ANATOMY & PHYSIOLOGY ONLINE COURSE - SESSION 8 – THE SENSES

Introduction - Illusions Reveal the Brain's Assumptions

We can recognize a friend instantly; full-face, in profile, or even by the back of his head. We can distinguish millions of shades of color, as well as 10,000 smells. We can feel a feather as it brushes our skin, hear the faint rustle of a leaf. It all seems so effortless: we open our eyes or ears and let the world stream in.

Yet anything we see, hear, feel, smell, or taste requires billions of nerve cells to flash urgent messages along cross-linked pathways and feedback loops in our brains, performing intricate calculations that scientists have only begun to decipher.

"You can think of sensory systems as little scientists that generate hypotheses about the world," says Anthony Movshon, an HHMI investigator at New York University. Where did that sound come from? What color is this, really? The brain makes an educated guess, based on the information at hand and on some simple assumptions.

We construct images unconsciously and very rapidly. Our brains are just as fertile when we use our other senses. In moments of anxiety, for instance, we sometimes hear things that are not really there. But suppose a leopard approached, half-hidden in the jungle; then our ability to make patterns out of incomplete sights, sounds, or smells could save our lives.

Sensing Change in the Environment

Everything we know about the world comes to us through our senses. Traditionally, we were thought to have just five of them: sight, hearing, touch, smell, and taste.

Scientists now recognize that we have several additional kinds of sensations, such as pain, pressure, temperature, joint position, muscle sense, and movement, but these are generally included under "touch." (The brain areas involved are called the "somatosensory" areas.)

Although we pay little attention to them, each of these senses is precious and almost irreplaceable; as we discover, to our sorrow, if we lose one. People usually fear blindness above all other disabilities. Yet deafness can be an even more severe handicap, especially in early life, when children learn language.

This is why Helen Keller's achievements were so extraordinary. As a result of an acute illness at the age of 19 months, she lost both vision and hearing and sank into a totally dark, silent universe. She was rescued from this terrible isolation by her teacher, Anne Sullivan, who managed to explain, by tapping signs into the little girl's palm, that things have names, that letters make up words, and that these can be used to express wants or ideas.

Helen Keller later grew into a writer (her autobiography, “The Story of My Life,” was published while she was still an undergraduate at Radcliffe College) and a well-known advocate for the handicapped. Her remarkable development owed a great deal to her determination, her teacher, and her family. But it also showed that when a sense (or two, in Helen Keller's case) is missing, another sense (in her case, touch) may be trained to make up for the loss, at least in part.

What we perceive through our senses is quite different from the physical characteristics of the stimuli around us. We cannot see light in the ultraviolet range, though bees can, and we cannot detect light in the infrared range, though rattlesnakes can. Our nervous system reacts only to a selected range of wavelengths, vibrations, or other properties. It is limited by our genes, as well as our previous experience and our current state of attention.

What draws our attention, in many cases, is change. Our senses are finely attuned to change. Stationary or unchanging objects become part of the scenery and are mostly unseen. Customary sounds become background noise, mostly unheard. The feel of a sweater against our skin is soon ignored. Our touch receptors, "so alert at first, so hungry for novelty, after a while say the electrical equivalent of 'Oh, that again,' and begin to doze, so we can get on with life," writes Diane Ackerman in “A Natural History of the Senses.”

If something in the environment changes, we need to take notice because it might mean danger; or opportunity. Suppose an insect lands on your leg. Instantly the touch receptors on the affected leg fire a message that travels through your spinal column and up to your brain. There it crosses into the opposite hemisphere (the right hemisphere of the brain controls the left side of the body, and vice versa) to alert brain cells at a particular spot on a sensory map of the body.

The brain's map of the body extends along a vertical strip of cerebral cortex near the center of the skull. The cortex; a large, deeply wrinkled sheet of neurons, or nerve cells, on the surface of the brain's two

hemispheres; governs all our sensations, movements, and thoughts.

The sensory map in humans was originally charted by the Canadian neurosurgeon Wilder Penfield in the 1930s. Before operating on patients who suffered from epilepsy, Penfield stimulated different parts of their brains with electrodes to locate the cells that set off their attacks. He could do this while the patients were awake, since the brain does not feel what is happening to it. In this way, Penfield soon learned exactly where each part of the body that was touched or moved was represented in the brain. He then showed it in his famous “homunculus”; cartoons of the somatosensory and motor areas.

Surprisingly, these maps do not accurately reflect the size of body parts but rather, their sensitivity. Arms and legs take up very little space, despite their length. The face and hands, which have greater sensitivity and complexity, are given more space; especially the tips of the fingers. Nevertheless, the signal that a mosquito has landed on the back of your left leg comes through loud and clear. In a fraction of a second, through a decision process that is not yet understood, this signal leads you to swat the insect at just the right place.

Vision, Hearing, and Smell: The Best-Known Senses

Ever since people have wondered about where their thoughts came from, they have tried to understand the human senses. Much was learned from observing the results of head injuries, as well as by dissecting postmortem human brains and the brains of animals.

In the 1930s and 1940s, scientists applied electrodes to the surface of the brain or placed them on the skull of humans to study "evoked responses," the changing rhythms of electrical signals in the brain in response to specific stimuli such as light or sound. Unfortunately, these signals from billions of brain cells proved almost impossible to unscramble.

When extremely thin microelectrodes became available in the late 1950s, researchers implanted them into the brains of living animals to spy on the activity of individual cells. Sharp popping sounds could be heard as specific neurons fired, and the scientists tried to find out what provoked these electrical discharges.

This is how David Hubel and Torsten Wiesel, who were then at Johns Hopkins University, began the groundbreaking experiments on the visual cortex of cats and monkeys for which they later won a Nobel prize.

They discovered that one neuron in the primary visual cortex at the back of a cat's brain might fire only when the animal's eye was exposed to a bright line at a particular location and angle, while another next to it would fire only in response to a line at a slightly different location and angle. No one had suspected that these neurons would dissect a scene; and respond to particular elements of it; with such amazing specificity. Hubel and Wiesel's success led to a general focus on the abilities of single neurons, especially in the visual system.

The past decade has seen an explosion of research on all the senses, partly because of the new tools supplied by molecular biology. Scientists can now focus ever more precisely on the work of sensory neurons, down to the level of specific genes and proteins within these neurons.

The visual system, whose activity involves roughly a quarter of the cells in the human cerebral cortex, has attracted more research than all the other sensory systems combined. It is also the most accessible of our senses.

The retina, a sheet of neurons at the back of the eye that any physician can see through an ophthalmoscope, is the only part of the brain that is visible from outside the skull. Research on the visual system has taught scientists much of what they know about the brain, and it remains at the forefront of progress in the neurosciences.

Research on hearing is also gathering momentum. One group of scientists recently discovered how receptor neurons in the ear; the so-called "hair cells"; respond to sounds. Another group explored how animals use sounds to compute an object's location in space. This may be a model of similar operations in the auditory system of humans.

The olfactory system, which was an almost total mystery until a few years ago, has become the source of much excitement. The receptor proteins that make the first contact with odorant molecules have been identified with the help of molecular genetics, and researchers are beginning to examine how information about smells is coded in the brain.

The use of molecular biology has enabled scientists to discover just how receptor neurons respond to light, to vibrations in the air, to odorant molecules, or to other stimuli.

The receptor neurons in each sensory system deal with different kinds of energy; electromagnetic, mechanical, or chemical. They look different from one another, and they exhibit different receptor proteins. But they all do the same job: converting a stimulus from the environment into an electrochemical nerve impulse, which is the common language of the brain.

More Than the Sum of Its Parts

From an understanding of this first step on the sensory pathway, researchers have edged up to analyzing how messages about a sensory stimulus travel through the brain to the cerebral cortex and how these messages are coded.

They know that nearly all sensory signals go first to a relay station in the thalamus, a central structure in the brain (named after the Greek word for "couch" because the cerebral hemispheres seem to rest comfortably on it). The messages then travel to primary sensory areas in the cortex (a different area for each sense). There they are modified and sent on to "higher" regions of the brain. Somewhere along the way, the brain figures out what the messages mean.

Many factors enter into this interpretation, including what signals are coming in from other parts of the brain, prior learning, overall goals, and general state of arousal.

Going in the opposite direction, signals from a sensory area may help other parts of the brain maintain arousal, form an image of where the body is in space, or regulate movement.

These interactions are so complex that focusing on the activity of single neurons; or even single pathways; is clearly not enough. Researchers are now asking what the central nervous system does with all the information it gets from its various pathways.

In more authoritarian times, scientists believed that the brain had a strictly hierarchical organization. Each relay station was supposed to send increasingly complex information to a higher level until it reached the very top, where everything would somehow be put together.

Instead of viewing the cortex as a rigid machine, scientists see it as "a dynamic pattern-processor and categorizer" that recognizes which categories go together with a particular stimulus, as best it can, every step of the way, according to Sejnowski. "There is no 'grandmother cell' at the top that responds specifically to an image of Grandma," he emphasizes. "We recognize a face by how its features are put together in relation to one another."

Sejnowski, a leader in the new field of computational neuroscience, studies neural networks in which the interaction of many neurons produces surprisingly complex behavior. He recently designed a computer model of how such a network might learn to "see" the three-dimensional shape of objects just from their shading, without any other information about where the light came from. After being "trained" by being shown many examples of shaded shapes, the network made its own generalizations and found a way to determine the objects' curvature.

Vision and the other senses evolved "to help animals solve vital problems; for example, knowing where to flee," says Sejnowski. Large populations of sensory neurons shift and work together in the brain to make this possible. They enable us to see the world in a unified way. They link up with the motor systems that control our actions.

These neurons produce an output "that is more than the sum of its parts," Sejnowski says. Just how they do it is a question for the next century.

How Do We See Colors?

Jeremy Nathans spent much of the past 17 years focusing on just one aspect of vision: how we see colors. "If a bright red beach ball comes whirling toward you, you see its color, shape, and motion all at once; but your brain deals with each of these characteristics separately," he explains. Neurons are relatively slow computing machines, says Nathans, an HHMI investigator at the Johns Hopkins University School of Medicine. "They take several milliseconds to go from input to output. Yet you see things in a fraction of a second; time for no more than 100 serial steps. This is why the system needs parallel processing."

Nathans became interested in how we see in color the day he heard of new discoveries about how we see in black and white. It was 1980, and he was a student at Stanford Medical School, he recalls, when Lubert Stryer and Denis Baylor, both of Stanford, described their remarkable findings about the workings of rod cells. Rod cells; one of two kinds of photoreceptor cells in the retina; enable us to see by the muted starlight of a hazy night. "Baylor showed that rod cells achieve the ultimate in light sensitivity;that they can respond to a single photon, or particle of light," says Nathans. "It was a beautiful experiment." (Baylor's work was done in

collaboration with Trevor Lamb and King-Wai Yau.)

Then Stryer explained how rhodopsin, the light-sensitive receptor protein in the disk membranes of rod cells, announces the arrival of this tiny pulse of light to the signaling machinery inside the cell. Stryer had found that rhodopsin could do this only with the help of an intermediary, called a G-protein, which belonged to a family of proteins that was already known to biochemists from their study of how cells respond to hormones and growth factors.

Nathans immediately realized this meant that the structure of rhodopsin itself might be similar to that of receptors for hormones. His mind began racing with possibilities. "And I ran; literally ran; to the library and started reading about vision," he says.

Until then, Nathans had been studying the genetics of fruit flies. But as he read a paper by Harvard University biologist George Wald; a transcript of Wald's 1967 Nobel prize lecture on "The Molecular Basis of Visual Excitation"; Nathans set off on a different course. He determined to do what Wald himself had wished to do 40 years earlier: find the receptor proteins in the retina that respond to color.

Rod cells function only in dim light and are blind to color. "Get up on a dark moonlit night and look around," suggests David Hubel of Harvard Medical School, a winner of the Nobel prize for his research on vision. "Although you can see shapes fairly well, colors are completely absent. It is remarkable how few people realize that they do without color vision in dim light."

But the human retina also contains another kind of photoreceptor cell: the cones, which operate in bright light and are responsible for high acuity vision, as well as color.

Rods and cones form an uneven mosaic within the retina, with rods generally outnumbering cones more than 10 to 1; except in the retina's center, or fovea. The cones are highly concentrated in the fovea, an area that Nathans calls "the most valuable square millimeter of tissue in the body."

Even though the fovea is essential for fine vision, it is less sensitive to light than the surrounding retina. Thus, if we wish to detect a faint star at night, we must gaze slightly to the side of the star in order to project its image onto the more sensitive rods, as the star casts insufficient light to trigger a cone into action.

Red, Green, and Blue Cones

In bright light, then, when the cones are active, how do we perceive colors?

Nathans' ambitious plan to isolate the genes that coded for the three color receptor proteins depended on Wald's view that the genes all evolved from the same primordial ancestor.

The only visual receptor protein that had been studied with any intensity at that time was bovine rhodopsin; from the rod cells of cows' eyes. Scientists had purified bovine rhodopsin and deduced the sequence of a fragment of the DNA that coded for it. Nathans used this information to construct a lure; a single strand of DNA; with which he fished out the complete gene for bovine rhodopsin from a sea of bovine DNA.

Next he used part of this bovine gene as a lure to catch the gene for human rhodopsin from the jumble of DNA in a human cell. This took less than a year "because the genes for human and bovine rhodopsin are virtually identical, despite an evolutionary distance of 200 million years between cattle and humans," Nathans says.

Finding the human genes for the color receptors proved more challenging, however, since these genes are less closely related to the gene for rhodopsin.

Nathans began to sift through DNA from his own cells. "I figured I'd be an unlimited source of DNA as long as I kept eating," he says. Eventually he fished out some pieces of DNA that belonged to three different genes, each of them clearly related to the rhodopsin gene.

"This coincidence; three genes, three types of cones; didn't escape our notice," he said. Furthermore, two of these genes were on the X chromosome; "exactly what one would expect," says Nathans, "since defects in red and green color vision are X-linked."

By experimenting with prisms as early as 1672, Isaac Newton made the fundamental discovery that ordinary "white" light is really a mixture of lights of many different wavelengths, as seen in a rainbow.

Objects appear to be a particular color because they reflect some wavelengths more than others. A

red apple is red because it reflects rays from the red end of the spectrum and absorbs rays from the blue end. A blueberry, on the other hand, reflects the blue end of the spectrum and absorbs the red.

Thinking about Newton's discovery in 1802, the physician Thomas Young, who later helped decipher the hieroglyphics of the Rosetta Stone, concluded that the retina could not possibly have a different receptor for each of these wavelengths, which span the entire continuum of colors from violet to red. Instead, he proposed that colors were perceived by a three-color code.

As artists knew well, any color of the spectrum (except white) could be matched by judicious mixing of just three colors of paint. Young suggested that this was not an intrinsic property of light, but arose from the combined activity of three different "particles" in the retina, each sensitive to different wavelengths.

We now know that color vision actually depends on the interaction of three types of cones; one especially sensitive to red light, another to green light, and a third to blue light. In 1964, George Wald and Paul Brown at Harvard and Edward MacNichol and William Marks at Johns Hopkins showed that each human cone cell absorbs light in only one of these three sectors of the spectrum.

Wald went on to propose that the receptor proteins in all these cones were built on the same plan as rhodopsin. Each protein uses retinal, a derivative of vitamin A, to absorb light; and each tunes the retinal to absorb a different range of wavelengths.

Wald believed that the three receptor proteins in cones probably evolved from the same primordial gene;and so did rhodopsin. They were all "variations on a central theme," Wald wrote in his Nobel lecture.

This evolutionary message was music to Nathans' ears. It meant that if the gene encoding only one receptor protein could be located, the genes encoding the other receptor proteins could be found by the similarity of the sequence of bases in their DNA.

"I realized while reading Wald's lecture," says Nathans, "that Wald had laid out the whole problem of the genetic basis of color vision, and that this problem was now solvable, completely solvable, by molecular genetic methods." Wald had taken the problem as far as he could, Nathans pointed out. "But lacking these molecular methods, he couldn't go any further."

Color Blindness: More Prevalent Among Males

Some 10 million American men; fully 7 percent of the male population; either cannot distinguish red from green, or see red and green differently from most people. This is the commonest form of color blindness, but it affects only .4 percent of women. The fact that color blindness is so much more prevalent among men implies that, like hemophilia, it is carried on the X chromosome, of which men have only one copy. (As in hemophilia, women are protected because they have two X chromosomes; a normal gene on one chromosome can often make up for a defective gene on the other.)

Wald and others had found that in color-blind men, the green or red cones worked improperly or not at all. Wald suggested that the genes for the red and green receptors were altered in these men. He also thought that these genes must lie near each other on the X chromosome. This tandem arrangement; which Nathans confirmed; probably results from the duplication of a DNA fragment in primates that occurred some 40 million years ago.

The primates of South America, which broke from the continent of Africa at about that time, possess only a single functional copy of a red or green gene, much like color-blind men. But in Old World primates; the monkeys and apes of Africa and the ancestors of humans; a primordial red-green gene must have duplicated and then diverged slightly in sequence, leading to separate receptors of the red and green type.

In keeping with this picture, Nathans found that the DNA sequences of the genes for red and green receptors differ by only 2 percent; evidence of their common origin and recent divergence.

Nathans himself is not color-blind. Before using his own DNA, he thoroughly tested his color vision to ensure that it was normal. Nevertheless, one of his initial findings presented a puzzle: Lying head to tail along his X chromosome were not just the two genes for the red and green receptors, but also an extra copy of the green receptor gene.

Here was the explanation for the prevalence of color blindness, he realized. Because the DNA sequences of the red and green receptor genes are so similar, and because they lie head to tail, it is easy for mistakes to occur during the development of egg and sperm, as genetic material is replicated and exchanged between chromosomes.

One X chromosome; like Nathans'; may receive an extra green receptor gene, for instance, or maybe even two. This does no harm. But then the other chromosome with which it is exchanging bits of genetic information is left with only a red receptor gene. The man who inherits this slightly truncated chromosome will be color-blind, bereft of the genetic information needed to make a green receptor.

More than 95 percent of all variations in human color vision involve the red and green receptors in men's eyes. It is very rare for anyone; male or female; to be "blind" to the blue end of the spectrum. Nathans provided a genetic explanation for this phenomenon. He showed that the gene coding for the blue receptor lies on chromosome 7, which is shared equally by men and women, and that this gene does not have any neighbor whose DNA sequence is similar. Blue color blindness is caused by a simple mutation in this gene.

Judging a Color

Seeing a color involves making comparisons. "All that a single cone can do is capture light and tell you something about its intensity," Nathans points out; "it tells you nothing about color."

To see any color, the brain must compare the input from different kinds of cone cells; and then make many other comparisons as well.

The lightning-fast work of judging a color begins in the retina, which has three layers of cells. Signals from the red and green cones in the first layer are compared by specialized red-green "opponent" cells in the second layer. These opponent cells compute the balance between red and green light coming from a particular part of the visual field. Other opponent cells then compare signals from blue cones with the combined signals from red and green cones.

On a broader scale, comparisons of neighboring portions of an image lead to our amazing ability to see colors as constants in an ever-changing world.

Nathans vividly remembers demonstrations of this "color constancy" by the late Edwin Land, the inventor of instant photography and founder of the Polaroid Corporation. Land and his colleagues had made a large collage of multi-colored geometric shapes, called a "Mondrian" after its resemblance to the works of the Dutch painter Piet Mondrian. They used three projectors that beamed light matching the wavelength-sensitivity of the three human cone types. With these projectors, the exact wavelength composition reflected from any given patch on the Mondrian could be exactly controlled.

"Land pointed out a patch on the Mondrian that looked orange in the context of the surrounding colors," Nathans recalls. "Then he gave me a tube, like the tube inside a paper towel roll, and had me look at this patch in isolation. And it wasn't orange anymore. It was a perfect red."

The patch was in fact painted orange, but Land had beamed a high-intensity long-wave light from the red end of the spectrum on it so that it reflected a high proportion of red light. Under normal viewing conditions, however; when the patch was surrounded by other Mondrian colors; Nathans still saw the orange figure by its true color.

Somehow, by comparing a patch of color to the surrounding colored region, the brain is able to discount the wavelength of the illuminating light and reconstruct the patch's real daylight color.

"Color constancy is the most important property of the color system," declares neurobiologist Semir Zeki of University College, London. Color would be a poor way of labeling objects if the perceived colors kept shifting under different conditions, he points out. But the eye is not a camera. Instead, the eye-brain pathway constitutes a kind of computer; vastly more complex and powerful than any that human engineers have built; designed to construct a stable visual representation of reality.

The key to color constancy is that we do not determine the color of an object in isolation; rather, the object's color derives from a comparison of the wavelengths reflected from the object and its surround. In the rosy light of dawn, for instance, a yellow lemon will reflect more long-wave light and therefore might appear orange; but its surrounding leaves also reflect more long-wave light. The brain compares the two and cancels out the increases.

Land's "Retinex" theory of color vision; a mathematical model of this comparison process; left open the question of where in the pathway between retina and cortex color constancy was achieved. This issue could only be addressed by studying the brain itself.

Working with anesthetized monkeys in the 1960s, David Hubel and Torsten Wiesel of Harvard Medical School had shown that the primary visual cortex (V1), a credit-card-sized region at the back of the

brain, possesses a highly organized system of neurons for analyzing the orientation of an object's outlines. But in their early studies they found few signs of color-sensitive cells. Then in 1973, Semir Zeki identified a separate area called V4, which was full of cells that crackled with activity when exposed to different colors.

A few years later, Edwin Land paid Zeki a visit in London. "He showed me his demonstration, and I was much taken by that," Zeki says. "I was converted, in fact. So I used his Mondrian display to study the single cells in area V4."

In this way, Zeki discovered that some of the cells in area V4 consistently respond to the actual surface color of a Mondrian patch, regardless of the lighting conditions. He believes these are the cells that perform color constancy.

More recently, with the aid of PET scans, Zeki found an area similar in location to the monkeys' V4 that is specifically activated in humans when they look at Mondrian color displays. The color displays also stimulate the primary visual area and an area that is adjacent to it, V2.

Much controversy exists about all aspects of the color pathway beyond the retina, however. Researchers disagree about the exact role of cells in human V1 and V2, about the importance of V4, about the similarities between monkey and human brains.

To resolve such issues, scientists await the results of further experiments on humans. The new, noninvasive brain-imaging techniques that can show the brain at work, may supply key answers. Within a few years, researchers hope, these techniques will reveal the precise paths of the neural messages that make it possible for us to see the wealth of colors around us.

The Strange Symptoms of Blindness to Motion

The patient had great difficulty pouring coffee into a cup. She could clearly see the cup's shape, color, and position on the table, she told her doctor. She was able to pour the coffee from the pot. But the column of fluid flowing from the spout appeared frozen, like a waterfall turned to ice. She could not see its motion. So the coffee would rise in the cup and spill over the sides. More dangerous problems arose when she went outdoors. She could not cross a street, for instance, because the motion of cars was invisible to her: a car was up the street and then upon her, without ever seeming to occupy the intervening space. Even people milling through a room made her feel very uneasy, she complained to Josef Zihl, a neuropsychologist who saw her at the Max Planck Institute for Psychiatry in Munich, Germany, in 1980, because "the people were suddenly here or there but I did not see them moving." The woman's rare motion blindness resulted from a stroke that damaged selected areas of her brain.

What she lost; the ability to see objects move through space; is a key aspect of vision. In animals, this ability is crucial to survival: Both predators and their prey depend upon being able to detect motion rapidly. In fact, frogs and some other simple vertebrates may not even see an object unless it is moving. If a dead fly on a string is dangled motionlessly in front of a starving frog, the frog cannot sense this winged meal. The "bug-detecting" cells in its retina are wired to respond only to movement. The frog might starve to death, tongue firmly folded in its mouth, unaware that salvation lies suspended on a string in front of its eyes.

While the retina of frogs can detect movement, the retina of humans and other primates cannot. "The dumber the animal, the smarter its retina," observes Denis Baylor of Stanford Medical School. The large, versatile brain of humans takes over the job, analyzing motion through a highly specialized pathway of neural connections.

This is the pathway that was damaged in the motion-blind patient from Munich. Compared to the complex ensemble of regions in the visual cortex that are devoted to perceiving color and form, this motion-perception pathway seems relatively streamlined and simple. More than any other part of the cortex, it has yielded to efforts to unveil "the precise relationship between perception and the activity of a sensory neuron somewhere in the brain," says Anthony Movshon, an HHMI investigator at New York University.

Consider what happens when we watch a movie, suggests Thomas Albright of the Salk Institute. Each of the 24 frames projected per second on the theater screen is a still photograph; nothing in a movie truly moves. The illusion of movement is created by the motion-processing system, which automatically fuses, for instance, the images of legs that shift position slightly from frame to frame into the appearance of a walking actor. The Munich patient is unable to perform this fusion. In life or in the movie theater, she sees the world as a series of stills.

"The motion system must match up image elements from frame to frame, over space and time," says Albright. "It has to detect which direction a hand is moving in, for instance, and not confuse that hand with a head when it waves in front of someone's face."

A Hot Spot in the Brain's Motion Pathway

Researchers have now traced the path of neural connections that make up the motion pathway and tested the responses of cells at different steps along this path.

Starting in the retina, large ganglion cells called magnocellular neurons, or M cells, are triggered into action when part of the image of a moving hand sweeps across their receptive field; the small area of the visual field to which each cell is sensitive. The M cells' impulses travel along the optic nerve to a relay station in the thalamus, near the middle of the brain, called the lateral geniculate nucleus. Then they flash to the middle layer of neurons in the primary visual cortex. There, by pooling together the inputs from many M cells, certain neurons gain a new property: they become sensitive to the direction in which the hand is moving across their window of vision. Such direction-sensitive cells were first discovered in the mammalian visual cortex by David Hubel and Torsten Wiesel, who projected moving bars of light across the receptive fields of cells in the primary visual cortex of anesthetized cats and monkeys. Electrodes very close to these cells picked up their response to different moving lines, and the pattern of activity could be heard as a crackling "pop-pop-pop" when the signals were amplified and fed into a loudspeaker.

The keystone of the motion pathway was discovered by Semir Zeki of University College, London, in an area of the cortex that lies just beyond the primary and secondary visual areas (V1 and V2), further from the back of the brain; a vast unexplored wilderness vaguely known as the “sensory association cortex.” "It was thought that somewhere in this mishmash of association cortex visual forms were recognized and associated with information from other senses, says John Allman of the California Institute of Technology. But studies in the owl monkey by Allman and Jon Kaas (who is now at Vanderbilt) and in the rhesus monkey by Semir Zeki revealed that the area was not a mishmash at all. Instead, much of it was made up of separate visual maps, each containing a distinct representation of the visual field. In 1971, Zeki showed that one of these visual maps was remarkably specialized. Though its cells did not respond to color or form, over 90 percent of them responded to movement in a particular direction. American scientists usually call this map MT (middle temporal area), but Zeki called it V5. He also nicknamed it "the motion area." "This very striking finding of this little hot spot, this little pocket, in which almost all the cells are sensitive for the direction of movement," says New York University's Anthony Movshon, was the impetus for many vision researchers to turn their attention to motion. Nowhere else in the visual cortex was there an area that seemed so functionally specialized.

The cells of this motion area, MT, are directly connected to the layer of direction-sensitive cells in the primary visual area, V1. And the two areas have a remarkably similar architecture. Hubel and Wiesel had discovered that V1 is organized into a series of columns. The cells in one column may fire only when shown lines oriented like an hour hand pointing to one o'clock, for instance, while the cells in the next column fire most readily to lines oriented at two o'clock, and so on around the dial. Amazingly, MT has the same kind of orientation system as V1, but in addition the cells in its columns respond preferentially to the direction of movement.

"When you see that an area, like V1 or MT, has this highly organized columnar structure," says Wiesel, "you get a sense of uncovering something fundamental about the way the cells in the visual area work."

Integrating Information About Movement

In perceiving motion, as in determining color, the brain constructs a view of the world from pieces of information that can themselves be mistaken or ambiguous.

Suppose you paint an X on a piece of paper and then move that paper up and down in front of someone's eyes. Direction-selective cells in the motion-pathway layer of V1; each of which sees only a small part of the scene; will respond to the diagonal orientation of each of the lines making up the X but will not register the movement of the X as a whole. How, then, is this overall movement sensed?

There must be two stages of motion analysis in the cortex, suggested Movshon and Edward Adelson, then a postdoctoral fellow at New York University (he is now a professor at the Massachusetts Institute of Technology). At the second stage, certain cells must integrate the signals regarding the orientation of moving lines and produce an overall signal about the motion of the whole object.

When Movshon presented this idea at an annual meeting of vision researchers in 1981, he was approached by William Newsome, an HHMI investigator at Stanford University, who was then a postdoctoral fellow at the National Institutes of Health. A lively three-hour dinner ensued and the two men resolved to collaborate. Together with Adelson, they would search for such cells in the motion area. The researchers soon found that one-third of MT's cells could, in fact, signal the direction in which a hand waves through space. Later on, Albright's research group showed that MT cells can detect "transparent" motion, such as a shadow sweeping across the ground. Then Allman and his colleagues discovered that many MT cells are able

to integrate motion information from a large swath of the scene. "Even though an MT cell may respond directly to just one spot in the visual field," says Allman, "the cells have knowledge of what's going on in the region surrounding them."

Using a computer display with a background texture that looks vaguely like a leafy forest, Allman showed that some MT cells will fire particularly furiously if the leafy background moves in a direction opposite to a moving object; the sort of visual pattern a cheetah would see when chasing an antelope along a stand of trees. If, however, the background moved in the same direction as the moving object, the cell's firing was suppressed. The cell acted as a large-scale detector of motion contrast, performing exactly the sort of operation an animal would need to sense a figure moving through the camouflage of the forest.

While MT cells do not respond to static forms and colors, Albright has found that they will detect a moving object much more easily if its form or color strongly contrasts with its background.

"Imagine you're looking down the concourse in Grand Central Station and you're supposed to find the woman in the red dress," says Albright. "There are hundreds of surrounding people moving in different directions. Yet there's no problem at all in detecting the woman in the red dress walking along. Your visual system uses the dress's color to filter out all the irrelevant noise around it and homes in on the moving object of interest."

Suppose scientists could record from the MT cells in a laboratory monkey looking at the woman in the red dress crossing Grand Central Station. They could determine that a particular cell fired when the woman in the red dress passed through its receptive field. But how would they know that the firing of this specific MT cell; and not a network of thousands of other cells in the brain, of which this cell is only one node; actually "causes" the monkey to perceive the woman's direction of movement? How could they ever get inside the monkey's mind and determine what it perceives?

Since Hubel and Wiesel's pioneering studies in the visual cortex, most visual scientists have assumed that the perception of form, color, depth, and motion corresponds to the firing of cells specialized to detect these visual qualities.

In a spectacular series of experiments conducted since the mid-1980s, Newsome, who is now a professor of neurobiology at Stanford University's School of Medicine, and his colleagues at Stanford have been directly testing this link between perception and the activity of specific neurons. They use a device that was developed in Movshon's laboratory at NYU: a blizzard of white dots moving on a computer monitor. When all the white dots are moving randomly, the display looks like a TV tuned to a nonbroadcasting channel. However, the experimenters can gradually raise the percentage of dots moving in the same direction. When 10 percent of the dots move coherently together, their motion becomes apparent. By 25 percent, it is unmistakable.

Movshon had found that whenever a human being could detect the dots' motion at all, he or she could also tell the direction in which the dots were moving. "This means that the part of the visual pathway carrying the information used for motion detection is also carrying a label that says what direction is being detected," says Movshon." This is precisely how one would expect MT, with its columns of direction-selective cells, to encode a moving target.

Next, Newsome began to teach rhesus monkeys to "tell" him what they saw on the computer screen. When they saw dots moving downward, for instance, the monkeys were supposed to move their eyes to a downward point on the screen. Correct answers were rewarded with fruit juice. Soon the monkeys could signal with eye movements that they saw the dots move in any of six directions around the clock. And after much training on low-percentage moving dot displays, the monkeys were able to perform nearly as well as Movshon's human subjects. Everything was in place. Newsome, Movshon, and their colleagues were ready to study the relationship between the monkeys' perception of motion and the activity of cells in particular columns of MT.

"We found, very much to our surprise," says Newsome, "that the average MT cell was as sensitive to the direction of motion as the monkey was." As more dots moved together and the monkey's ability to recognize their direction increased, so did the firing of the MT surveying the dots. If the monkeys were actually "listening" to the cells in a single MT column as they made their decision about the direction of movement of the dots on the screen, could the decision be altered by stimulating a different MT column, the researchers wondered. So they stimulated an MT "up" column electrically while the monkeys looked at the downward-moving display. This radically changed the monkeys' reports of what they saw.

"It was an unforgettable experience," remembers Newsome. "We got the first of what became known in the lab as 'Whoppers'; when the effects of microstimulation were just massive. Fifty percent of the dots would move down, and yet if we'd stimulate an 'up' column, the monkey would signal up with its eyes."

The monkeys' perceptual responses no longer seemed to be driven by the direction of dots on the screen. Instead, the animals' perceptual responses were being controlled by an electric stimulus applied to specific cells in the brain by an experimenter. These experiments, says Movshon, "close a loop between what the cells are doing and what the monkey's doing." Allman calls the finding "the most direct link that's yet been established between visual perception and the behavior of neurons in the visual cortex."

It is still possible, however, that when the dots are moving down and the experimenters stimulate an MT "up" column, the stimulation changes what the monkey "decides" without actually changing what it "sees." "This is a key question," says Newsome. "We now know a lot about the first and last stages of this process. But we are almost totally ignorant about the decision process out there in the middle; the mechanism that links sensory input to the appropriate motor output. How does the decision get made?" It is a burning question not only for research on the visual system, but for all of cognitive neuroscience, Newsome believes. The answer would provide a bridge from the study of the senses, where so much progress has been made, to the much more difficult study of human thought. At long last, Newsome says, "we're now poised to approach this question."

Signals From a Hair Cell

An unusual dance recital was videotaped in David Corey's lab at Massachusetts General Hospital recently. The star of the performance, magnified many times under a high-powered microscope, was a sound-receptor cell from the ear of a bullfrog, called a hair cell because of the distinctive tuft of fine bristles sprouting from its top.The music ranged from the opening bars of Beethoven's Fifth Symphony and Richard Strauss' "Thus Spake Zarathustra" to David Byrne and the Beatles.

As the music rose and fell, an electronic amplifier translated it into vibrations of a tiny glass probe that stimulated the hair cell, mimicking its normal stimulation in the ear. The bristly bundle of "stereocilia" at the top of the cell quivered to the high-pitched tones of violins, swayed to the rumblings of kettle drums, and bowed and recoiled, like tiny trees in a hurricane, to the blasts of rock-and-roll.

The dance of the hair cell's cilia plays a vital role in hearing, Corey explains. Now an HHMI investigator at MGH and Harvard Medical School, Corey was a graduate student at the California Institute of Technology when he began working with James Hudspeth, a leading authority on hair cells. Together, the two researchers have helped discover how movements of the cilia, which quiver with the mechanical vibrations of sound waves, cause the cell to produce a series of brief electrical signals that are conveyed to the brain as a burst of acoustic information.

In humans and other mammals, hair cell bundles are arranged in four long, parallel columns on a gauzy strip of tissue called the basilar membrane. This membrane, just over an inch long, coils within the cochlea, a bony, snail-shaped structure about the size of a pea that is located deep inside the inner ear.

Sound waves generated by mechanical forces, such as a bow being drawn across a string, water splashing on a hard surface, or air being expelled across the larynx, cause the eardrum; and, in turn, the three tiny bones of the middle ear; to vibrate. The last of these three bones (the stapes, or "stirrup") jiggles a flexible layer of tissue at the base of the cochlea. This pressure sends waves rippling along the basilar membrane, stimulating some of its hair cells.

These cells then send out a rapid-fire code of electrical signals about the frequency, intensity, and duration of a sound. The messages travel through auditory nerve fibers that run from the base of the hair cells to the center of the cochlea, and from there to the brain. After several relays within the brain, the messages finally reach the auditory areas of the cerebral cortex, which process and interpret these signals as a musical phrase, a dripping faucet, a human voice, or any of the myriad sounds in the world around us at any particular moment.

The Goal: Extreme Sensitivity and Speed

Because of the hair cell bundles' uncanny resemblance to little antennae and their location in the inner ear, the cells had long been suspected of playing an important role in hearing. This view was bolstered by clinical evidence that the majority of hearing impairments; which affect some 30 million Americans; involve damage to hair cells. There are only 16,000 hair cells in a human cochlea, compared to some 100 million photoreceptors in the retina of the eye, and they are extremely vulnerable. Life in a high-decibel society of pounding jackhammers, screeching subway cars, and heavy metal rock music can take a devastating toll on them. But whatever the cause; overexposure to loud noises, disease, heredity, or aging; people tend to lose 40 percent of their hair cells by the age of 65. And once destroyed, these cells do not regenerate.

"The mechanics of the hair cell are fascinating; the fact that simply pushing a little bundle of cilia magically allows us to hear. And the cells are beautiful. I never get tired of looking at them," says David Corey. Corey and James Hudspeth, an HHMI investigator at the Rockefeller University, have explored the

microscopic inner workings of hair cells in finer and finer detail over the past 20 years, gaining a solid understanding of how the cells work.

Some pieces of the puzzle have fallen into place recently with the discovery of a unique mechanism that endows hair cells with their two most distinctive properties; extreme sensitivity and extreme speed.

Protected deep inside the skull, hair cells cannot easily be studied in living creatures. Yet once they are removed from laboratory animals, these cells quickly die. Even now, Corey acknowledges, "a good experiment would be to study three or four cells for maybe 15 minutes each." Though such experiments are now routine in their labs, they remain tricky. The measurements are so delicate that they are usually carried out on a table mounted on air-cushioned legs, to reduce any external movements or vibrations; otherwise, the building's own vibration would deafen a hair cell in seconds.

Hudspeth found that an unused swimming pool built on bedrock in a basement at the University of California, San Francisco, where he worked previously, made the perfect laboratory for hair cell experiments; especially after he had it filled with 30 truckloads of concrete for more stability.

Hair cells from bullfrogs were exposed by removing the sacculus, a part of the inner ear, and pinning the pinhead-sized tissue to a microscope slide. Working under a microscope, Hudspeth and Corey were then able to manipulate an individual hair cell's bundle of cilia with a thin glass tube. They slipped the tube over the bundle's 50 to 60 stereocilia, which are arranged like a tepee on the top of each hair cell, and moved the tube back and forth, deflecting the bundle less than a ten thousandth of an inch. The hair cell's response was detected by a microelectrode inserted through the cell membrane.

Corey and Hudspeth found that the bundle of stereocilia operated like a light switch. When the bundle was prodded in one direction; from the shortest cilia to the tallest; it turned the cell on; when the bundle moved in the opposite direction, it turned the cell off.

Based on data from thousands of experiments in which they wiggled the bundle back and forth, the researchers calculated that hair cells are so sensitive that deflecting the tip of a bundle by the width of an atom is enough to make the cell respond. This infinitesimal movement, which might be caused by a very low, quiet sound at the threshold of hearing, is equivalent to displacing the top of the Eiffel Tower by only half an inch.

At the same time, the investigators reasoned that the hair cells' response had to be amazingly rapid. "In order to be able to process sounds at the highest frequency range of human hearing, hair cells must be able to turn current on and off 20,000 times per second. They are capable of even more astonishing speeds in bats and whales, which can distinguish sounds at frequencies as high as 200,000 cycles per second," says Hudspeth.

Photoreceptors in the eye are much slower, he points out. "The visual system is so slow that when you look at a movie at 24 frames per second, it seems continuous, without any flicker. Contrast 24 frames per second with 20,000 cycles per second. The auditory system is a thousand times faster."

Tip Links Pull Up the Gates of Ion Channels

Unlike other types of sensory receptor cells, hair cells do not rely on a cascade of chemical reactions to generate a signal. Photoreceptor cells in the eye, for instance, require a series of intricate interactions with a G protein and a second messenger before their ion channels close, sending a signal to the brain. This process would be much too slow to deal with sounds. Hair cells have to possess a mechanism that allows their ion channels to open and close more rapidly than those of any other sensory receptor cells. Therefore hair cells use something very much like a spring that opens their channels when the cilia bend, without the need for a time-consuming chemical exchange.

Corey and Hudspeth first theorized in the early 1980s that such a "gating spring" mechanism existed. They proposed that hair cells had a previously unknown type of ion channel; a channel directly activated by mechanical force. They also developed a biophysical theory to account for the hair cells' rapid response. But their theory didn't tell them where the channels were or what the spring was. By painstakingly measuring the electrical field around the cilia with an electrode, Hudspeth detected a tiny drop in voltage at the cilia's tips, as if the current were being sucked into a minute whirlpool. This led him to conclude that the channels through which charged particles move into the cell, changing its electrical potential, were located at the cilia's tips. He then reasoned that the gating springs that opened these channels should be there as well. The springs themselves were first observed in 1984, in electron microscope images taken by James Pickles and his colleagues in England. Called tip links, these minute filaments join each stereocilium to its tallest neighbor. Pickles pointed out that the geometry of the cilia bundle would cause the bundle to stretch the links when it was deflected in one direction and relax them when it was moved in the other. If the tip links were the hypothetical gating springs, it would

explain everything.

"This was a completely new kind of mechanism, unlike anything ever observed before," says Corey, who provided compelling evidence that the tip links pull on the channels. By "cutting" the tip links with a chemical, Corey could stop the cell's response cold. "Within less than a second, as the tip links became unstable, the whole mechanical sensitivity of the cell was destroyed," Corey observed.

Recently, both he and Hudspeth have independently investigated another property of hair cells: their ability to adapt to being deflected. At first, when a hair cell bundle is deflected, the ion channels open. But if the bundle remains deflected for a tenth of a second, the channels close spontaneously. It appears from electron microscope images and physiological evidence that the channels close when the tip links relax. This is related to the activity of the tip links' attachment points, which can move up and down along the cilia to fine-tune the tension on the channels. When the attachment points move down, the tip links are relaxed and the ion channels close.

While the researchers are still trying to figure out what enables the attachment points to move, they strongly suspect that myosin plays a role. Myosin is the protein that gives muscle cells their ability to contract. Both the Hudspeth and Corey labs have now cloned and sequenced the gene for a particular type of myosin in hair cells, and both have found that this myosin is located at the tips of the stereocilia, near the ion channels. A cluster of such molecules in each stereocilium could provide the force to move the attachment point up or down.

Slight movements of the attachment points allow the hair cell to set just the right amount of tension on each channel so it is maximally sensitive. They also permit the cell to avoid being overloaded when it is barraged by sound.

A second type of hair cell in the highly specialized cochlea of mammals may enable us to distinguish the quietest sounds. These outer hair cells, which are shaped like tiny hot dogs, look distinctly different from inner hair cells. The outer hair cells have a peculiar ability to become shorter or longer in microseconds when stimulated, doing so with a flamboyant, bouncy, up-and-down motion not found in any other cell type. They outnumber inner hair cells 3 to 1. Yet the 4,000 inner hair cells are connected to most of the auditory nerve fibers leading to the brain and are clearly the main transmitters of sound.

The precise function of the outer hair cells is still unclear. Auditory researchers speculate that these cells may serve as an amplification mechanism for tuning up low-frequency sound waves, possibly by accelerating the motion of the basilar membrane.

Hudspeth is also intrigued by the possibility that outer hair cells may be responsible for something that has puzzled researchers for years: the fact that our ears not only receive sounds, but emit them as well. When sensitive microphones are placed in the ear and a tone is played, a faint echo can be detected resonating back out again. Such otoacoustic emissions are considered normal; in fact, their presence in screening exams of newborn babies is thought to be indicative of healthy hearing. However, in certain cases, otoacoustic emissions can be spontaneous and so intense that they are audible without the aid of special equipment.

"In some people, you can actually hear them. The loudest ones ever recorded were in a dog in Minnesota, whose owner noticed the sound coming out of the animal's ear and took the dog to a specialist, who did recordings and analysis," says Hudspeth. "What may be happening is that the amplification system driven by the movements of outer hair cells is generating feedback, like a public address system that's tuned up too high," he speculates, adding that such otoacoustic emissions gone awry may account for certain unusual forms of tinnitus, or ringing in the ear.

Hudspeth and Corey's research is providing such a detailed picture of the hair cell that it is now possible to start identifying the individual proteins making up the tip links, ion channels, and motor mechanisms involved, as well as the genes that produce them. Malfunctions in those genes, resulting in defects in these important structures, may be the cause of inherited forms of deafness.

A Brain Map of Auditory Space

At Caltech in the mid-1970s, Masakazu (Mark) Konishi began studying the auditory system of barn owls in an effort to resolve a seemingly simple question: Why do we have two ears?

While most sounds can be distinguished quite well with one ear alone, the task of pinpointing where sounds are coming from in space requires a complex process called binaural fusion, in which the brain must compare information received from each ear, then translate subtle differences into a unified perception of a single sound; say a dog's bark; coming from a particular location.

Konishi, a zoologist and expert on the nervous system of birds, chose to study this process in owls. The ability to identify where sounds are coming from based on auditory cues alone is common to all hearing creatures, but owls; especially barn owls; excel at the task. These birds exhibit such extraordinary sound localization abilities that they are able to hunt in total darkness.

Together with Eric Knudsen, who is now conducting his own research on owls at Stanford University, Konishi undertook a series of experiments in 1977 to identify networks of neurons in the brains of owls that could distinguish sounds coming from different locations. He used a technique pioneered by vision researchers, probing the brains of anesthetized owls with fine electrodes. With the electrodes in place, a remote-controlled sound speaker was moved to different locations around the owl's head along an imaginary sphere. As the speaker moved, imitating sounds the owl would hear in the wild, the investigators recorded the firing of neurons in the vicinity of the electrodes.

Over the course of several months, Konishi and Knudsen were able to identify an area in the midbrain of the birds containing cells called space-specific neurons; about 10,000 in all; which would fire only when sounds were presented in a particular location. Astonishingly, the cells were organized in a precise topographic array, similar to maps of cells in the visual cortex of the brain. Aggregates of space-specific neurons, corresponding to the precise vertical and horizontal coordinates of the speaker, fired when a tone was played at that location.

Regardless of the level of the sound or the content of the sound, these cells always responded to the sources at the same place in space. Each group of cells across the circuit was sensitive to sound coming from a different place in space, so; when the sound moved, the pattern of firing shifted across the map of cells; Knudsen recalls.

The discovery of auditory brain cells that could identify the location of sounds in space quickly produced a new mystery. The lens of the eye projects visual space onto receptors on a 2-dimensional sheet, the retina, and the optic nerve fibers project the same spatial relationships to the brain; says Konishi. But in the auditory system, only the frequency of sound waves is mapped on the receptor layer, and the auditory nerve fibers project this map of frequency to the brain. How can the brain create a map of auditory space, based only on frequency cues? The answer, Konishi believes, may shed light on how the brain and the auditory system process all sounds.

The Value of Having Two Ears

As a rapid stream of impulses arrives from the hair cells in the ear, the auditory system filters out a few simple, discrete aspects of complex sounds. Information about how high- or low-pitched a sound is, how loud it is, and how often it is heard is then channeled along separate nerve pathways to higher-order processing centers in the brain, where millions of auditory neurons can compute the raw data into a recognizable sound pattern. The hair cells themselves contribute to this filtering process by responding to different frequencies at different locations along the basilar membrane. The cells at the bottom of the membrane respond more readily when they detect high-frequency sound waves, while those at the top are more sensitive to low-frequency sounds.

David Corey compares the arrangement to the strings of a grand piano, with the high notes at the base of the cochlea, where the basilar membrane is narrow and stiff, and the bass notes at the apex, where the membrane is wider and more flexible.

Hair cells also convey basic information about the intensity and duration of sounds. The louder a sound is at any particular frequency, the more vigorously hair cells tuned to that frequency respond, while their signaling pattern provides information about the timing and rhythm of a sound.

Konishi hypothesized that such timing and intensity information was vital for sound localization. So he placed microphones in the ears of owls to measure precisely what they were hearing as the portable loudspeaker rotated around their head. He then recorded the differences in time and intensity as sounds reached each of the owl's ears. The differences are extremely slight. A sound that originates at the extreme left of the animal will arrive at the left ear about 200 microseconds (millionths of a second) before it reaches the right ear. (In humans, whose sound localization abilities are keen but not on a par with those of owls, the difference between a similar sound's time of arrival in each ear would be about three times greater.)

As the sound source was moved toward the center of the owl's head, these time differences diminished, Konishi observed. Differences in the intensity of sounds entering the two ears occurred as the speaker was moved up and down, mostly because the owl's ears are asymmetrical; the left ear is higher than eye level and points downward, while the right ear is lower and points upward. Based on his findings, Konishi delivered signals separated by various time intervals and volume differences through tiny earphones inserted into the owls' ear canals. Then he observed how the animals responded.

Because owls' eyes are fixed in their sockets and cannot rotate, the animals turn quickly in the direction

of a sound, a characteristic movement. By electronically monitoring these head-turning movements, Konishi and his assistants showed that the owls would turn toward a precise location in space corresponding to the time and intensity differences in the signals. This suggested that owls fuse the two sounds that are delivered to their two ears into an image of a single source; in this case, a phantom source. "When the sound in one ear preceded that in the other ear, the head turned in the direction of the leading ear. The longer we delayed delivering the sound to the second ear, the further the head turned," Konishi recalls.

Next, Konishi tried the same experiment on anesthetized owls to learn how their brains carry out binaural fusion. Years earlier, he and Knudsen had identified space-specific neurons in the auditory area of the owl's midbrain that fire only in response to sounds coming from specific areas in space. Now Konishi and his associates found that these space-specific neurons react to specific combinations of signals, corresponding to the exact direction in which the animal turned its head when phantom sounds were played. "Each neuron was set to a particular combination of time and intensity difference," Konishi recalls.

Konishi then decided to trace the pathways of neurons that carry successively more refined information about the timing and intensity of sounds to the owl's midbrain. Such information is first processed in the cochlear nuclei, two bundles of neurons projecting from the inner ear. Working with Terry Takahashi, who is now at the University of Oregon, Konishi showed that one of the nuclei in this first way station signals only the timing of each frequency band, while the other records intensity. The signals are then transmitted to two higher-order processing stations before reaching the space-specific neurons in the owl's midbrain.

One more experiment proved conclusively that the timing and intensity of sounds are processed along separate pathways. When the researchers injected a minute amount of local anesthetic into one of the cochlear nuclei (the magnocellular nucleus), the space-specific neurons higher in the brain stopped responding to differences in time, though their response to differences in intensity was unchanged. The converse occurred when neurons carrying intensity information were blocked.

"I think we are dealing with basic principles of how an auditory stimulus is processed and analyzed in the brain. Different features are processed along parallel, almost independent pathways to higher stations, which create more and more refined neural codes for the stimulus," says Konishi. "Our knowledge is not complete, but we know a great deal. We are very lucky." Konishi has been able to express the mechanical principles of the owl's sound localization process as a step-by-step sequence. He has collaborated with computer scientists at Caltech in developing an "owl chip" that harnesses the speed and accuracy of the owl's neural networks for possible use in computers.

At Stanford University, Eric Knudsen has been conducting experiments on owls fitted with prism spectacles to determine whether distortions in their vision affect their sound localization abilities. Despite their exceptionally acute hearing, he has found, the owls trust their vision even more. When they wear distorting prisms, their hunting skills deteriorate over a period of weeks as their auditory systems try to adapt to the optical displacement of the prisms. "The visual system has ultimate control and basically dictates how the brain will interpret auditory localization cues," Knudsen says.

He is also examining a particular network of neurons in the animals' brains where he believes auditory and visual system signals converge. "This network makes it possible for the owls to direct their eyes and attention to a sound once it's heard," Knudsen explains. His research is part of a new wave of studies that focus not just on single sensory pathways, but on how the brain combines information it receives from many different sources.

Bat Sounds and Human Speech

Perhaps the finest achievement in sound processing is the ability to understand speech. Since this is a uniquely human trait, it would seem difficult to study in animals. Yet a researcher at Washington University in St. Louis believes it can be examined by working with bats.

Bats navigate and locate prey by echolocation, a form of sonar in which they emit sound signals of their own and then analyze the reflected sounds. Nobuo Suga, who has spent nearly 20 years investigating the neural mechanisms used by bats to process the reflected signals, is convinced that such research can shed light on the understanding of human speech. When Suga slowed down recordings of the high-frequency, short-duration sounds that bats hear, he found that their acoustic components were surprisingly similar to those of mammalian communication, including human speech. There were some constant frequencies and noise bursts, not unlike vowel and consonant sounds, as well as frequency-modulated components that were similar to those in combinations of phonemes such as "papa."

Suga further demonstrated that each of these acoustic elements is processed along a distinct pathway to higher-order neurons. Those neurons then combine and refine different aspects of the sonar pattern

in much the same way that space-specific neurons combine the timing and intensity cues of sound signals.

Suga also identified maps of neurons in the bats' auditory cortex which register slight variations in each of these components of sound. The bat's brain uses such neuronal maps to register changes in its surroundings. Humans may use similar maps to process the basic acoustic patterns of speech, though speech requires additional, higher-level mechanisms, he points out.

"The ability to recognize variations in sound is what enables us to understand each other. No two people pronounce vowels and consonants in exactly the same way, but we are able to recognize the similarities," says Suga. He believes that neuronal maps may also play a role in human voice recognition; the ability to recognize who is speaking as well as what is being said.

The Vivid World of Odors

After taking a mixture of mind-altering drugs one night, Stephen D., a 22-year-old medical student, dreamed that he had become a dog and was surrounded by extraordinarily rich, meaningful smells. The dream seemed to continue after he woke up; his world was suddenly filled with pungent odors. Walking into the hospital clinic that morning, "I sniffed like a dog. And in that sniff I recognized, before seeing them, the twenty patients who were there," he later told neurologist Oliver Sacks. "Each had his own smell-face," he said, "far more vivid and evocative than any sight-face." He also recognized local streets and shops by their smell. Some smells gave him pleasure and others disgusted him, but all were so compelling that he could hardly think about anything else.

The strange symptoms disappeared after a few weeks. Stephen D. was greatly relieved to be normal again, but he felt "a tremendous loss, too," Sacks reported in his book “The Man Who Mistook His Wife for a Hat and Other Clinical Tales.” Years later, as a successful physician, Stephen D. still remembered "that smell-world; so vivid, so real! It was like a visit to another world, a world of pure perception, rich, alive, self-sufficient, and full...I see now what we give up in being civilized and human." Being civilized and human means, for one thing, that our lives are not ruled by smells. The social behavior of most animals is controlled by smells and other chemical signals. Dogs and mice rely on odors to locate food, recognize trails and territory, identify kin, and find a receptive mate. Social insects such as ants send and receive intricate chemical signals that tell them precisely where to go and how to behave at all times of the day.

But humans "see" the world largely through eyes and ears. We neglect the sense of smell and often suppress our awareness of what our nose tells us. Many of us have been taught that there is something shameful about odors. Yet mothers can recognize their babies by smell, and newborns recognize their mothers in the same way. The smells that surround us affect our well-being throughout our lives.

Smells also retain an uncanny power to move us. A whiff of pipe tobacco, a particular perfume, or a long-forgotten scent can instantly conjure up scenes and emotions from the past. Many writers and artists have marveled at the haunting quality of such memories.

In “The Remembrance of Things Past,” French novelist Marcel Proust described what happened to him after drinking a spoonful of tea in which he had soaked a piece of madeleine, a type of cake: "No sooner had the warm liquid mixed with the crumbs touched my palate than a shudder ran through my whole body, and I stopped, intent upon the extraordinary thing that was happening to me," he wrote. "An exquisite pleasure had invaded my senses...with no suggestion of its origin... "Suddenly the memory revealed itself. The taste was of a little piece of madeleine which on Sunday mornings...my Aunt Leonie used to give me, dipping it first in her own cup of tea....Immediately the old gray house on the street, where her room was, rose up like a stage set...and the entire town, with its people and houses, gardens, church, and surroundings, taking shape and solidity, sprang into being from my cup of tea." Just seeing the madeleine had not brought back these memories, Proust noted. He needed to taste and smell it. "When nothing else subsists from the past," he wrote, "after the people are dead, after the things are broken and scattered...the smell and taste of things remain poised a long time, like souls...bearing resiliently, on tiny and almost impalpable drops of their essence, the immense edifice of memory."

Proust referred to both taste and smell and rightly so, because most of the flavor of food comes from its aroma, which wafts up the nostrils to cells in the nose and also reaches these cells through a passageway in the back of the mouth. Our taste buds provide only four distinct sensations: sweet, salty, sour, and bitter. Other flavors come from smell, and when the nose is blocked by a cold, most foods seem bland or tasteless. Both smell and taste require us to incorporate; to breathe in or swallow; chemical substances that actually attach themselves to receptors on our sensory cells. Early in evolution, the two senses had the same precursor, a common chemical sense that enabled bacteria and other single-celled organisms to locate food or be aware of harmful substances. How we perceive such chemical substances as odors is a mystery that, until recently, defeated most attempts to solve it. Anatomical studies showed that signals from the olfactory cells in the nose reach the olfactory area of the cortex after only a single relay in the olfactory bulb. The olfactory cortex, in turn, connects

directly with a key structure called the hypothalamus, which controls sexual and maternal behavior.

When scientists tried to explore the details of this system, however, they hit a blank wall. None of the methods that had proved fruitful in the study of vision seemed to work. To make matters worse, very little was known about the substances to which the olfactory system responds. The average human being, it is said, can recognize up to 10,000 separate odors. We are surrounded by odorant molecules that emanate from trees, flowers, earth, animals, food, industrial activity, bacterial decomposition, and other humans. Yet when we want to describe these myriad odors, we often resort to crude analogies: something smells like a rose, like sweat, or like ammonia.

Our culture places such low value on olfaction that we have never developed a proper vocabulary for it. In “A Natural History of the Senses,” poet Diane Ackerman notes that it is almost impossible to explain how something smells to someone who hasn't smelled it. There are names for all the pastels in a hue, she writes but none for the tones and tints of a smell. Nor can odors be measured on the kind of linear scale that scientists use to measure the wavelength of light or the frequency of sounds. "It would be nice if one smell corresponded to a short wavelength and another to a long wavelength, such as rose versus skunk, and you could place every smell on this linear scale," says Randall Reed, an HHMI investigator at the Johns Hopkins University School of Medicine who has long been interested in olfaction. "But there is no smell scale," since odorant molecules vary widely in chemical composition and three-dimensional shape. To find out how these diverse odorant molecules trigger our perception of smell, researchers needed to examine the olfactory cells and identify the receptor proteins that actually bind with the odorants.

Finding the Odorant Receptors

"We think that we smell with our noses, but this is a little like saying that we hear with our ear lobes," writes Gordon Shepherd, professor of neuroscience at Yale University. "In fact, the part of the nose we can see from the outside serves only to take in and channel the air containing odorous molecules." The neurons that sense these molecules lie deep within the nasal cavity, in a patch of cells called the olfactory epithelium.

Perched behind a sort of hairpin turn at the very top of the nasal cavity, the olfactory epithelium is only a few centimeters square. It contains some 5 million olfactory neurons, plus their supporting cells and stem cells. Actually, there are two such patches; one on each side of the nose; lying in a horizontal line just below the level of the eye. Each olfactory neuron in the epithelium is topped by at least 10 hair-like cilia that protrude into a thin bath of mucus at the cell surface. Somewhere on these cilia, scientists were convinced, there must be receptor proteins that recognize and bind odorant molecules, thereby stimulating the cell to send signals to the brain.

The receptor proteins would be the key to answering two basic questions about olfaction, explains Richard Axel, an HHMI investigator at Columbia University. First, how does the system respond to the thousands of molecules of different shapes and sizes that we call odorants; "does it use a restricted number of promiscuous receptors, or a large number of relatively specific receptors?" And second, how does the brain make use of these responses to discriminate between odors?

The string of discoveries that totally changed the study of olfaction resulted from a new emphasis on genetics. Instead of hunting for the receptor proteins directly, Richard Axel and Linda Buck, who was then a postdoctoral fellow in Axel's group and is now an HHMI investigator at Harvard Medical School, looked for genes that contained instructions for proteins found only in the olfactory epithelium.

Their efforts produced nothing at first. "Now we know why our initial schemes failed," says Axel. "It's because there are a large number of odorant receptors, and each was expressed only at a very low level." Finally, Buck came up with what Axel calls "an extremely clever twist." She made three assumptions that drastically narrowed the field, allowing her to zero in on a group of genes that appear to code for the odorant receptor proteins. Her first assumption based on bits of evidence from various labs was that the odorant receptors look a lot like rhodopsin, the receptor protein in rod cells of the eye. Rhodopsin and at least 40 other receptor proteins criss-cross the cell surface seven times, which gives them a characteristic, snake-like shape. They also function in similar ways, by interacting with G proteins to transmit signals to the cell's interior. Since many receptors of this type share certain DNA sequences, Buck designed probes that would recognize these sequences in a pool of rat DNA. Next, she assumed that the odorant receptors are members of a large family of related proteins. So she looked for groups of genes that had certain similarities. Third, the genes had to be expressed only in a rat's olfactory epithelium. "Had we employed only one of these criteria, we would have had to sort through thousands more genes," says Axel. "This saved several years of drudgery."

Buck recalls that "I had tried so many things and had been working so hard for years, with nothing to show for it. So when I finally found the genes in 1991, I couldn't believe it! None of them had ever been seen before. They were all different but all related to each other. That was very satisfying." The discovery made it possible to study the sense of smell with the techniques of modern molecular and cell biology and to

explore how the brain discriminates among odors. It also allowed researchers to "pull out" the genes for similar receptor proteins in other species by searching through libraries of DNA from these species. Odorant receptors of humans, mice, catfish, dogs, and salamanders have been identified in this way.

The team's most surprising finding was that there are so many olfactory receptors. The 100 different genes the researchers identified first were just the tip of the iceberg. It now appears that there are between 500 and 1,000 separate receptor proteins on rat and mouse and probably human olfactory neurons. "That's really a lot of genes," Axel says. "It's 1 percent of the genome! This means that, at least in the rat, 1 out of every 100 genes is likely to be engaged in the detection of odors." This staggering number of genes reflects the crucial importance of smell to animals.

How Rats and Mice and Probably Humans Recognize Odors

Large as the number of receptors may be, it is probably smaller than the number of odors we can recognize. "Most likely, the number of odorants far exceeds the number of receptor proteins by a ratio of at least 10 to 1," Axel says. "In that case, how does the brain know what the nose is smelling?"

The visual system needs only three kinds of receptors to distinguish among all the colors that we can perceive, he points out. These receptors all respond to the same thing; light. Light of different wavelengths makes the three kinds of receptors react with different intensity, and then the brain compares these receptors' signals to determine color. But the olfactory system must use a different strategy in dealing with the wide variety of molecules that produce odors. To figure out this strategy, Axel began by asking how many kinds of receptor proteins are made in a single olfactory neuron. "If a single neuron expresses only a small number of receptors, or a single receptor, then the problem of determining which receptors have been activated reduces to determining which neurons have been activated," he says.

He thought he would make more rapid progress by working with simpler organisms than rats. So he turned to fish, which respond to fewer odorants and were likely to have fewer receptors.

From studies with catfish, whose odorant receptors proved very similar to those of rats, Axel and his associates soon concluded that a given olfactory neuron can make only one or a few odorant receptors. (Buck and her colleagues have come to the same conclusion from their work with mice.)

The next step was to find out how these odorant receptors and the neurons that make them are distributed in the nose. Also, what parts of the brain do these neurons connect with? "We wanted to learn the nature of the olfactory code," Axel says. "Do neurons that respond to jasmine relay to a different station in the brain than those responding to basil?" If so, he suggested, the brain might rely on the position of activated neurons to define the quality of odors.

Each olfactory neuron in the nose has a long fiber, or axon, that pokes through a tiny opening in the bone above it, the cribriform plate, to make a connection, or synapse, with other neurons. This synapse actually forms in the olfactory bulb, which is a part of the brain. A round, knob-like structure, the olfactory bulb is quite large in animals with an acute sense of smell but decreases in relative size as this ability wanes. Thus, bloodhounds, which can follow the scent of a person's tracks for long distances over varied terrain, have larger olfactory bulbs than humans do, even though humans are more than twice the total size of these dogs.

In the olfactory epithelium of the nose, Axel and Buck's groups found, neurons that make a given odorant receptor do not cluster together; instead, these neurons are distributed randomly within certain broad regions of the epithelium, called expression zones, which are symmetrical on the two sides of the animals' nasal cavities. Once the axons get to the olfactory bulb, however, they reassort themselves so that all those expressing the same receptor converge on the same place in the olfactory bulb. The result is a highly organized spatial map of information derived from different receptors. "The brain is essentially saying something like, 'I'm seeing activity in positions 1, 15, and 54 of the olfactory bulb, which correspond to odorant receptors 1, 15, and 54, so that must be jasmine," Axel suggests. Most odors consist of mixtures of odorant molecules. Therefore, other odors would be identified by different combinations. Surprisingly, the spatial map is identical in the olfactory bulbs of all the mice that have been tested, Buck says. As she points out, this information provided the key to an ancient riddle.

The Memory of Smells

Scientists have long wondered how we manage to remember smells despite the fact that each olfactory neuron in the epithelium only survives for about 60 days, to be replaced by a new cell. In most of the body, neurons die without any successors. But as the olfactory neurons die, a layer of stem cells beneath them constantly generates new olfactory neurons to maintain a steady supply.

"The riddle was, how can we remember smells when these neurons are constantly turning over and the

new crop has to form new synapses?" says Buck. "Now we know the answer: Memories survive because the axons of neurons that express the same receptor always go to the same place." And so some stages of olfaction are beginning to yield to researchers. But many mysteries remain. For example, what happens to information about smells after it has made its way from the olfactory bulb to the olfactory cortex? How is it processed there? How does it reach the higher brain centers, in which information about smells is linked to behavior? Some researchers believe that such questions can best be answered by studying the salamander. This lizard-like creature's nasal cavity is a flattened sac. "You can open it up more or less like a book" to examine how its olfactory neurons respond to odors, says John Kauer, a neuroscientist at Tufts Medical School and New England Medical Center in Boston, Massachusetts, who has been working on olfaction since the mid 1970s. Salamanders will make it possible to analyze the entire olfactory system from odorant receptors to cells in the olfactory bulb, to higher levels of the brain, and even to behavior, Kauer thinks. His research group has already trained salamanders to change their skin potential; the type of behavioral response that is measured in lie detector tests whenever they perceive a particular odor.

To study the entire system non-invasively, Kauer uses arrays of photodetectors that record from many sites at once. He applies special dyes that reveal voltage changes in the membranes of cells. Then he turns on a video camera that provides an image of activity in many parts of the system. "We think this optical recording will give us a global view of what all the components do when they operate together," says Kauer. He hopes that "maybe 10 years from now, or 20 years from now, we'll be able to make a very careful description of each step in the process." This would be amazing progress for a sensory system that was virtually unexplored five years ago. Axel and Buck's discoveries have galvanized the study of olfaction, and scientists now flock to this field, aroused by the possibility of success, at last, in solving its mysteries.

Sniffing Out Social and Sexual Signals

In addition to our sense of smell, do we have the ability to sense certain chemical signals emitted by people around without being aware of it? Many other mammals use a separate set of sensory receptor cells in their nose to receive social and sexual information from members of their own species, and there is growing suspicion that we do, too.

A whiff of airborne chemicals from a female mouse, for instance, may spur a male mouse to mate immediately. Certain chemical messages from other males may make him aggressive. Other messages may produce changes in his physiology as well as in that of the responding female.

The effects of such messages would be far less obvious in humans. If we do receive chemical signals from people in our vicinity, these signals must compete with many other factors that influence our behavior. Yet our physiology may be just as responsive to chemical messages as that of other mammals. It is known that certain chemical messages from other mice lead to the onset of puberty in young males, while a different set of signals brings young female mice into estrus. Similarly, there are some suggestions that women may alter their hormonal cycles when exposed to chemical signals from other people.

In the past five years, scientists have become extremely interested in these signals, as well as in the "accessory olfactory system" that responds to them in many animals. This system starts with nerve cells in a pair of tiny, cigar-shaped sacs called the vomeronasal organs (VNOs), where the signals are first picked up. "The VNO appears to be a much more primitive structure that uses a different set of molecular machinery than the main olfactory system," says Richard Axel, who has become intrigued with this system. "It seems to work in a different way and we don't know how."

The VNOs are located just behind the nostrils, in the nose's dividing wall (they take their name from the vomer bone, where the nasal septum meets the hard palate). In rodents, at least, signals travel from the VNO to the accessory olfactory bulb (rather than to the main olfactory bulb) and then, as Sally Winans of the University of Michigan showed in 1970, to parts of the brain that control reproduction and maternal behavior. "It's an alternate route to the brain," explains Rochelle Small, who runs the chemical senses program at the National Institute on Deafness and Other Communication Disorders in Bethesda, Maryland. If the accessory olfactory system functions in humans as it does in rodents, bypassing the cerebral cortex, there is likely to be no conscious awareness of it at all.

Triggers of Innate Behavior

This signaling system is particularly important to animals that are inexperienced sexually. Experiments by Michael Meredith, a neuroscientist at Florida State University in Tallahassee, Charles Wysocki, of the Monell Chemical Senses Center in Philadelphia, and others have shown that the VNOs play a key role in triggering sexual behavior in naive hamsters, mice, and rats. A virgin male hamster or mouse whose vomeronasal organs are removed generally will not mate with a receptive female, they found, even if the male's main olfactory nerves are undamaged. Apparently, the VNOs are needed to start certain chains of behavior

that are already programmed in the brain. Losing the VNOs has a much less drastic effect on experienced animals, says Wysocki, who has been studying the VNOs for about 20 years. When male mice have begun to associate sexual activity with other cues from females, including smells, they become less dependent on the VNOs. Sexually experienced males whose VNOs are removed mate almost as frequently as intact males.

Do human beings have VNOs? In the early 1800s, L. Jacobson, a Danish physician, detected likely structures in a patient's nose, but he assumed they were non-sensory organs. Others thought that although VNOs exist in human embryos, they disappear during development or remain "vestigial" imperfectly developed. Recently, researchers have come to a different conclusion. Both VNOs and vomeronasal pits; tiny openings to the VNO in the nasal septum; have been found in nearly all patients examined by Bruce Jafek, an otolaryngologist at the University of Colorado at Denver and David Moran, who is now at the University of Pennsylvania's Smell and Taste Center in Philadelphia. "This has opened up the possibility of a new sensory system in humans," says Rochelle Small. "We were often told that the VNO does not exist in adults, so we have taken a big step just to show that the structure is there." She cautions that we still don't know whether this organ actually has connections to the brain, however. "The question now," she says, "is what its function might be."

Pheromones and Mammals

Just what do the VNOs of rodents or, perhaps, humans respond to? Probably pheromones, a kind of chemical signal originally studied in insects. The first pheromone ever identified (in 1956) was a powerful sex attractant for silkworm moths. A team of German researchers worked 20 years to isolate it. After removing certain glands at the tip of the abdomen of 500,000 female moths, they extracted a curious compound. The minutest amount of it made male moths beat their wings madly in a "flutter dance." This clear sign that the males had sensed the attractant enabled the scientists to purify the pheromone. Step by step, they removed extraneous matter and sharply reduced the amount of attractant needed to provoke the flutter dance. When at last they obtained a chemically pure pheromone, they named it "bombykol" for the silkworm moth, "Bombyx mori" from which it was extracted. It signaled, "come to me!" from great distances. "It has been soberly calculated that if a single female moth were to release all the bombykol in her sac in a single spray, all at once, she could theoretically attract a trillion males in the instant," wrote Lewis Thomas in “The Lives of a Cell.”

In dealing with mammals, however, scientists faced an entirely different problem. Compared to insects, whose behavior is stereotyped and highly predictable, mammals are independent, ornery, complex creatures. Their behavior varies greatly, and its meaning is not always clear. What scientists need is "a behavioral assay that is really specific, that leaves no doubt," explains Alan Singer of the Monell Chemical Senses Center. A few years ago, Singer and Foteos Macrides of the Worcester Foundation for Experimental Biology in Massachusetts did find an assay that worked with hamsters but the experiment would be hard to repeat with larger mammals.

It went as follows: First the researchers anesthetized a male golden hamster and placed it in a cage. Then they let a normal male hamster into the same cage. The normal hamster either ignored the anesthetized stranger or bit its ears and dragged it around the cage. Next the researchers repeated the procedure with an anesthetized male hamster on which they had rubbed some vaginal secretions from a female hamster. This time the normal male hamster's reaction was quite different: instead of rejecting the anesthetized male, the hamster tried to mate with it. Eventually Singer isolated the protein that triggered this clear-cut response. "Aphrodisin," as the researchers called it, appears to be a carrier protein for a smaller molecule that is tightly bound to it and may be the real pheromone. The substance seems to work through the VNO, since male hamsters do not respond to it when their VNOs have been removed.

Many other substances have powerful effects on lower mammals, but the pheromones involved have not been precisely identified and it is not clear whether they activate the VNO or the main olfactory system, or both. Humans are "the hardest of all" mammals to work with, Singer says. Yet some studies suggest that humans may also respond to some chemical signals from other people. In 1971, Martha McClintock, a researcher who is now at the University of Chicago (she was then at Harvard University), noted that college women who lived in the same dormitory and spent a lot of time together gradually developed closer menstrual cycles. Though the women's cycles were randomly scattered when they arrived, after a while their timing became more synchronized. McClintock is now doing a new study of women's menstrual cycles, based on her findings from an experiment with rats. When she exposed a group of female rats; let's call them the "A" rats; to airborne "chemosignals" taken from various phases of other rats' estrous cycles, she discovered that one set of signals significantly shortened the A rats' cycles, while another set lengthened them. Now she wants to know whether the same is true for humans; whether there are two opposing pheromones that can either delay or advance women's cycles. In this study, she is focusing on the exact time of ovulation rather than on synchrony.

The most direct scientific route to understanding pheromones and the VNO may, once again, be through genetics. Working with sensory neurons from the VNOs of rats, Catherine Dulac and Richard Axel found a new family of genes that "are likely to encode mammalian pheromone receptors," they reported

in 1995. Axel and Buck's teams also found a similar family in the VNO's of mice. Both groups estimate there must be 50 to 100 distinct genes of this kind in VNO neurons. Since then, Buck's team and that of Catherine Dulac, who is now an HHMI investigator at Harvard, have found a second family of likely pheromone receptors in mammalian VNOs; these, too, are expected to include about 100 genes. "Now we have to match up pheromones and receptors," Buck declares. Once the genes for such receptors are definitively identified, it should be relatively easy to find out whether equivalent genes exist in humans. Scientists could then determine, once and for all, whether such genes are expressed in the human nose. If they are, the receptors may provide a new scientific clue to the compelling mystery of attraction between men and women; some evidence of real, measurable sexual chemistry.

Brain Scans That Spy on the Senses

For centuries, scientists dreamed of being able to peer into a human brain as it performs various activities; for example, while a person is seeing, hearing, smelling, tasting, or touching something. Now several imaging techniques such as PET (positron emission tomography) and the newer fMRI (functional magnetic resonance imaging) make it possible to observe human brains at work. To create images, researchers gave volunteers injections of radioactive water and then placed them, head first, into a doughnut-shaped PET scanner. Since brain activity involves an increase in blood flow, more blood and radioactive water streamed into the areas of the volunteers' brains that were most active while they saw or heard words. The radiation counts on the PET scanner went up accordingly. This enabled the scientists to build electronic images of brain activity along any desired "slice" of the subjects' brains.

Much excitement surrounds a newer technique, fMRI, that needs no radioactive materials and produces images at a higher resolution than PET. In this system, a giant magnet surrounds the subject's head. Changes in the direction of the magnetic field induce hydrogen atoms in the brain to emit radio signals. These signals increase when the level of blood oxygen goes up, indicating which parts of the brain are most active. Since the method is non-invasive, researchers can do hundreds of scans on the same person and obtain very detailed information about a particular brain's activity, as well as its structure. They no longer need to average the results from tests on different subjects, whose brains are as individual as fingerprints.

The Next Generation of Brain Scans

Messages from the senses travel so swiftly through the brain that imaging machines such as PET and fMRI cannot keep up with them. To track these messages in real time, scientists now use faster methods; electrical recording techniques such as MEG (magnetoencephalography) or EEG (electroencephalography). These techniques rely on large arrays of sensors or electrodes that are placed harmlessly on the scalp to record the firing of brain cells almost instantaneously. Their data may then be combined with anatomical information obtained by structural MRI scans.

One of the first experiments in which structural MRI was used jointly with MEG produced a three-dimensional map of the areas of the brain that are activated by touching the five fingers of one hand. A New York University research team headed by Rodolfo found this map to be distorted in the brain of a patient who had two webbed fingers since birth. A few weeks after the man's fingers were separated by surgery, however, parts of his brain reorganized and the map became almost normal.

The next generation of imaging technology will use functional MRI (fMRI) in various combinations with MEG and EEG, predicts John Belliveau, director of cognitive neuroimaging at the Massachusetts General Hospital in Cambridge. Functional MRI shows activity deep in the brain with high spatial resolution. It is relatively slow, however, since it is based on the blood-flow response, which takes about 450 milliseconds. "If you do a visual stimulation experiment, four to five different areas may have turned on within that time," Belliveau says. "We know where those areas are, but we don't know which one turned on first." By contrast, EEG's spatial resolution is relatively poor, but because of its speed it may reveal the sequence of events. His group has already done some EEG recordings right inside the magnet of an fMRI machine, to get simultaneous measurements. Together, such techniques will offer scientists a glimpse of how information from the senses is processed in different parts of the brain. Building on the studies shown here, the new hybrids may then begin to tackle neural networks. They may help researchers examine how various parts of the brain exchange information and; most intriguing; how sensory information leads to thought.

Progress Continues

One by one, the very earliest stages in our perception of sights, sounds, smells, and taste are giving up their secrets through molecular genetics. A recent entry: two genes that encode what appear to be taste receptor proteins, newly identified by HHMI investigator Charles Zuker of the University of California, San Diego, and Nicholas Ryba of the National Institute of Dental and Craniofacial Research. The researchers think that the TR1 receptor, which was isolated from the taste buds of rats and mice, may recognize sweet (which usually means nutritious), while the TR2 receptor recognizes bitter. Both receptors seem distantly related to

the receptors for pheromones.

But how do signals from sense receptors reach other parts of the brain? And how does the brain interpret these signals and respond to them? Progress has been much slower in this area. Some of the most interesting findings about brain connections that lead to perception come from studies of smell; particularly from the work of Richard Axel and Linda Buck, who have solved long-standing problems in this field. "One riddle was, how can we remember smells over long periods of time when the olfactory neurons in the epithelium survive for only about 60 days, to be replaced by new cells which have to form new synapses?" says Buck. "Now we know the answer: Memories survive because the axons of neurons that express the same receptor always go to the same location in the brain."

How We Recognize Odors

In March 1999, Buck proved that mammals recognize and process odors through a code based on varying combinations of receptors. She likens olfactory receptors to letters of the alphabet, which can be used over and over again to compose a vast vocabulary.

At the Life Electronics Research Center in Amagasaki, Japan, Buck and her colleagues wafted 30 different odorants over some 600 olfactory nerve cells they had taken from the noses of mice. A special dye inside these cells lit up whenever an odorant receptor had been stimulated. Then, at Harvard, the scientists analyzed each responding cell's RNA to identify the olfactory protein it produced. In this way, they found out which receptors had been triggered by which odorants. They concluded that mammals use different combinations of receptors to recognize smells and to distinguish, for instance, between the odors of roses and of goats.

Linking Odors and Behavior

That same month, Axel reported that he had discovered odor-detecting receptors in the fruit fly Drosophila; a finding that could open the way to linking odor perception to behavior. Fruit flies are tractable experimental subjects and have sophisticated scent-sniffing organs, which they use to recognize a large repertoire of aromas. Axel's team identified 11 genes that encode Drosophila odor receptors. He estimates they belong to a family of between 100 and 200 genes and plans to use these genes to study how specific odors influence the flies behavior. If his group succeeds in identifying the receptors that are activated by odors that induce mating, for instance, the researchers may be able to map the neural circuitry of the mating response. This could lead to a simple way of preventing crop-eating insects from reproducing. Going further, Axel hopes to link certain olfactory connections in the flies brains to specific kinds of learning and memory.

The Erotic Nose

Exploring the vomeronasal organ, or VNO, which some scientists now call "the erotic nose", two teams of researchers announced in April 1999 that they had mapped out how sensory neurons in the VNOs of mice connect to specific areas of the accessory olfactory bulbs. One team was led by Peter Mombaerts of the Rockefeller University; the other was led by two HHMI investigators, Catherine Dulac of Harvard University and Richard Axel. Both groups suggest, but have not yet proved, that pheromones bind to special receptors on sensory neurons in the VNOs of mice. This is difficult to demonstrate, they point out, because very few mammalian pheromones have been identified.

Do Humans Sense Pheromones?

The best evidence that humans communicate through pheromones comes from Martha McClintock, who in 1998 completed a study in which she manipulated the timing of women's menstrual cycles. Every day for two months, she and Kathleen Stern of the University of Chicago collected cotton pads from the armpits of nine women in various phases of their ovulatory cycles and then wiped these pads just under the noses of 20 other women, who were asked not to wash their faces for the next 6 hours. The recipients did not know the source of the compounds and could smell only the alcohol, which served both as a control and as a carrier of the compound. Women who had been exposed to pads from women in the follicular phase (before ovulation) ovulated earlier, shortening their menstrual cycles. However, pads taken from the same donors during their time of ovulation had the opposite effect, delaying the recipients ovulation and lengthening their menstrual cycles. "This study provides definitive evidence of human pheromones", the researchers say. "Well-controlled studies of humans are now needed to determine whether there are other types of pheromones, with effects that are as far-reaching in humans as they are in other species."

Researchers still do not know how humans sense pheromones, however. If; unlike the VNOs of mice; the human VNOs turn out to be nonfunctional, humans may sense pheromones through ordinary odor receptors in the nose, after all.

ANATOMY AND PHYSIOLOGY ONLINE COURSE - SESSION 8 - QUESTION & ANSWERS

NAME: _____

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PHONE: _____

FAX: _____

E-MAIL: _____

Please be sure to fill out the information above, complete the test and e-mail or fax it back to us at iridology@netzero.net or 530-878-1119. We will grade your question & answer session and will let you know if we have questions or comments.

Please answer T or F to each of the following:

1. Nearly all sensory signals go first to a relay station in the thalamus. _____
2. Rod cells; one of two kinds of photoreceptor cells in the retina; enable us to see by the muted starlight of a hazy night. _____
3. Objects appear to be a particular color because they reflect some wavelengths more than others. _____
4. Some 10 million American men; fully 7 percent of the male population; either cannot distinguish red from green, or see red and green differently from most people. _____
5. More than 98 percent of all variations in human color vision involve the red and green receptors in men's eyes. _____
6. In humans and other mammals, hair cell bundles are arranged in four long, parallel columns on a gauzy strip of tissue called the basilar membrane. _____
7. People tend to lose 55 percent of their hair cells by the age of 65. And once destroyed, these cells do not regenerate. _____
8. There are 16,000 hair cells in a human cochlea. _____
9. Our ears not only receive sounds, but emit them as well. _____
10. The amplification system of the ear, driven by the movements of outer hair cells, is generating feedback, like a public address system that's tuned up too high. Such otoacoustic emissions gone awry may account for certain unusual forms of tinnitus, or ringing in the ear. _____
11. A sound that originates at the extreme left of the animal will arrive at the left ear about 300 microseconds (millionths of a second) before it reaches the right ear. _____
12. The social behavior of most animals is controlled by smells and other chemical signals. _____
13. The smells that surround us affect our well-being throughout our lives. _____
14. Olfactory neurons in the epithelium only survive for about 40 days. _____
15. The first pheromone was identified in 1958. _____