Near-infrared spectroscopy (NIRS) study designed to monitor brain activation patterns during sleep. The subject (*inset*) is wearing the NIRS probe. The researcher is looking at the EEG interface. [Courtesy of Tufts University, Medford, Mass., and the EEG Laboratory, New England Medical Center, Boston, Mass.]

Noninvasive Imaging of the Brain

Gary Boas

Near-infrared spectroscopy provides a noninvasive, nonionizing and portable means to image brain function. Researchers have already begun to explore its potential for a variety of applications, including diagnosis and treatment of depression, schizophrenia and Alzheimer's disease, as well as stroke rehabilitation. In time, the technique may contribute to important advances in psychiatry. It already offers the ability to monitor brain function continuously at bedside.

The human brain, with its vast network of neural connections and its potential for a seemingly endless variety of behaviors, constitutes one of the final frontiers of medicine. Over the course of recent decades, techniques such as positron emission tomography (PET), magnetoencephalography (MEG) and functional magnetic resonance imaging (FMRI) have contributed to a more thorough understanding of how the brain works. But many questions remain to be answered. Near-infrared spectroscopy (NIRS), one of the most recent entrants into the arena of brain imaging techniques, may help to shed more light on the functioning of the brain. NIRS can provide information about oxygenation in the brain noninvasively, without the use of ionizing radiation and at bedside. For this reason, it may also contribute to advances in psychiatry and other areas. Specifically, researchers have begun to explore its potential for the diagnosis and treatment of depression, schizophrenia and Alzheimer's disease, as well as for stroke rehabilitation. If the technique lives up to its early promise, it may prove to be a viable tool for these and other clinical applications.

Measurement of oxygenation

NIRS offers information about oxygenation based on the optical properties of hemoglobin, the protein in the blood that

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carries oxygen. Because oxygenated and deoxygenated hemoglobin have distinct absorption properties, the degree of oxygenation in tissue can be determined by shining light into tissue and measuring the amount of light that emerges, unabsorbed. Near-infrared light affords deeper penetration into tissue, and is therefore the spectral range of choice for measuring cerebral oxygenation. Although attempts to measure cerebral oxygenation with near-infrared light date back to the mid-1930s, when Kurt Kramer demonstrated transmission through an animal's skull,[1] most researchers point to the late 1970s as the beginning of the modern era of near-infrared spectroscopy.

Frans Jöbsis, a researcher at Duke University, had been studying the enzyme cytochrome oxidase. He wanted to measure oxygenation of the enzyme in the brain, but because of the thickness of the skull wasn't sure whether such a thing was possible. Since measurement with near-infrared light allowed for better penetration into tissue, he eventually decided to focus on the oxidation reduction (redox) of cytochrome oxidase with an absorption peak in the near-infrared range. To test the approach, he performed an experiment in which light was transmitted from two monochromators into the head of a cat and detected with a photomultiplier tube as it exited the opposite side.

Jöbsis published his findings in a paper in the December 1977 issue of *Science* in which he described how the relatively high degree of transparency of biological materials in the near-infrared range allows for real-time, noninvasive monitoring of oxygen sufficiency in tissue.[2] Initially, he based the technique on the absorption properties of cytochrome c oxidase, but soon after the *Science* paper was published, he turned his attention to the absorption properties of hemoglobin. "I was trying to rid the enzyme signal of the influence of blood, which is a much stronger signal," he says. "Once I'd done that I realized that, in my hands, I had the algorithms for measuring the blood in oxygenated and deoxygenated states." A handful of researchers around the world picked up on the technique—particularly as it applied to the study of blood oxygenation. In Rome, Marco Ferrari and

Judith Hahn, of the BBC science program "Tomorrow's World," presents the first NIRS system being used on a baby in the neonatal intensive care unit at University College Hospital, London, in late 1984. The NIRS system is the 6 ft high instrument rack on the left (controlled by a then state of the art Olivetti M64 PC). [Courtesy of University College London, Department of Medical Physics & Bioengineering.]

colleagues set out to explore its potential. In 1982, they presented findings from the first human studies with near-infrared spectroscopy.

Parallels with animal research

In London, meanwhile, David Delpy had begun to investigate clinical applications of the technique. Delpy, who worked in neonatal intensive care monitoring, had been looking for new ways to "see" inside newborns' heads. "In 1977 or 1978," he says, "I heard Frans Jöbsis give a talk about how he'd been measuring oxygenation in the brains of cats. A cat's head is about 4.5 centimeters in diameter; the head of a premature baby is about five or six centimeters. I thought, if you can do it on a cat, with a bit of engineering you might be able to do it on the head of a baby." He was right; by the end of 1984, he and colleagues at University College, London, had designed and tested a NIRS instrument for bedside monitoring in neonatal intensive care.

Further developments in the late 1980s and early 1990s helped transform NIRS into an imaging modality suitable for a wide range of applications in psychiatry and cognitive studies in general. First was the introduction of time-resolved, frequency-domain and spatially resolved spectroscopy. Originally, because they employed only continuous-wave light measured at a single point, NIRS systems could provide only relative measurements—not quantitative information about tissue oxygenation. To produce absolute measurements, researchers needed additional information, such as the length of time it takes for light to travel through the tissue being examined.

Enter Britton Chance. Chance had already had a long and distinguished career in biomedical optics when, in 1988, he turned his attention to NIRS, and specifically to the limitations of the technique that prevented quantitation. Chance and colleagues hypothesized that by using picosecond laser pulses they could obtain quantitative information about the optical characteristics of the tissue.[3] Other researchers, including Delpy,[4] Enrico Gratton[5] and Joseph Lakowicz,[6] had been working on the problem as well. The combined efforts of these researchers led to the development of time-resolved frequency-domain spectroscopy (the frequency-domain signal is the Fourier transform of the original, time-domain signal). These approaches provide for quantitation of optical characteristics of the tissue and therefore offer much more robust information about oxygenation.

The second major development was the emergence of diffuse optical tomography (DOT) in the early 1990s.[7,8] DOT enables researchers to produce images of absorption by dividing the region of interest into thousands of volume units, called voxels, calculating the amount of absorption in each (the forward model) and then simply putting the voxels back together (the inverse problem). "Light diffusion provides a mathematical formalism for imaging," says Arjun Yodh, a University of Pennsylvania researcher who, with Britton Chance, spearheaded the development of DOT. "Once one accepts the basic assumptions about transport, then it is straightforward to formulate the tomographic inverse problem."

The drive to portability

Technology has kept pace with these advances. Over the years, designers of NIRS systems have added multiple sources and detectors, leading to increased coverage of areas of interest, and improved the systems' sensitivity and specificity. At the same time, individual

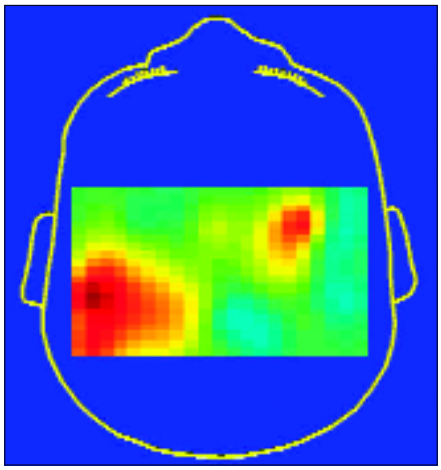
components have become smaller and more reliable. NIRS systems today often consist of little more than a probe with fiber optic sources and detectors, a piece of dedicated hardware no larger than a small suitcase and a laptop computer. Thus, researchers and clinicians can count on a degree of portability unavailable—even inconceivable—for other imaging modalities, such as functional magnetic resonance imaging.

The theoretical and technological advances of the past 10 to 15 years have opened the door to a range of applications, including some that involve imaging of the adult brain, which for many years had been inaccessible to NIRS. "Probably the hottest topic at the moment," says Delpy, "is use of the system for monitoring brain activation in functional brain studies." Researchers have known for decades that performing tasks and processing various stimuli produce corresponding changes in the brain, be they neuronal, metabolic or vascular. Functional magnetic resonance imaging and positron emission tomography are commonly employed to image the changes. But these modalities are, in some ways, limited in application: FMRI requires that the subject lie relatively still in a narrow tube-like space, while PET relies on ionizing radiation dyes as contrast agents. NIRS employs no ionizing radiation and allows for a wide range of movement; it's possible, for example, for the subject to walk around a room while wearing a NIRS probe.

Since the mid-1990s, an increasing number of researchers have performed functional brain studies with near-infrared spectroscopy. They have investigated cerebral responses to visual, auditory and somatosensory stimuli, as well as the motor system and language, and subsequently begun to construct maps of functional activation showing the areas of the brain associated with particular stimuli and activities.

Applications in psychiatry ...

On the clinical side, NIRS may one day contribute to the diagnosis and treatment of depression, schizophrenia and Alzheimer's disease, as well as to stroke rehabilitation. Already, researchers are using the technique to help shed light on the pathogenesis of psychiatric disorders. "Interest [in] using functional NIRS is rapidly increasing," says Ferrari, "because of its potential to explore noninvasively the specificity of frontal and prefrontal cortical areas in performing neuropsychological tests in psychiatric patients." A 1996 study by Okada and colleagues found, for example, that patients with depression exhibited either a "nondominant hemisphere response pattern" or a "bilateral response pattern" during a mirror drawing task,[9] in which the patient traces a figure while looking at its mirror reflection. Matsuo and colleagues found that patients with depression showed less activity in the frontal lobe than did healthy subjects.[10]



NIRS-DOT image of cerebral blood flow in a newborn during passive motor tasks. [Courtesy of the Photon Migration Imaging Lab, Massachusetts General Hospital, Charlestown, Mass.]

Okada and colleagues have also looked at activation of different sections of the brain in schizophrenic patients performing the same mirror drawing task.[11] Here again, they found different patterns of activation than they did in control subjects. Similarly, Fallgatter and Strik have reported that schizophrenic patients do not exhibit the typical pattern of right-lateralized activation during a continuous performance test,[12] a computer-based test used to identify attention problems. Finally, several groups have performed NIRS studies of patients with Alzheimer's, investigating the changes brought about by the disease.[13-16] Hock and colleagues, for example, monitored patients during verbal fluency tasks and found decreases both in oxygenated hemoglobin and in the total concentration of hemoglobin in the parietal lobe, one of the areas of the brain that typically degenerates in Alzheimer's patients.[15] This suggests that a reduced oxygen supply during activation of brain function may play a role in the pathogenesis of the disease.

Ultimately, cognitive studies of patients with psychiatric disorders may inform diagnoses; having identified the areas of the brain in which functional activation is impaired or otherwise affected, researchers and clinicians may be able to establish criteria by which to determine whether the patient has a particular disorder. "You want a quantitative desaturation measure to know which part of the brain is in danger," says Chance. "If an activation occurs, then you can be confident that that part of the brain is capable of doing its job, that it's not compromised by Alzheimer's, stroke and so forth." Hock and colleagues and Hanlon and colleagues have begun to explore the potential of NIRS for diagnosing Alzheimer's disease.[13, 16] As the technology develops further, researchers will likely look into its potential for diagnosing other disorders as well.

... and treatment monitoring

NIRS may also prove useful for treatment monitoring, as suggested by a 2000 study by Eschweiler and colleagues.[17] "Certain activation patterns as revealed by NIRS may predict responsiveness of depression to repetitive transcranial magnetic stimulation therapy," says Arno Villringer, a Berlin Neuro Imaging Centre researcher who has published widely on functional NIRS studies of the human brain. "More research has to be done on the predictability of success. If this research confirms early findings, then this kind of application has a bright clinical future."

Stroke rehabilitation is another promising application area. Recovery from stroke is possible primarily because of brain plasticity, a process by which the brain reorganizes itself, repairing damaged connections or creating new ones to compensate for the

loss. Knowing how the brain achieves this result can help determine whether rehabilitation has been successful for individual stroke patients; by monitoring recovery, clinicians will be able to adjust treatment as necessary and perhaps even predict outcome. In a 2000 study by Saitou and colleagues,[18] researchers employed NIRS to measure oxygenation in the affected prefrontal cortex in post-stroke patients with hemiplagia performing certain rehabilitation tasks. They found that the technique may be especially useful for determining changes in oxygenation during exercises with affected lower limbs.

The future

NIRS isn't yet ready to be introduced into the clinic. Large-scale clinical trials are required to show that the technique has sufficient sensitivity and specificity, as well as predictability. In addition, clinicians need to know how to understand the NIRS signal: most have never looked at a signal that contains information about tissue oxygenation. Although it may be some time before clinical acceptance, it is already clear that NIRS can contribute to an array of applications, noninvasively, continuously and at bedside. Indeed, it seems that the history of this technique is just beginning.

NIRS may be especially useful for determining changes in brain oxygenation during exercises with affected lower limbs.

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