

# BROKEN SYMMETRY

THE FACT THAT THE TWO SIDES OF MANY ANIMALS' BRAINS ARE NOT MIRROR IMAGES—PARTICULARLY IN HUMANS—MAY ULTIMATELY HELP TO EXPLAIN THE DIFFERENCES IN BEHAVIOR BETWEEN SPECIES AND EVEN AMONG INDIVIDUALS.

BY RICHARD SALTUS

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PROJECT DUE FRIDAY

$$A^2 + 2B + C = X$$

MASHA'S PARTY SATURDAY NIGHT

MOM'S BIRTHDAY  
MAY 20

BAND PRACTICE  
TUESDAY NIGHT





Human  
beings  
see order,  
beauty, and  
perfection in  
symmetry—  
witness  
the  
popularity  
of the  
balanced  
geometric  
patterns  
of Amish  
quilts and  
oriental rugs.

Our eyes and brains are innately attuned to symmetry and deviations from it, even in other humans. “People will pick out the most perfectly symmetrical (computer-generated) faces as the most attractive,”

notes HHMI investigator Oliver Hobert, a neuroscientist at Columbia University.

In some important circumstances, however, *asymmetry* rules. Hobert, a fan of the intricate, repeating, and symmetrical geometries of Islamic art and architecture, focuses his research on the asymmetrical nature of the brain. Outwardly, it appears to be made up of a matched pair of gray, wrinkled hemispheres. But on closer inspection, certain brain regions have broken symmetry in terms of shape, structure, size, or function. The two sides of the human brain differ most radically in the way they process information. In effect, the two hemispheres “think” in contrasting ways. The left side controls speech and language processing, math, and logical thought, while the right hemisphere deals in spatial and face recognition, emotional control, and artistic abilities.

Fossil evidence suggests that left-brain, right-brain differences began showing up in the expanding brains of prehuman hominids around 2 million years ago. Present-day nonhuman primates also show brain asymmetries, though they are less pronounced than in humans. Asymmetric brain structures are probably widespread and have been discovered in creatures as varied as chickens, toads, fish, bees, and worms, including the roundworm *Caenorhabditis elegans*.

The first discoveries of functions localized in different hemispheres of the human brain came about 150 years ago, when speech and language were traced to left-hemisphere locations that weren’t duplicated in the right half. Since then,

many other specialized functions have been traced to one hemisphere or the other, and the field has lately been given fresh impetus with tools such as confocal microscopy, novel animal models, techniques for tagging cells with antibodies and fluorescent proteins, and large-scale gene-expression analyses.

#### **Molecular Tug of War**

Breaking symmetry involves some very complex biology in the course of embryonic development. Starting out as a ball of identical cells, the embryo divides along axes—head and tail, front and back, left and right sides. Initially, the cells on the two sides of the brain are identical, but they differentiate in response to genetic signals. The question is not only how they become different from each other, but what determines whether a cell is “left” or “right?”

Fortunately for neuroscientists, brain asymmetries have been identified in two of the simple, well-understood model organisms routinely used in developmental studies—the nematode *C. elegans* and the striped, minnow-like zebrafish. (The geneticist’s favorite model, the fruit fly, has not been of much use here as not many asymmetries have been found in its brain.)

“Our goal is to use zebrafish to look at asymmetries to see how they are generated, from genes through circuitry to behavior,” says Stephen Wilson, professor of developmental genetics at University College London. The zebrafish has a number of convenient qualities, including a small but “conspicuous” brain asymmetry and the fact that its embryos are transparent, says Miguel L. Concha, an





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OLIVER HOBERT

So how does this unbalanced brain affect the fish’s behavior? Wilson, Concha, and others believe the neural asymmetry makes it possible for the animal’s two eyes to have different, specialized functions. It was previously known that one eye scans the environment for novel stimuli such as predators, while the other pays attention to other zebrafish. Wilson’s group found that when a zebrafish is trained to look into a mirror, it tends to use the same eye. Then they created mutants with reversed brain asymmetries—and the eye preferences were reversed as well. While this doesn’t clinch the case, it is strong evidence supporting the structure–behavior connection. Moreover, it looks as if the lateral assignment of the functions is the same in all members of the species—a kind of organized behavioral specialization with survival implications.

**Competing Sides**

In a similar quest, Hobert has turned to an even simpler model—*C. elegans*, the roundworm with a primitive nervous system made up of just 302 cells. This little worm has evolved a slight asymmetry to sharpen its detection of food-related chemical cues in the environment. In the *C. elegans* embryo, certain chemosensory nerve cells, called ASE neurons, are initially identical. By the time the worm has hatched, however, cells on the left side (ASEL) of the head region have expressed receptors that are sensitive to certain chemicals, while the neurons on the right (ASER) are tuned to different compounds.

“What that means is that asymmetry is derived,” says Hobert, and it raises the question: how does “same” become “different?”

After generating hundreds of thousands of mutant *C. elegans*, Hobert and his colleagues discovered variants that lacked the asymmetry. These mutants had either left-sided neurons or right-sided neurons but not both, as in normal worms. These clues led the scientists to identify several molecular regulators that normally decide the fate of some ASE neurons to be “left” and others to be “right.” In principle, it’s much like the competitive process that Concha found in the zebrafish.

One of the decisive molecules turned out to be a micro-RNA—a small, single-stranded RNA with a gene-silencing function similar to the one performed by RNA interference. This molecule, dubbed *Isy-6*, is expressed only in the left-sided ASE neurons. It represses “right-sided” gene activity, which ordinarily would be the default case, thereby allowing left-orientation gene programs to do their work. In certain *C. elegans* mutants, *Isy-6* is knocked out; as a result, right orientation is “de-repressed” so that all ASE neurons are right-sided.

As with the zebrafish research, Hobert can’t quite follow the trail to identify the first signal in the embryo that triggers asymmetrical nerve-cell fates. But the worm findings have put on the table a mechanism that, like the processes being uncovered in the zebrafish, may be a general method adopted by higher animals.

“The discovery that there are asymmetries in invertebrate nervous systems is in itself exciting, and I predict that insights gained from these studies (i.e., of *C. elegans*) will be very relevant to the human story, although with some very major differences,” says David C. Van Essen, a brain researcher at Washington University and a member of the HHMI Scientific Review Board. Van Essen notes that his colleagues have used functional MRI to reveal previously unknown nerve networks in human brains that allow the two hemispheres to communicate with each other more closely than had been thought. These findings fit with previous



**CHOOSING SIDES** Through a clever use of asymmetry, the roundworm *C. elegans* makes an odor-sniffing nerve cell do double duty. The AWC neuron takes two slightly different forms—AWC-ON and AWC-OFF, tuned for different scents—randomly destined for opposite sides of the worm. ✱ But since the scent-sensors can end up on either side, how does nature ensure there will always be one of each type? HHMI investigator Cornelia Bargmann at The Rockefeller University has discovered that the developing AWC cells choose up sides in a brief “chat” via cellular channels called gap junctions that form in the embryo—then vanish when their job is done. — R.S.





**Oliver Hobert**, Columbia University; **Miguel Concha**, University of Chile; and **Christopher Walsh**, Harvard Medical School, are making early inroads into the origins of asymmetry in the brain.

observations that the opposite side of the brain can often compensate when an important, localized function like speech is lost through a stroke or disease.

### Right-Left Genes in Human Brains

In the early 1860s, French physician Paul Broca found that a man who had become almost speechless after infection with syphilis had damage in a part of the left hemisphere now known as “Broca’s area.” Broca inferred, from this and other brain studies, that this left-brain structure controlled speech, as damage in the corresponding area of the right hemisphere did not affect speaking ability. This finding was the first strong evidence of lateralization of brain functions in human beings.

One hundred fifty years later, scientists are beginning to understand what genetic programs guide asymmetry and lateralization. It’s a logical assumption that some genes are expressed differently in the right and left brains—as in the zebrafish and *C. elegans*—though studies of the brains of

human adults haven’t turned up any significant differences, according to Christopher A. Walsh, an HHMI investigator at Harvard Medical School and Beth Israel Deaconess Medical Center in Boston.

Reasoning that it might be more fruitful to hunt for differences in gene expression during development when asymmetries are being established, Walsh and his colleagues obtained fetal brain tissue from an NIH-funded repository. They analyzed and compared gene activity in tissue from the left hemisphere area where language centers form and tissue from the corresponding area of the right hemisphere.

The researchers reported in *Science* in 2005 that 27 genes (the group has since found 13 more) were differentially expressed in the left and right hemispheres, particularly in the perisylvian regions—those around a landmark structure called the Sylvian fissure—that are specialized in the left hemisphere for language.

The activity of one gene in particular, *Lmo4*, was markedly reduced in the tissue from the left-brain region. In the corresponding tissue from the right side, which

isn’t destined to have language functions, *Lmo4* was expressed at normal levels. How this asymmetric gene activity is related to language functions remains unknown, but Walsh views these findings as an important clue to a still-obscure mechanism for generating asymmetry in the human brain. At the same time, it will send researchers on a search for even earlier molecular signals that, as in the roundworm and the zebrafish, regulate the necessary imbalance in gene expression to begin with.

Such painstaking research efforts in organisms of varying complexity could explain relationships between brain asymmetries and behavior. Walsh predicts that much will be learned about how the diverse specialization within our complex, asymmetric brains distinguishes humans from all other animals. Further, the true understanding of asymmetry may help illuminate brain function not just in relation to species but also on the individual level. There is, after all, a unique interplay of left- and right-brain skills that governs each person’s perceptual tendencies and his or her way of being in the world. ■