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WORKING WONDERS

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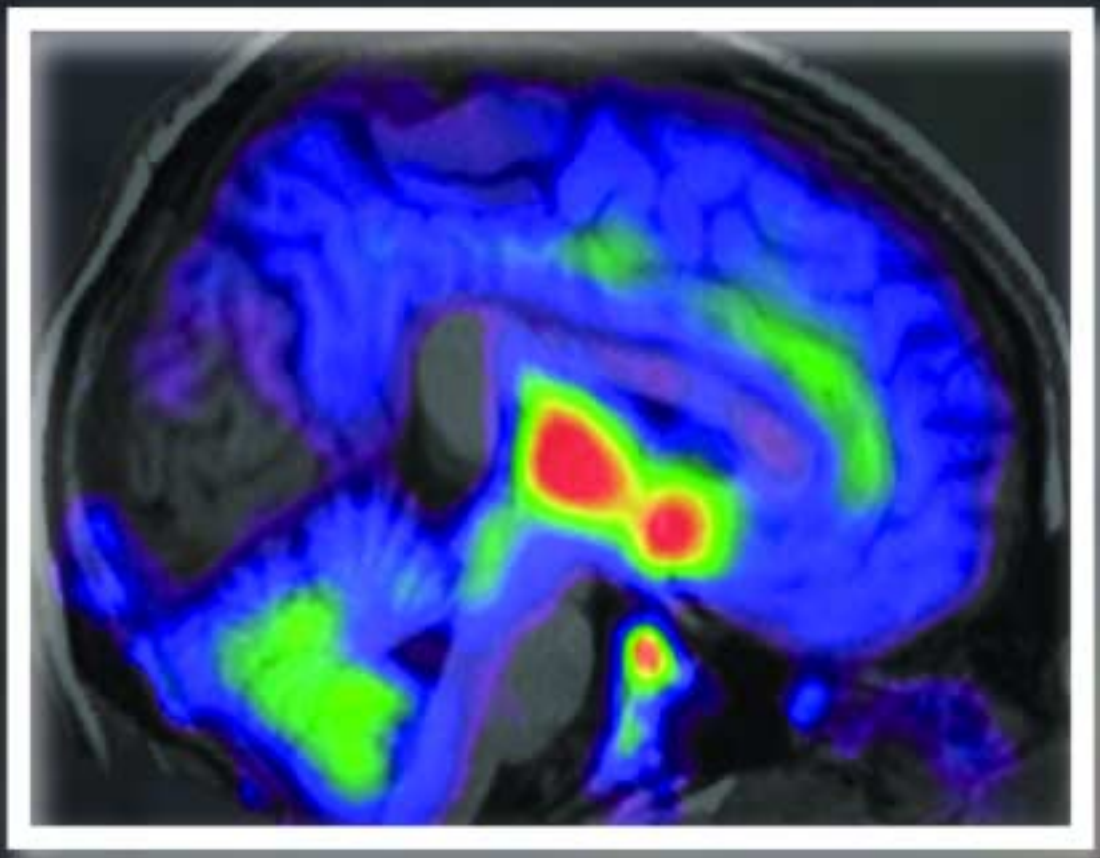
Mapping the Brain

At U-M's Mental Health Research Institute, studies are producing new insight into how we think and feel



By Eric J. Lerner

Sagittal view of the distribution of μ-opioid receptors in a healthy volunteer. Concentrations range from low (blue) to higher (green and yellow) to highest (red), as measured with positron emission tomography and a selective radiotracer. The PET scan is superimposed over a gray-scale magnetic resonance image.
Photo: courtesy of Jon-Kar Zubieta

How does the brain integrate the work of billions of neurons into a single conscious experience? In recent years, brain researchers struggling towards an understanding of this profound question have shifted from viewing the brain as a hierarchy of individual cells to seeing it as a symphony of cooperating assemblies of neurons. Thinking is thus seen as the shifting pattern in time and space of the activity of these neuron assemblies.

At the University of Michigan's Mental Health Research Institute (MHRI), a half dozen researchers, some collaborating with colleagues in the Department of Psychology, have been using advanced mapping technology to see how the various tasks that the mind carries out are distributed within the brain. By analogy, where in the brain's orchestra are the woodwinds, the brass and the string sections? These studies have started to reveal how some of the simplest mental tasks such as recognizing words, objects and places are carried out, how we keep objects in short term memory, and how diseases such as depression alter the way we experience emotions.

Efforts to map the brain have a long history and much is known about the locations of certain very basic functions, such as seeing, hearing and control over muscles. But how these basic functions become integrated at higher levels, generally in the frontal part of the brain, has remained mysterious.

in Action

The development of new mapping technologies is now allowing researchers to catch the brain in the act of thinking and, in the process, is generating new insights that help in the diagnosis and treatment of brain diseases, as well as in the fundamental effort to understand the biological basis for mental activity.

While many brain mapping groups have focused on techniques using the electroencephalogram (EEG) and the magnetoencephalogram (MEG) that can capture fast brain actions but have poor spatial resolution, most of the work at MHRI uses technologies that have much finer spatial resolution, although they average brain activity over periods of seconds. The different techniques are complementary and, together, are beginning to form a much clearer view of how the brain functions.

Mapping emotions

We feel as well as think with our brains, and our emotions can be studied by brain mapping, including the way they become abnormal in mental illnesses. Jon-Kar Zubieta, M.D., Ph.D., assistant professor of psychiatry and of radiology, is seeing how the brain regulates emotional functioning, both in healthy volunteers and in patients suffering from depression and substance abuse. "We are focusing on chemicals called endorphins and how they modulate the expression of emotions in the brain. We know that these endorphins, which are brain chemical messengers (so-called neurotransmitters), are involved in adaptation to stressful situations, and that stress is involved in the development of depression and substance abuse in predisposed individuals. We are now capable of labeling the receptors for those endorphins, using PET scans to examine how and where in the brain these chemicals are able to regulate emotional reactions," Zubieta says. Using the mapping technique of positron emission tomography, small amounts of radioactive materials can be used to trace neuronal activity, or the concentration of various proteins. Radiation from these tracers can then be detected and used to map the location of changes in neuronal function or in those proteins. (See accompanying article, "Brain maps old and new.")

In one of these studies, Zubieta asks subjects to think about a sad experience in their life during the PET scan and to recall that sad emotion. During that experience, there are changes in the chemical responses of certain regions of the brain, especially the amygdala and the anterior cingulate. In patients suffering from severe, clinical depression, those chemical responses are abnormal, with different patterns than those observed in healthy volunteers. "We see in these patients large releases of endorphins in certain areas of the brain, especially in the anterial temporal lobe, that do not show up in healthy subjects. However, there is a fair amount of variability in these responses, with some depressed patients showing changes more similar to those of non-depressed volunteers."

Photo: Martin Vloet

Jon-Kar Zubieta

What is the difference between the two sets of depressed patients, one with a normal or close-to-normal brain response and the other with a very abnormal one? "We did not find any correlation at all with the severity of the symptoms," points out Zubieta, "but we are finding a relationship with responses to antidepressant medication. Those with the more abnormal pattern did not respond to medication, but those with the more normal pattern did."

These findings suggest that abnormalities in brain chemicals associated with the brain's adaptation to stress may herald poorer responses to antidepressant treatment. A considerable number of patients diagnosed with severe depression do not respond completely to available treatments. The study of these mechanisms may ultimately improve current treatments for depression.

"Emotions are extremely complex and there is no clear picture presented by the brain scans — there are no happy or sad areas that show up consistently," cautions Stephan Taylor, M.D. (Residency 1993), assistant professor of psychiatry. Taylor, in collaboration with Israel Liberzon, M.D. (Residency 1992), associate professor of psychiatry, has used brain mapping to study the relationship of emotions and working memory — how emotional attachment can affect the ease with which something is remembered. "What we and other researchers find is that while specific areas are active in specific situations, the same emotions will affect different ➤

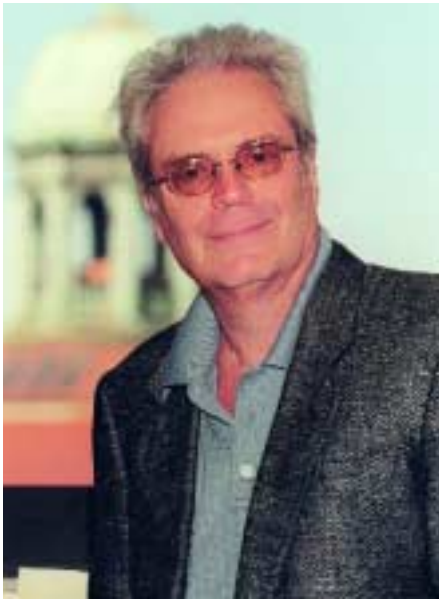
areas in different experimental contexts." He and his colleagues have been trying to pull together work done by various groups using different sets of mapping techniques, but the task is a difficult one. "Hopefully, as we get more data from brain scans, we will find new and more subtle ways to characterize emotions that will be far more accurate than our primitive categories like happiness and sadness," he speculates.

Measuring how our brains cope with pain

Endorphins are not only involved with emotions, they also have a big effect on pain. Endorphins are also released by the brain to reduce the sensations of pain. They are chemically related to powerful drugs like opium and morphine, but are naturally produced by the body.

Pain management poses a major problem for physicians, because pain is not objectively measurable. While physicians are aware that patients with similar physical conditions perceive different levels of pain, they have trouble taking these variations into account when prescribing painkillers and other treatment. Is a given patient really feeling more pain or just less tolerant of pain?

Photo: Martin Vloet



Edward E. Smith

Zubieta and his colleagues have taken a step toward objectively measuring with their PET mapping techniques how pain is regulated by the brain. They injected the jaws of a group of volunteers with a saline solution that temporarily produced pain resembling that caused by temporo-mandibular joint disorder, or TMJ, a common cause of chronic pain. As a control, they alternated the saline with injections of a non-pain-causing solution, using each in a 20-minute cycle. Neither the experimenters nor the subjects knew if the control or the saline solution was being used at a given time. The volunteers rated their pain level, and a computer feedback mechanism adjusted the amount of saline to maintain the intensity of the pain at a constant level.

In the meantime, Zubieta's team was mapping the release of endorphins in the subjects' brains with a PET scanner. Says Zubieta, "We saw an intense release of endorphins activating their receptors in a number of brain areas, including the anterior cingulate, frontal cortex, amygdala, thalamus and hypothalamus," which are brain regions involved in the processing of emotions or sensations. The more endorphins that were released, the lesser the experience of pain as rated by the volunteers.

When the team examined the responses of different volunteers, they found that some subjects released far more endorphins than others, and it was those volunteers that subjectively rated the pain the least. "These differences may show why some people react to pain differently than others," Zubieta points out. It also could provide a way to objectively measure individual subjective responses to pain and to anti-pain medications, and perhaps help to explain why some chronic pain conditions like TMJ and fibromyalgia become persistent in some but not other patients.

Photo: Martin Vloet

Stephan Taylor

The specialized brain

One of the key discoveries of brain mapping research is how specialized certain areas of the brain can be, at least in a given experimental context. Edward E. Smith, Ph.D., senior research scientist at MHRI and a professor in the College of Literature, Science and the Arts' Department of Psychology, has been looking with his colleagues at the way brain regions cooperate to carry out tasks using working memory. In such tasks, separate regions appear to be responsible for verbal memory, spatial memory, and executive functions like selectively attending to some sources of information.

Working memory — the memory we use to keep things in mind for a few seconds, like phone numbers — lends itself to experimental studies of brain specialization because it can be tested rapidly over and over again in short sessions and because it integrates in simplified fashion some of the basic functions used in memory generally. Beginning in the mid-1990s Smith and his collaborators, including Patricia A. Reuter-Lorenz, Ph.D., associate professor of psychology, John Jonides, Ph.D., professor of psychology, and Christy

Marsheutz, Ph.D., began studying working memory using PET scanning.

However, in the past two years, Smith and others have shifted their work to a newer and more potent mapping technique, functional magnetic resonance imaging (fMRI), a variant of the familiar MRI scans. Unlike standard MRI which maps static structures in the body, fMRI detects changes in blood flow, so it can, like PET, trace increases in neuronal activity. "There are many advantages of fMRI over PET," Smith explains. "The spatial resolution is finer — down to a few millimeters. Its time response is faster as well, dropping from several seconds with PET to one or two seconds with fMRI. In addition, it's entirely noninvasive, requiring no radioactive materials — which also makes it cheaper to use."

Photo: D.C. Goings

Patricia Reuter-Lorenz

Photo: Michael Marsland

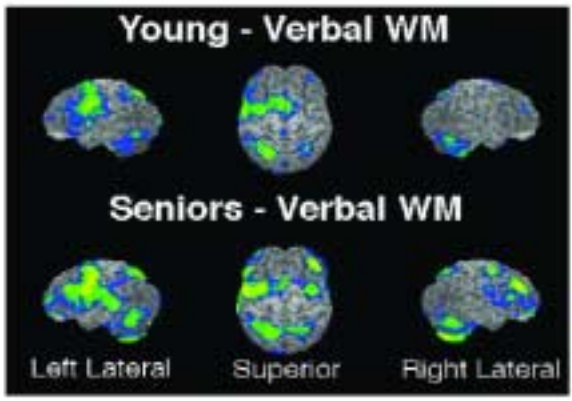
Christy Marshuetz

The studies show that as different parts of simple tasks are performed, different areas of the brain are activated, in varying combinations. Most short-term memory tasks involve three steps — memorizing an initial object; rehearsing the memory to retain it, as when we repeat a phone number over and over until we dial it; and retrieval, as when a memory is used to compare the object with a stimulus. These steps can be distinguished experimentally. For example, a test of pure rehearsal involves asking subjects to repeat a letter over and over, while pure recognition might involve matching test letters to a single letter given at the beginning. A task involving all three steps might be to look at a group of letters and then a few seconds later, see if a new letter corresponded to any in the group.

"What we learn by subtracting the areas activated in these different situations is that there are regions specializing in each task," Smith says. A specific area called the dorsolateral prefrontal cortex or DLPFC, is activated mainly when tasks involve switching attention, such as alternating between recognizing a letter and a number. Another region on the right side of the brain is involved only in short-term memory of images, while another on the left side is involved only in memory of words and letters. Still others are active only during rehearsal or recognize portions of the tasks.

But what is still more interesting is the way that the tasks performed by certain regions changed depending on circumstances, giving clues to how the tasks were being carried out. In one test, researchers looked at the areas that were activated in a test that required subjects to remember the order in which letters were shown, and specifically how far apart certain letters were in the order. The work, performed by Marshuetz and colleagues, showed that the area that became more and more active as the difference in order increased was the same one that was involved in numerical calculations. It thus seems that in the brain there is a close relation between quantity and order, a result that makes sense, since our basic ideas of numbers seems to have emerged from counting, an ordering process.

The studies also showed that the harder the task, the larger the neuronal assemblies that worked on it, and the larger the flow of blood. For example, when subjects were asked to compare letters with those that had been seen two or three tests before, more activity was observed than for the simple comparison of letters with the immediately previous test. In accord with our subjective perception, when we are "thinking hard" our brain is actually burning more energy — perhaps by 10-15 percent — than when we are just resting.



Colored regions indicate the areas of younger and older brains activated during verbal working memory tasks, demonstrating a higher degree of left lateralization in younger adults compared with more bilateral activity in older adults. ©1999 from the Primer of Cognitive Aging, D. Park and N. Schwarz, eds. Reproduced by permission of Taylor & Francis, Inc.

The generalized brain

The specialization of brain function is not the only story that brain mapping studies tell. As the brain ages, the high degree of specialization evident in ➤

young adult subjects becomes replaced with a more complex pattern: the older brain seems to be more of a generalist. One of Smith's colleagues in the Department of Psychology, Patricia Reuter-Lorenz, has concentrated on understanding how normal, healthy human brains change with age.

"In one recent series of studies, we looked at short term memory tasks that involved inhibition," explains Reuter-Lorenz, "both in a group of adults in their 20s and another group in their 60s and 70s." Subjects were supposed to respond to letters they had just seen as part of a group. But to complicate the tasks, a letter that had been seen in a recent previous test was shown. Since the letter was familiar, there was a tendency to respond to it, but this impulse had to be inhibited to provide the correct answer. For all subjects, response times were a bit longer for the confusing letters, and delays and inaccuracies were somewhat greater for older subjects than for younger ones. (Older subjects' response times increased by about seven percent, compared with four percent for younger subjects.)

Kirk Frey

"The interesting result was shown in the brain scans," says Reuter-Lorenz. "When the younger subjects were dealing with the inhibition task, a specific area in the brain was activated that was not used in the other cases. But in the older adults, this did not happen — the areas activated in the inhibition case were just the same as the other cases. It seems as if the younger brains are using a higher degree of specialization to get a somewhat faster response time."

Other studies by Reuter-Lorenz and Smith confirm the idea that human brains become less specialized with normal aging. For example, the tendency for the left hemisphere to be involved in verbal tasks and the right in spatial ones breaks down with increasing age, and areas in both hemispheres become involved in both types of tasks. "Only certain parts of the brain are involved in a given task, but there is much more overlap between the areas involved in one task and those in another in older adults, and there are more areas involved in each task," Reuter-Lornez points out. "We don't yet know the reason for this. The brain might be compensating for the lower efficiency of neurons by bringing more of them into a task, or more positively, the older brain, with a richer base of experience, is using a richer combination of experiences and skills to perform a task, even at the expense of doing it slightly slower."

Sick brains and well

The more that brain mapping shows how the normal brain functions, the more useful it becomes for diagnosing disease as well. Kirk Frey (M.D., Ph.D. 1984), professor of radiology and neurology and senior research scientist at MHRI, has shown that PET scans indicating the uptake of specific neurochemicals can be used to measure the progression of both Parkinson's and Alzheimer's diseases and indicate how patients are responding to medications. "The advantage of PET scanning is that you can see the very uneven distribution of labeled neurochemicals, a distribution that is sensitive to brain damage in these two diseases." By carefully selecting the neurochemical to label, Frey has been able to distinguish the level of damage in the brain, despite the brain's attempts to compensate chemically for the damage. Such studies can provide a test of medication efficiency that is more objective and accurate than tests of patients' performance.

While brain mapping is being applied for diagnosis, to a large extent the field remains in its early stages. "We are just starting to pull together the information from different types of mapping, such as fMRI, EEG, MEG and PET," Taylor emphasizes. "It's only in the past few years that we have started to have good time-and-space resolution and we still have not achieved both at once." In the next few years, as the growing mass of brain mapping data is integrated together, a far clearer picture will develop of how huge assemblies of neurons in different parts of the brain work together to produce our thoughts and feelings.

Brain maps old

The first technique used for brain mapping was the electroencephalogram (EEG), which measured the oscillating electrical potentials over various parts of the scalp. This has good time resolution, but it is difficult to interpret and has poor spatial resolution, since electrical fields are severely distorted in passing through the brain and especially through the skull. A more sophisticated version of EEG, coming into use in the last decade, maps correlations between EEG patterns in different parts of the brain — that is, it shows which parts of the brain are in phase with another at a given frequency of oscillation.

Two models of the brain

Until five years ago, the dominant model of the brain was hierarchical, focused on individual neurons and patterned on the way digital computers work. In brief, the hypothesis held that single neurons operated by detecting features in the environment. At the base level, individual neurons in the optic region of the brain, for example, would detect simple features, such as lines and edges. At the next level, higher order neurons integrated data from the hundreds of lower order neurons to which each was linked to detect more sophisticated features — a red ball, for example, or green squares. At the highest level, cardinal neurons would integrate sensations of higher order neutrons to recognize concepts such as "grandmother's face."

Problems confronted the hypothesis from the start. First, there was the "binding" problem — how could information obtained by different means be bound together into a single perception? How could the neuron that recognized grandmother's face, the neuron that recognized her voice, and the one that recognized the word "grandmother" all work together to create a single perception of grandmother? Closely linked with this was how billions of individual neurons could produce a single consciousness.

A competing model, now becoming dominant, contends that the brain stores and processes information only when millions of neurons work together, with their electric potentials correlated or synchronized in patterns at various frequencies. Large-scale electrical fields produced by the brain and recorded as electroencephalograms can only be produced by the cooperative actions of many neurons, the theory holds. These cell assemblies, as they are called, are not anatomical entities. Rather, they are temporary functional collections of neurons scattered across wide areas, or even throughout the brain, whose firings are correlated or synchronized at a given frequency.

The newer model makes it much easier to understand the data from brain mapping which show that close coordination of several relatively large regions of the brain are essential for almost any activity. In turn, since the model hypothesizes that it is the patterns of brain activity in space and time that are important, not the states of individual neurons, it makes brain mapping essential to understanding how the brain works.

and new

Since magnetic fields produced by currents in the brain are less distorted, magnetoencephalograms (MEG), which measure these fields, give more precise three-dimensional maps but still do not have resolution finer than a few centimeters.

In positron emission tomography (PET) scans, chemicals are labeled with radioactive materials which emit positrons, the positively charged anti-particles to ordinary electrons. These travel only a very short distance before they encounter electrons and are annihilated, releasing tiny amounts of gamma rays. Since these travel in straight lines, their origin can be mapped very accurately, showing where the chemical is concentrated. Often this technique is used to measure change in blood flow, and thus brain activity.

The most recently developed mapping technique, functional magnetic resonance imaging, like ordinary MRI, detects radio signals from atomic nuclei as they oscillate in a strong electronic magnetic field. One of the more sensitive fMRI techniques, flow-sensitive inversion recovery, measures relaxation times in flowing blood — the time it takes for a signal from a batch of nuclei to decline. These times are faster when flow is increased because of greater turbulence in the blood. At high magnetic fields (up to four T), this technique can deliver spatial resolution of less than one millimeter in three dimensions. However, since it takes a second or two for the brain to increase blood flow, time resolution is still far less than for EEG and MEG.