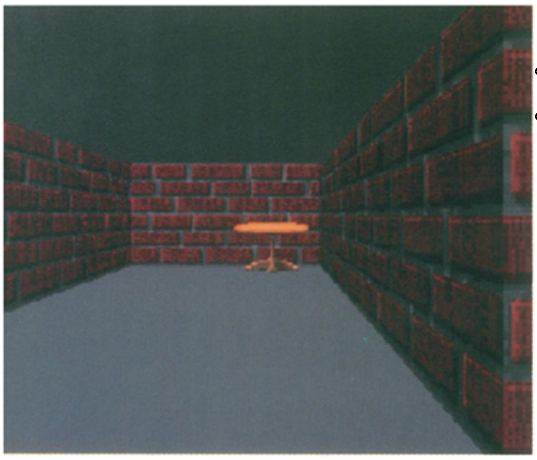

Images: Aguirre et al.

Volunteers explore a brick wall maze from a first-person perspective.

Brains in Space

Virtual reality helps explain how the brain finds its way

By JOHN TRAVIS

Not long after attending a neuroscience lecture last February, Geoffrey K. Aguirre returned to another important activity: playing video games with his fellow graduate students. While roaming the three-dimensional maze on the computer screen, killing enemy soldiers and recovering objects, Aguirre kept mulling over what he had heard at the lecture.

The talk had covered the hippocampus, a seahorse-shaped region of the brain with a number of clearly identified roles in learning and memory. Specifically, the lecture touched on studies in which rats ran through mazes while investigators recorded the electric activity of the animals' hippocampal cells.

These researchers found that the rats used so-called place cells in the hippocampus to construct a mental map of the maze. When a rat was in one part of the maze, specific place cells would fire off electric impulses. In another region of the maze, different place cells would fire.

As Aguirre traveled through his virtual maze in the computer game, he compared himself to the rats. "I nudged one of my friends and joked that my place cells were probably firing so much that we could image their activity," he recalls.

Aguirre's friends dismissed the jest, but his adviser, Mark D'Esposito, who studies memory at the Hospital for the University of Pennsylvania in Philadelphia, found inspiration in the joke. D'Esposito saw a unique opportunity to combine two high-tech marvels: brain imaging and virtual reality.

As Aguirre reported at the Society for Neuroscience meeting in San Diego last November, the Penn group has now married these technologies. The ability to image brain activity as people explore a computer-generated virtual environment should expand the usefulness of imaging, according to Aguirre and his colleagues.

Researchers have been frustrated because brain-imaging techniques require that a participant remain motionless during an experiment. Therefore, before the advent of virtual reality, the answers to many questions had seemed to lie beyond reach. How, for example, does the brain learn new routes when a person explores a novel environment? What areas of the brain does a person use to recall those spatial maps? What brain regions are active when a person learns to associate landmarks with locations?

"We're trying to identify regions of the brain involved in different strategies of learning, and once we have those, we can examine the effects of environment on them," says John A. Detre of the Penn group.

To view the brain as it experiences virtual reality, Aguirre, D'Esposito, and Detre recruited physicist David C. Alsop, who works with the functional magnetic resonance imaging (fMRI) machine at the hospital. A relatively new technique, fMRI is supplanting positron emission tomography (PET) as the favored method of providing pictures that reflect brain activity.

For traditional MRI, a person's head lies within a large cylindrical magnet, whose magnetic field harmlessly excites the atoms inside the brain into emitting weak radio waves. The frequencies and intensities of those radio waves depend on the type and number of atoms with which the magnetic field interacts. Investigators can convert those data into high-resolution still pictures of the brain's anatomy.

In fMRI, investigators take a rapid succession of MRI scans designed to detect the changing abundance of oxygen throughout the brain. This enables them to visualize small increases in blood flow to various regions of the brain. These increases appear to indicate greater activity by cells.

Functional MRI offers a major advantage over PET, which monitors similar changes in brain activity. For PET, in contrast to fMRI, investigators must inject a radioactive tracer into the bloodstream. The fear that even the low levels of radioactivity in the tracer may cause brain damage dissuades most people from submitting to more than a few PET scans.

Like other brain-imaging techniques, however, fMRI does not allow the participant to move during scanning. A person's head must remain still, says Aguirre. Otherwise, investigators can't compare successive scans and overlay them on a brain map created by a normal MRI scan. This restriction has largely limited fMRI experiments to mapping the effects on the brain of simple visual or auditory stimuli or of mental tasks such as rhyming.

To expand the repertoire of fMRI experiments to tasks that normally require movement, the Penn group is now thrusting volunteers into virtual environments. The investigators use a projection system similar to that found in large-screen televisions. In a darkened room, a volunteer lying inside the fMRI machine views a computer-generated environment in an overhead mirror that reflects images from a screen near his or her feet.

Although the setup provides a limited field of view, participants report that the current system is engaging, says Detre. For future work, the team may invest in wraparound goggles that provide more realistic depictions of virtual environments.

For their current projects, the investigators have simply adapted commercial video games, which create realistic three-dimensional environments. "We would have a hard time improving on what game makers are doing right now," says Aguirre.

He and his colleagues initially chose a game called Wolf-3D, which presents a player with a first-person, three-dimensional view of a maze constructed of brick walls. Using an editing program, the investigators designed their own maze and placed a visible object, such as a table, in each cul-de-sac. By pressing buttons on a game pad to move themselves in any direction, volunteers can visually travel through the maze while still lying in the fMRI machine.

Aguirre's volunteers explored freely until they could accurately draw the maze and the location of each object. "We wondered what would happen if we created a task that had at its core spatial learning," says Aguirre.

To obtain the brain-imaging data, the fMRI machine scanned individuals for 6 minutes at a time. During that period, the volunteers alternated between viewing the test maze and viewing a featureless control maze in which they could only move in a circle. "They spent 45 seconds in each task, switching back and forth between them," says Aguirre.

Investigators designed the control task to activate most of the areas of the brain, such as the visual cortex, that the test maze does; the control should not activate the regions needed to develop, store, and recall complex spatial representations. By subtracting the brain activity spurred by the control task from that provoked by the experimental task, investigators could identify regions of interest.

In a follow-up experiment, the scientists instructed the participant to navigate back and forth between a specified object and the starting position of the maze. This second task activates brain regions needed for the retrieval of spatial data, says Aguirre.

Based on the rat studies, "we thought we would find hippocampal activity," says D'Esposito. Yet, among the nine volunteers tested, no obvious areas of the hippocampus lit up.

That doesn't mean the hippocampus was inactive while negotiating the maze, caution the researchers. Neuroscientists have had a devilish time imaging hippocampal activity with fMRI, they note.

One explanation—and there are others—holds that the hippocampus is always ablaze with activity. "It's so metabolically active all the time, it never turns off," says D'Esposito. Consequently, investigators may find the differences in activity between the control task and the experimental task too small to discern.

Other brain regions did flare into action. They include areas, called the parahippocampal gyri, that lie under the hippocampus. In some of the volunteers, an area within the parahippocampal gyrus in the left hemisphere of the brain showed increased activity during the experimental task; in others, the gyrus on the right glowed. In the rest, brain activity rose in both gyri.

The parahippocampal activity wasn't completely unexpected, since these brain regions have complex interconnections with the hippocampus. Furthermore, says Aguirre, a 1987 study of four brain-damaged individuals demonstrated that the parahippocampal gyri are crucial to the storage and recall of spatial information.

After having strokes, these people had developed an unusual condition called topographic disorientation. "They had no ability to learn a new route or to travel a familiar route they once knew," says Aguirre.

When Aguirre looked at the published brain scans of the four patients, he found a clear connection to his current research. "There's one little spot [in the parahippocampal gyrus where] all of them have damage. That spot is pretty much identical to where we see activity," says Aguirre.

A few other regions of the brain appear to become active during the exploration of the maze as well. "These areas are also known to be involved in spatial orientation and are known to connect to the parahippocampus," says Aguirre.

For their next foray into virtual reality and brain imaging, the Penn group has simulated the Morris water maze, an animal experiment developed by Richard G. Morris of the University of Edinburgh. "It's a test of learning and memory that's been used extensively in rodents," says Aguirre.

Brain regions such as the parahippocampal gyri are active (red) during maze exploration.

Investigators place a mouse into a large tank of opaque water. Hidden beneath the water is a platform that the mouse, frantically swimming about, eventually finds. Researchers then put the animal in other parts of the tank, repeating the challenge. Normally, the mouse learns visual cues on the walls around the tank to help determine the position of the platform and begins to find it more quickly.

"What really determines your location in space? That's the question [the Morris water maze is] asking. How do you know where you are? There are a variety of ways to determine location. This is a kind of visual triangulation," says Jack M. Loomis, a psychologist at the University of California, Santa Barbara.

Some investigators have employed the Morris water maze to examine the brain regions upon which this kind of spatial memory depends. In 1982, for example, Morris showed that damaging a rodent's hippocampus usually prevents the animal from improving its performance on repeated trials. Other researchers use the maze to study the effects of chemical compounds on memory. Initial animal tests of potential Alzheimer's drugs often involve the task.

Researchers would like to duplicate the challenge of the Morris water maze for humans, but that feat would prove difficult in a laboratory. To create a virtual water maze, the Penn group once again edited an existing video game.

In the newly created virtual environment, a person can move about in a large tank. Three pillars of the same color appear on the walls surrounding the tank. If, while moving through the tank, the person lands on the hidden platform, he or she is instantly transported to another random spot in the tank and begins searching again. The control task for the experiment, says Aguirre, is simply moving to a visible platform in the tank.

Instead of creating a mental map of a maze that extends beyond one's vision, as in the initial series of experiments, an individual must learn to triangulate the platform's location. "The only way to know where the platform is is to know where all three cues are. It's a pretty faithful replication of the original Morris task," says Aguirre.

He and his colleagues have just started collecting brain-imaging data with the new virtual environment. For further development of the simulated water maze and related projects, the group has submitted a funding proposal to the Office of Naval Research. "They're very interested in navigation of virtual environments," explains Loomis, whose work on how people explore virtual spaces receives military funding.

In addition to providing a better understanding of how a normal brain interacts with the outside world, the marriage of fMRI and virtual reality may help explain the abnormal brain. "I can see tremendous value in the type of work they're doing, especially if they can look at different populations of people who have deficiencies and determine something about the reason for those deficits," says Loomis.

Though few investigators now work with virtual environments, he says, neuroscientists and psychologists should embrace the technique. Researchers "have been reluctant to do things in the real world because they like the controlled laboratory environment. Virtual displays give you the best of both worlds. They allow you to study the richness of the real world but at the same time maintain the kind of control you don't have in the real world," says Loomis.

Research using virtual reality is also undeniably fun. "I'm the only guy I know who can justify buying video games on grant money," laughs Aguirre. □