ON THE BRAIN

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Women are from Venus, Men are From Mars—But are Their Brains the Same?

CONTENTS

In his popular book *Men are from Mars, Women are from Venus,* relationship counselor John Gray extolled the differences between men and women, alluding to men as Mars, the Roman god of war, and women as Venus, the Roman goddess of love and beauty. While these differences do not apply to all men and women, scientists do know that their brains are different in many subtle, yet critical ways.

The premise that men's and women's brains are different has been around for years. Yet, says Jill M. Goldstein, Ph.D., professor of psychiatry and medicine at Harvard Medical School, scientists know very little about sex differences in the brains of humans. Director of research at the Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital, Goldstein studies sex differences in the normal brain and how these might help us better understand sex differences in psychiatric disorders.

Structural differences

This much we do know: Research conducted over the past 25 years shows that, on average, women perform better at certain types of verbal and emotional tasks, while men perform better at certain types of math and spatial skills. These sex-specific differences, however, do not hold for all types of verbal or math skills, and, says Goldstein, there is more variability in performance within one sex than there is between the sexes.

Scientists have found that both sexes tend to use one hemisphere of the brain more than the other for certain verbal tasks, but that women rely less strongly on a single hemisphere than men for these tasks. Thus, they determined, certain "thinking" skills are more dependent on one hemisphere in the male brain, while women may use both hemispheres.

In addition, research has shown that certain areas of the hypothalamus are different in men and women. For example, the preoptic area, which is involved in mating behavior, is more than twice as large in men as it is in women. Some research suggests that the corpus callosum, the largest white matter structure in the brain that serves as the major pathway connecting the brain's right and left hemispheres, is larger and more developed in women. Other scientists, using magnetic resonance imaging scans, argue, however, that there is no sex difference or that differences exist only in certain parts of the corpus callosum. Canadian researchers have shown that women have more nerve cells in the frontal lobe, the area of the brain responsible for reasoning, planning, parts of speech, emotions, and problem solving.

Goldstein's own research, using MRI scans of male and female brains, suggests that parts of the frontal cortex—for example, regions responsible for inhibitory function—are relatively larger in women, as are parts of the limbic system, such as the hippocampus, which is implicated in memory functions. In men, the scans show a relatively larger parietal cortex, which governs visuospatial processing, and a larger amygdala, which controls arousal and aggression.

No 'one-size-fits-all brain'

Thus, there is no unisex brain, no one-size-fits-all brain. And, yet, while scientists know that male and female brains are different, Goldstein says we're only now starting to understand why these differences occur.

continued on page 2

continued from page 1

"Over the past 25 years," she says, "we have developed imaging tools [MRI, functional MRI and PET scans] to look at the brains of living human beings. We can now see how the brain reacts while performing cognitive or affective tasks and under different hormonal conditions in women, such as during the menstrual cycle. An understanding of normal sex differences in the brain will help us understand how the brain goes awry differently in men and women with the same mental disorders."

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A large body of research exists on the effects of sex hormones on brain development and function. Among the highlights:

- Studies have found that there are critical pre- and postnatal periods during which the action of androgens, male sex hormones such as testosterone, either indirectly masculinize the brain through the aromatization (conversion by the enzyme aromatase) of testosterone to estrogen or that testosterone has some direct effects on the sexual differentiation of the brain. The female brain is protected from being "over-estrogenized," says Goldstein, because alpha-fetoprotein, a protein produced in the developing fetus, prevents the female brain from receiving too much estrogen. Thus, she adds, the two brains begin in the same mode, but the influence of sex hormones and the direct effects of genes determine which develop into males and which develop into females.
- A study conducted by Carnegie Mellon University researchers found that sex hormones alter the development of certain brain structures during puberty and that these changes last into adulthood. Using magnetic resonance microscopy, which is similar to MRI but produces images at a much higher resolution, the scientists discovered that specific brain structures implicated in cognition and neuropsychiatric disorders change during puberty under the influence of sex hormones. They found that the "childhood" brains of mice are similar in males and females, but that high levels of hormones during puberty lead to dramatic differences in the size of the brain structures in adult male and female mice, including those regions involved in emotion, learning and memory.
- University of British Columbia scientists determined that estradiol, a form of estrogen, has complex interactions with learning, memory and brain cell growth. The researchers discovered that these interactions are different in male and female brains, which may help explain the differences in cognitive ability between men and women, as well as the differences in their susceptibility to mental diseases.
- Yet another group of researchers at the University of Michigan examined the effect of sex hormones on pain and the stress-response system in the brain. These scientists found that the influence of reproductive hormones may affect how men and women perceive and experience chronic pain. Women suffer diseases characterized by unremitting pain more often than men.

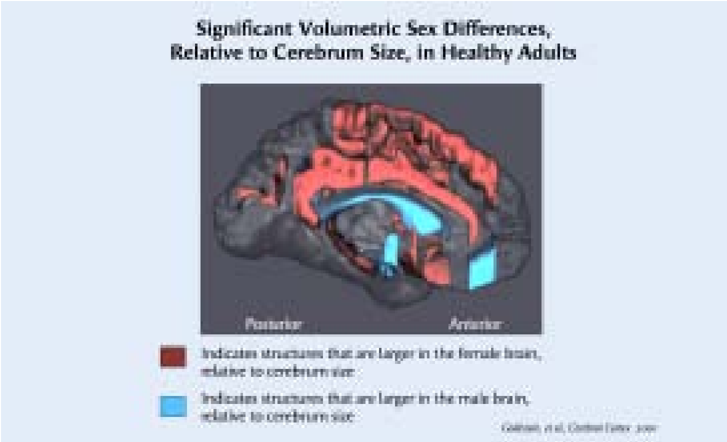
Further, says Goldstein, hormonal changes are important in how the brains of men and women age. As women age, the loss of hormones from menopause is implicated in memory deficits.

Determining differential risk

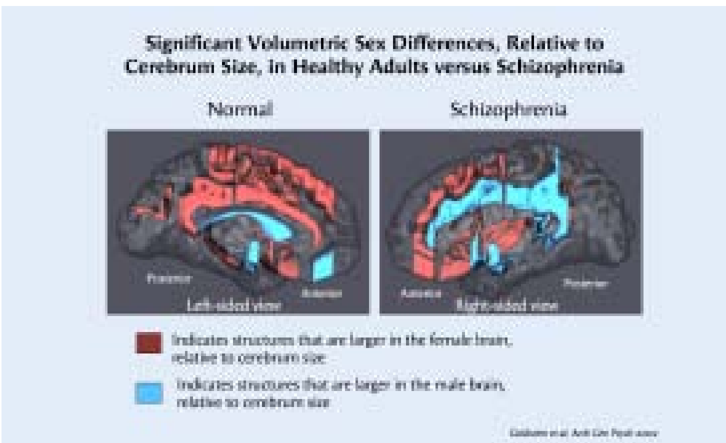
Goldstein's work focuses on why there are sex differences in the incidence and prevalence of psychiatric disorders, such as depression and anxiety, which are more prevalent in women, and schizophrenia, which is slightly higher in men. Her work is geared toward determining what happens during brain development that places men and women at a differential risk for adult onset psychiatric disorders with fetal origins.

"Sex differences in clinical medicine and women's health are not just about reproductive functioning, which was the thinking 30 or 40 years ago," she says. "We've begun to understand that sex differences permeate every tissue in the body."

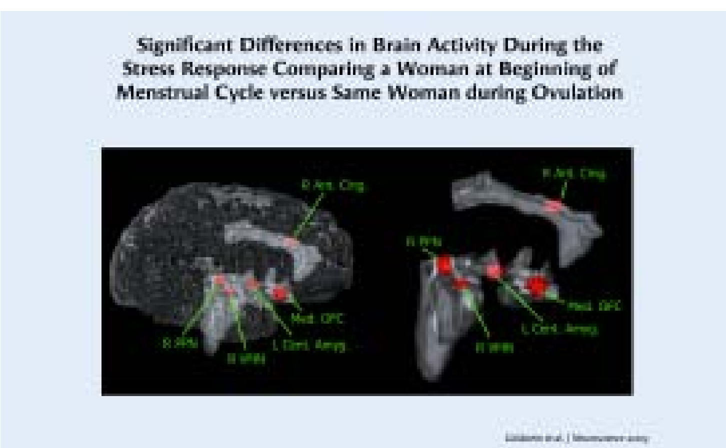
In order to understand the diseased brain, she argues, we need to understand the differences in the normal brains of men and women. "An understanding of what goes wrong differently in the brains of men and women in different diseases," she says, "will contribute to the development of sex-specific treatments and prevention strategies."



SLIDE 1 Slide showing brain regions that were volumetrically different in the male and female brain, relative to total brain size. These regions have been identified in animal studies as key regions implicated in the sexual differentiation of the brain during fetal development.



SLIDE 2 Slide showing that normal sexual dimorphisms are disrupted in the neurodevelopmental disorder, schizophrenia, a disorder in which there are known fetal risk factors that occur during the same period of time as the sexual differentiation of the brain.



SLIDE 3 Slide showing that hormones are likely critical in understanding differences in brain activity (or brain functioning) in regions that are normally sexually dimorphic. In the case above, women were exposed to visual images that invoked the anatomy of the stress response. These brain regions are highly sexually dimorphic and have a high density of hormonal receptors. We showed that these brain regions activated differently depending on whether a woman was at the beginning of her menstrual cycle versus mid-cycle (during ovulation). Our current study shows that sex differences in the stress response may be in part explained by these hormonal variations across the cycle.

Steven E. Hyman Joins HMNI Council

Dr. Joseph B. Martin has appointed Steven E. Hyman, MD, Provost of Harvard University, as a council member of the HMNI

Provost Steve Hyman

STEVEN E. HYMAN, MD, the Provost of Harvard University is Professor of Neurobiology at Harvard Medical School. From 1996 to 2001, he served as Director of the National Institute of Mental Health (NIMH), the component of the US National Institutes of Health charged with generating the knowledge needed to understand and treat mental illness. Before serving as Director of NIMH, Dr. Hyman was Professor of Psychiatry at Harvard Medical School, Director of Psychiatry Research at Massachusetts General Hospital , and the first faculty Director of Harvard University's Mind, Brain, and Behavior Initiative. In the laboratory he studied the molecular biology of neurotransmitter action. Dr. Hyman is a member of the Institute of Medicine of the National Academy of Sciences and of the American Academy of Arts and Sciences. He currently serves as Editor of the Annual Review of Neuroscience. He received his BA from Yale College in 1974 summa cum laude, and his MA from the University of Cambridge in 1976, which he attended as a Mellon fellow studying the history and philosophy of science. He earned his MD from Harvard Medical School in 1980.

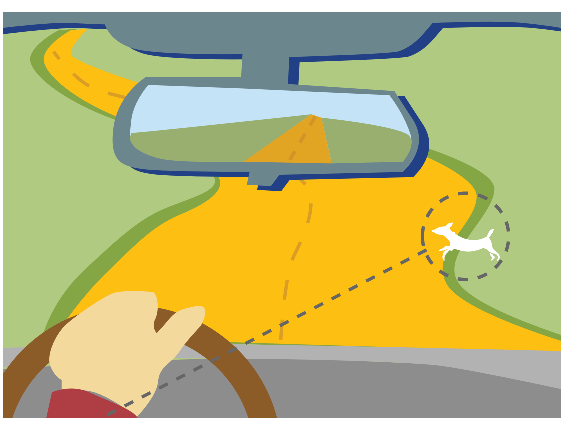
Finding Waldo

Have you ever wondered what goes on in your brain as you search for Waldo, the bespectacled hiker in the red-and-white striped bobble hat and sweater, in a *Where's Waldo?* book? How does your brain sift through so many stimuli —Waldo's dog Woof, his girlfriend Wenda, his magical friend Wizard Whitebeard, and thousands of other tiny people and objects—bombarding your eyes as you search for Waldo?

The ability to focus our attention on one thing as opposed to another is one of the most fundamental aspects of mental activity. Attention is critical in determining what we perceive, making the difference between seeing something or not noticing it at all. Neurobiologist John Maunsell, Ph.D., of Harvard Medical School, says that paying attention is essential to tasks such as finding Waldo, and provides important insights into the inner workings of the visual system.

Applying knowledge to sensory input

In his laboratory, Maunsell studies how attention changes the way individual neurons represent visual information and how those changes affect behavior. He and his team examine both individual neurons and groups of neurons, looking for a fuller understanding of how the 1.2 billion nerve cells in the visual brain "create a unitary perception of the visual world." Each of these neurons is specialized to signal when a particular type of stimulus appears in the visual field. For example, some respond to an edge with a particular orientation, while others are selective for certain colors or patterns.



In animal studies, Maunsell and his colleagues have examined how attention works to improve behavioral performance and obtained clues about what goes wrong in attentional disorders. They have found that most neurons respond more strongly to a particular stimulus when the animal pays attention to that stimulus. "When we direct our attention to objects in our field of vision," he says, "the brain cells that represent that part of the scene have their sensitivity turned up, while those reporting about other regions are turned down. Our brains modulate our representation of the visual world based on what we're focusing on." In this way, attention strengthens neuronal signals that represent the part of the visual scene the viewer considers important, while suppressing other visual signals.

"Attention changes the sensory input to incorporate what we know about the current state of the world," Maunsell says. "If something weird is likely to happen on one side of the room, you pay attention to that part of the room. This mechanism allows us to translate knowledge of the world to enhance the visual images we process."

Defining features in the visual world

The term "visual attention" refers to many processes that help us find, extract and define features in the visual environment. There are distinct forms of attention, says Maunsell, one driven by sensory stimulus, the other by an internal mechanism. "Endogenous attention" occurs when we direct our attention to something under our control such as when we focus on reading instructions. "Exogenous attention" is the consideration we pay to the sudden appearance of a stimulus. For example, our exogenous attention is at work as we drive down the street and notice a child playing at the curb. Maunsell notes that the brain is "hardwired" for exogenous attention so that our gaze is drawn to conspicuous objects in our visual field, even those on the periphery.

Researchers have attributed these exogenous processes with activity in the brain's attentional control network. This network includes the brain's frontal and parietal regions, as well as the visual cortex, the part of the brain that receives input from the retina, the thin layer of neural cells at the back of the eye that responds to light and sends signals via the optic nerve to the brain for visual representation. Other studies have shown that the visual cortex is influenced by top-down signals (those that transmit information synthesized from experiences), which change its activity depending on where attention is directed.

Maunsell's work is directed at understanding the circuits and systems in the brain that redirect and control attention. Exactly how the brain makes this happen is not well understood, he says. Progress on this difficult subject will have important implications for understanding what happens when attention doesn't work—either through everyday lapses or in attention disorders.

"When we pay attention to an object," says Maunsell, "neurons that represent that object fire more strongly and produce a stronger signal, just as if that object was brighter. Thus, the things we're looking at are enhanced. The neuronal signals are stronger and a clearer image is produced. Without that benefit, every sensory task becomes more difficult."

'Hair trigger responses' and 'false alarms'

We don't just attend to places; we also attend to colors and other features. When doing *Where's Waldo* searches, for example, certain cells in our visual brain respond to red and white stripes, while others respond to horizontal edges. Searching for Waldo selectively enhances the responses of those neurons, so that the brain's representation of Waldo is stronger relative to other parts of the picture, creating what Maunsell says is a "hair-trigger response" to Waldo.

But, while Waldo is dressed in red and white, with horizontal stripes on his shirt and hat, many of the other items in the illustrations are also red or white or other closely related colors, or have pronounced horizontal edges. The penalty for this mechanism, says Maunsell, is "false alarms," which the makers of the Waldo illustrations, who clutter the scenes with reds and whites, as well as horizontal lines, exploit.

So, as comedian Michael Ian Black said of Waldo in the VH1 television series "I Love the 90s: Part Deux": "You look for Waldo and they trick you because you think, 'Oh, I'll key in on the red-and-white shirt.' Nah, no, no, no. We've thought of that, sir. There's red-and-white towels, there's red-and-white tents. . . ." Good luck searching!

Giving Meaning to What We See

Humans are not born with the capacity to identify objects on sight. Rather, we learn to categorize familiar visual images—like "chair," "table," or "car"—through experience. Understanding what these images means allows us to respond appropriately when we encounter one of them, so we know, for example, to sit in a chair and eat on a table, not the other way around.

In a recent study, researchers at Harvard Medical School have identified the area of the brain where such categorization and learning takes place, opening up new ways to explore what goes wrong in the brains of people with learning and memory disorders.

Learning as a 'result of experience'

While scientists know a great deal about how the brain processes simple visual features, such as colors and angles, they know far less about how the brain recognizes and learns the meaning of visual stimuli, such as how to recognize the difference between a car and a truck—and that both are vehicles. The process of grouping related visual images into categories allows the brain to organize stimuli according to meaning. This, in turn, makes it possible for us to quickly make sense of our surroundings and react appropriately.

"Categorization is a process by which the brain assigns meaning to sensory stimuli," says David J. Freedman, Ph.D., a research fellow in neurobiology at HMS and co-author of the study that appeared in *Nature*. "Through experience, we learn to group stimuli into categories. . . which is critical for rapidly and appropriately selecting behavioral responses," like eating an apple rather than throwing it at someone.

In the study, HMS researchers discovered that the activity of neurons in an area of the brain called the parietal cortex both determines the category of visual images and encodes, or converts, the information for future use. This suggests that this region of the brain is part of the neural circuitry that learns and recognizes the meaning of the things we see.

Neural circuits give meaning

Freedman and his colleagues taught monkeys to play an easy computer game in which they grouped patterns of moving images into one of two categories. The researchers monitored the activity of neurons in the lateral intraparietal (LIP)

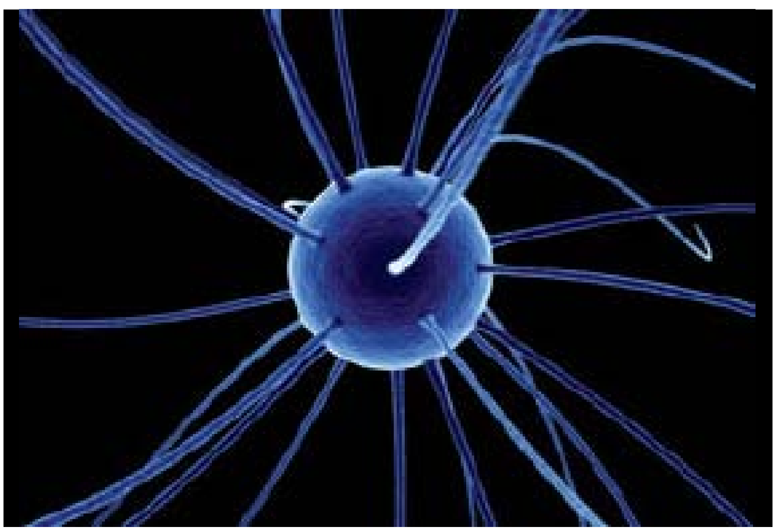
continued on page 7

Mirror, Mirror on the Brain

A man you recognize as an acquaintance approaches you on the street, with his arms raised. Is he coming to hug you…or kill you? How does your brain interpret his intentions?

The answer, says Amir Lahav, Sc.D., a post-doctoral fellow in the Department of Neurology at Beth Israel Deaconess Medical Center, may lie in a small group of nerve cells in the brain called mirror neurons.

First identified in the premotor cortex of macaque monkeys by Italian scientists in the early 1990s, mirror neurons are a subset of neurons that fire both when we perform an action and when we observe the same action performed by others. "The surprising part [about mirror neurons]," says Lahav, "is that they fire not only when an individual performs an action, but also when the individual observes or listens to sound associated with the action (for example, door knocking). The 'wow' part is that premotor neurons are not supposed to fire, at least intuitively, when you don't move."



The discovery of mirror neurons has implications for understanding not only the actions of others, but their intentions as well; that is, the social meaning of their actions. Mirror neurons have also been linked to empathy, as certain regions of the brain are active when a person experiences an emotion and when they see another person experience a similar emotion. That may be why we tear up when we see someone else cry. Scientists also believe that the human mirror neuron system is implicated in cognitive disorders like autism, language acquisition, and learningby imitation.

Accidental finding

The Italian researchers discovered mirror neurons almost by accident, says Lahav. Initially, they were interested in the electrical activity of single neurons in the monkey brain. The researchers implanted thin wires into a region of a monkey's brain (ventral premotor cortex) that is involved in planning and carrying out movements. When the monkey grabbed an object, brain cells in that region fired. Then, one of the scientists walked into the lab and raised some food to his mouth. When he did so, the same brain cells that fired earlier fired again, even though the monkey did not move. This led the researchers to call these nerve cells "mirror neurons" because the action observed by the monkey mirrored the action that was taken.

While it is yet to be proven that mirror neurons exist in humans, Lahav says there is a "high correlation" between the regions of the brain where mirror neurons were found in monkeys and where scientists see activity in the human brain. Still, he adds, there is very little scientific evidence of single motor neurons in human brains, as there are in monkey's brains. Thus, when it comes to humans "it would be more reasonable and scientifically appropriate to call it a mirror neuron *system* or *network*," Lahav says. "We can identify [through functional imaging techniques] brain regions that are highly involved when we do things, but to say we can identify specific individual neurons in the brain is a stretch."

Linking mirror neurons to disease, learning

Scientists also believe that mirror neuron deficiency is linked to autism, a developmental brain disorder that is characterized by impaired social interaction, difficulties with verbal and non-verbal communication, and repetitive behaviors.

Researchers, led by Nouchine Hadjikhani, M.D., of the Martinos Center for Biomedical Imaging at Massachusetts General Hospital and an associate professor of radiology at HMS, found that people with autism have significant thinning in regions of the brain where the mirror neuron system is located. The findings, she and her colleagues write in *Cerebral Cortex*, "suggest that the social and emotional deficits characteristic of autism may reflect abnormal thinning of the MNS [mirror neuron system] and the broader network of cortical areas subserving social cognition."

While most studies have focused on visual aspects of mirror neurons (such as in the observation of actions), Lahav's research focuses on the function of mirror neurons in the auditory–motor domain. His recent study, published in *The Journal of Neuroscience* in January, shows that when we learn new actions that have an audible output, the brain automatically links the regions responsible for performing the action with those connected with the sound. His findings build on existing evidence of a mirror neuron system in the human brain.

Lahav's team taught by ear nine subjects with no previous musical training to play a five–note song on a digital piano. They then conducted functional MRI scans while the students listened to the music they played and music with which they were unfamiliar. When the familiar music was played, the students showed particular activity in a frontoparietal network, including specifically an area of the brain called Broca's area, which is equivalent to the main region where mirror neurons were found in monkeys. The same was not true when the students listened to music they did not know how to play.

"When you listen to something you know how to play," says Lahav, "you can simply match with an existing neural representations. When you listen to something you don't know how to play, there's almost nothing [in your brain] to compare it to."

continued on page 8

Giving Meaning to What We See

continued from page 5

and middle temporal (MT) areas of the monkeys' parietal cortices while they played the game. The team observed that activity of neurons in the LIP area corresponded to the monkeys' decisions about how to categorize the patterns. Neurons in the MT area recognized differences in the patterns' visual appearance, but did not divide them into categories.

"The learning process took the representation of direction and reorganized the information," says Freedman. "This is one of the first demonstrations of parietal cortex learning as a result of experience."

Freedman works in the laboratory of HMS neurobiologist John Assad, Ph.D., which specializes in the study of the parietal cortex. Researchers in the lab have studied the LIP area, which undergoes massive reorganization during learning, and the MT area, which plays an important role in visual processing, particularly of the direction of motion. The bulk of the lab's work looks at how the activity of individual brain cells contributes to visual perception and other cognitive functions like attention and decision making.

While scientists know that the parietal cortex plays an important role in managing spatial attention, they have not examined its role in terms of learning. Freedman says that the parietal cortex receives visual input and is connected to the frontal and temporal lobes, which play a role in memory, language and problem solving; researchers are now "taking advantage of our base of knowledge [about the parietal cortex] to ask questions about learning."

Parallels to memory and learning disorders

While there are "broad parallels" between his discoveries and what scientists might expect to find in the brains of people with memory or learning disorders, Freedman says it is too early to draw direct comparisons just yet. The researchers are trying to determine which parts of the brain are involved in learning, but Freedman says it is "too soon to take specific details of the changes in parietal brain activity and say they are the root of learning and memory disorders in humans."

In the short–term, the results of the research will be used to plan new experiments that both study the role of the parietal cortex in learning and map out neural circuits in the visual learning process. This research, Freedman says, is critical for developing a basic understanding of how the brain learns and stores new information.

"Once we understand the details of the brain's role in the learning process and how it encodes categories in normal people," Freedman says, "we'll be a step closer to understanding what goes wrong in people who have learning and memory disorders. We anticipate that this information will be extremely useful for understanding and addressing an array of neurological diseases and disorders that affect learning and memory, including Alzheimer's, schizophrenia, attention deficit disorder, amnesia, and stroke."

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Mirror, Mirror on the Brain
continued from page 7

How we can take advantage of mirror neurons for clinical purposes? Lahav believes that the observed activation in motor-related brain regions found when people listened to the sound of actions can, in fact, translate into motor benefits when later performing those actions. He is currently leading a unique rehabilitation program for stroke survivors, in which patients produce sound while performing therapeutic exercises that are essential for daily living. Working with Gottfried Schlaug, M.D., Ph.D., of BIDMC and an associate professor at Harvard Medical School, Lahav uses a set of cameras to convert patients' movement into sound in real time. Then, in addition to physical training, patients also listen to the sound they have created to further reinforce the learned skills by strengthening mirror-neuron circuits in their brain.

"We have so far some promising preliminary results," says Lahav, "but further brain imaging research and clinical trials are still required to test the functionality of the mirror-neuron system in brain damaged patients and the effectiveness of such therapy."

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