional Identification of an Aggression Locus in the Mouse Hypothalamus.** Dayu Lin, Maureen P. Boyle, Piotr Dollar, Hyosang Lee, E. S. Lein, Pietro Perona and David J. Anderson in *Nature*, Vol. 470, pages 221–226; February 10, 2011.