shining *new* light on brain function

Near-IR systems offer handheld and even non-contact methods for monitoring brain functions like problem solving.

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Brain function imaging has become an important technique for figuring out how the brain works. Using techniques such as magnetic resonance imaging (MRI) and CT scans, scientists have observed the brain in action, watching different areas "light up" as a test subject struggled to recall a word or perform a calculation. Now near-IR (NIR) imaging is providing yet another tool for these studies. Using IR radiation, we can measure changes in blood flow and relative oxygenation in different parts of the forebrain in response to various stimuli, essentially mapping problem-solving processes (see figure 1).

The sensor for NIR images of the brain is a fairly massive object, even when microsources and detectors are mounted in the image pad and more so when an array of well-clad optic fibers couple to the head (see fig. 2 on pg 5). Instead, our sensor is held in place on the forehead by Ace bandages and Velcro straps with sources and sensors embedded in soft plastic. In our student summer program, during which we used this sensor to make several thousand observations, we sometimes observed outlier signals often due to head movements as illustrated by the histogram display of oxygenation changes for each pixel.

The result of the data analysis gives the histogram display that is usually a normal distribution of several hundred studies for each pixel, from which most of the data fit in a Gaussian distribution. In many cases we obtained more than 400 observations on certain pixels. The magnitude of the signal abscissa is the micromolar increment of oxygenated hemoglobin or, in other cases not shown, the micromolar increment of blood volume (total oxy- plus deoxyhemoglobin). However, the fraction of these observations that fit a normal distribution (Gaussian curve) is usually about 70% to 80%. To give an impression of how selective is each of the pixels to the nature of the cortical response to the challenge of problem solving (five-letter anagrams), we display these histograms in their approximate projection upon Brodman's areas 9 and 10. We further codify the display by taking those data fitting a normal distribution. The figure of merit is

the product of the mean value of the Gaussian, times the number of observations included in the Gaussian, divided by the FWHM of the Gaussian.

One area under study is whether the response of the forebrain is different when a subject tells the truth from when the subject lies. In the guilty/knowledge test, well known to psychologists, a subject is asked a question and either lies or responds truthfully. Using NIR imaging techniques, we can look at a series of pixels and see that the brain behaves differently depending on the answer given. These studies have been carried out on a large number of subjects, but since no subject gives exactly the same forebrain response, we present the results of many hundreds of tests on a single individual (see figure 3). In this case, the merit for the individual pixels is very high for the left upper region when the subject tells a lie, yet when the subject tells the truth, that region has a lower score and only one pixel is illuminated.

For such studies, as well as using NIR for imaging muscle function or detecting cancer (optical mammography), the question of data reproducibility, both for a given patient and within a number of subjects or patients, is of paramount importance. In all these areas, the reproducibility depends on how well the sensor system, light source, and detector couple to the tissue. How well can the sensor be placed and replaced? How well is the position maintained during movement and motion?

a different approach

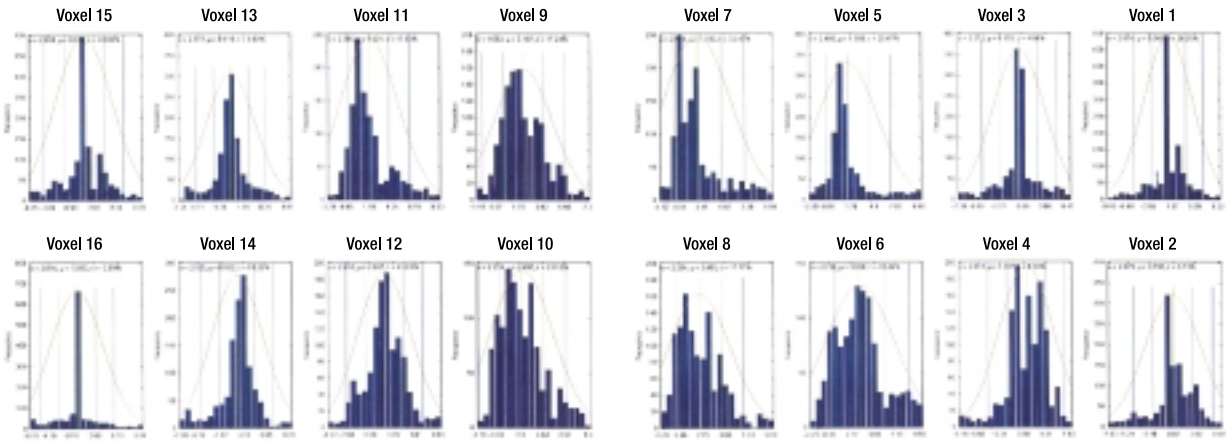
One solution to the brain motion problem is to make a handheld unit and scan it over the forebrain, as is done with ultrasound (see figure 4). This requires miniaturization, as students Yu Chen and Chien Liu have demonstrated. We have discovered that the phased-array NIR optical system can be operated at low (audio) frequencies with two sources and one detector. This system, being a handheld differential system that records rapidly, can readily detect subsurface optical signals with 2 to 3 mm resolution.

With this system, we can scan the forebrain during functional activation procedures in which the increased blood volume or oxygenation changes may be continued for an interval of 30 to 60 s, giving us time to seek voxels in which the blood volume and/or oxygenation has increased. Such positions can be marked and confirmed during successive stimulations. The discovery of an optical discontinuity is marked by the acoustic and numerical readout. This system is also ideal for scanning the human breast for cancer detection because regions difficult to reach with a fixed-probe setup—near the nipple or near the junction of the breast to the chest—can readily be scanned. Finally, such a device is ideal for lymph-node scanning in which the region behind the breast can be scanned following the usual injection of sulfur colloid, and, in this case, indocyanine green to mark the position of the sentinel node.

The handheld phased-array localizer simulates ultrasound in deployment but explores the two key features of breast cancer and brain function—increased blood flow and volume, and increased metabolic rate in functional or cancerous regions. The NIR optical detector is much simpler and less power intensive. Even with the printed circuit of electronic technology, it can be handheld and pocket sized; with Complementary metal-oxide semiconductor (CMOS) technology, pen sized. Thus, optics/electronics combinations lead to remarkably efficient, cost-effective, user- and patient-friendly medical devices.

Another method, in which the optical system can be made light enough to be fastened directly to the forehead or breast with adhesive, is made possible by telemetry. Here, the amount of electronics in the probe is minimal; a central light source transmits photons through the brain cortex to remote detectors and is equipped with a small radio transmitter of the kind that unlocks the door to your car (see figure 5). It weighs about 0.5 g and transmits at 400 or 900 MHz using surface mount technology. We propose to fabricate this

Figure 1 Histograms of prefrontal activation data captured while subjects solved anagrams show number of tests as a function of post solution oxygenation; histograms are listed by position on the probe.



system with CMOS; it will be postage-stamp size, just held onto the forehead by a bandage, so that the probability of motion artifacts is much less.

This is a rather simple system. The sensor consists of a silicon photodiode, with a pre-amp that gives enough signal for the voice channel of a small radio transmitter. The sensor is illuminated by a pair of nearby NIR LEDs at 730 and 850 nm that send diffusing photons. The receiver is synchronized by the received signals themselves. In fact, the signal-to-noise ratio (SNR) of telemetry is extraordinarily good (over 20:1 on human arm ischemia). The dual-wavelength sensor is attached to the arm. Arm exercise gives a reliable signal. The absorption signal at 730 nm increases as a result of increased extraction of oxygen from oxyhemoglobin (creating more deoxyhemoglobin, which absorbs at 730 nm). We can measure the blood volume change by capturing the sum of signals at the two wavelengths. At cessation of muscle contractions, the deoxyhemoglobin reoxygenates (creating more oxyhemoglobin), indicating recovery to the resting values. (fig. 6 on pg 5) The SNR for this system is so high because the sensor is attached to the arm firmly.

The telemetered technology will also benefit from integration with wireless-phone technology. One can transmit signals by the cell-phone systems (Othello or Bluetooth), which operate at 900 or 2400 MHz. An added local oscillator and mixer will step down the signal to 200 or 100 MHz. The NIR source and detector operate at this frequency, and the output from a photomultiplier tube (PMT) can be upshifted to the high radio frequencies. The sine and cosine components of phase and amplitude are obtained as they are in a cell-phone system.

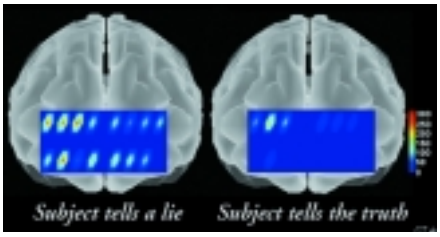


Figure 3 A number of pixels (blue box, upper left), show lies result in increased prefontal lobe activation.

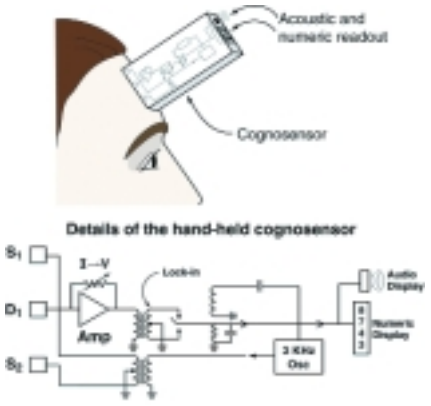


Figure 4 A handheld phased-array cognosensor uses a 3-kHz carrier for modulating the LED sources (730/850 nm) and a simple phase-sensitive detector and audible and numerical display. The device can detect the presence of prefrontal brain activation or when applied to the breast, subsurface cancer.

avoiding contact

The current practice in NIR studies is to have the light source and the sensor in close contact with the skin in order to avoid light leakage from source to detector. In general, the source is carefully shielded from the detector, particularly in systems using continuous light and systems using phase detection. We have developed a time-domain system that permits location of both source and detector several meters away from the forehead or breast. The time difference between the arrival of specular reflections and the delayed photon migration signals can be as much as several nanoseconds, which is sufficient to allow deconvolution of the two.

Thus, the ultimate system is one that

the legend of Britton Chance

Sitting in his office at the University of Pennsylvania, Britton Chance could easily just rest on his laurels, content. Words like "legend" come to mind.

But what else do you call a man who fished with Ernest Hemingway and has the stuffed marlin to prove it, who patented the original autopilot for ships, who won both an Olympic Medal and a National Medal of Science, and who helped the WWII war effort as part of teams that developed radar-pointing mechanisms for anti-aircraft guns and the ground position indicator to direct radar-guided bombs to their targets?

Throw in Chance's doctorate in physical chemistry from the University of Pennsylvania and another in physiology from Cambridge University, countless papers and awards, and the accolades from his peers that firmly establish Chance as the father of imaging and spectroscopy of activations in tissue.

Chance's connection to biology and chemistry started before he was born, with a father who developed a carbon-monoxide detector that replaced the canaries in Pennsylvania coal mines and an uncle who developed a separation process for slate from coal. It continued with Chance's experiments showing the first details of how enzymes work and later how mitochondria produce cellular energy through adenosine triphosphate. When tools were not available for his experiments, Chance built his own, including dual-beam spectrometers and magnetic resonance spectrometers, among others.

Today, Chance continues to support the exploration of life in all its forms, including the use of short-pulse, near-IR light to explore brain activity. Not bad work for the 20th century. One can only imagine what he will accomplish in the next. *—Winn Hardin*

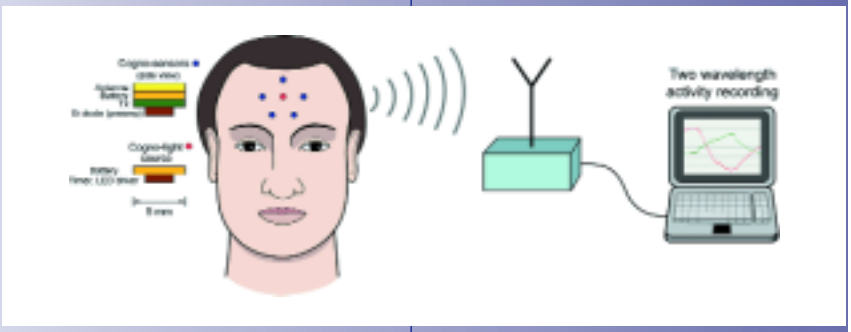


Figure 5 A small light source and sensors can transmit data to a remote system.

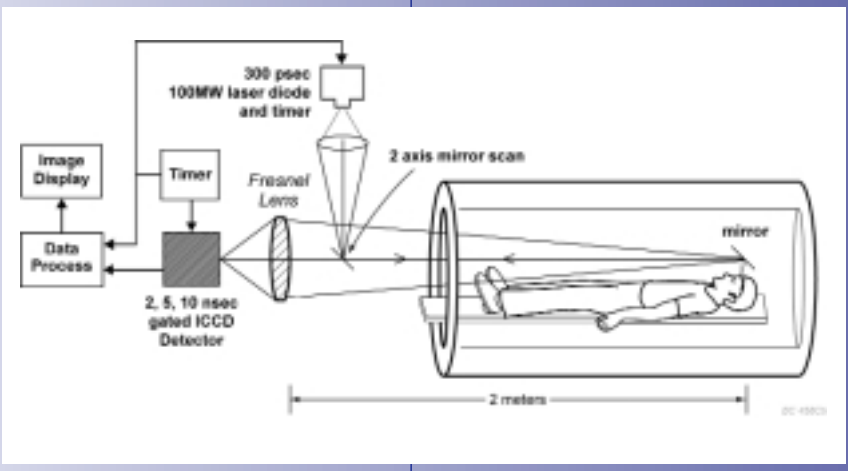


Figure 8 Non-contact TRS features co-axial illumination ICCD detector and servo controller of illumination position.

does not make any contact with tissue at all but still obtains reflectance and diffusive signals. We use time-resolved imaging to deconvolve the reflectance signal. One can time-deconvolve the early reflectance signals from the late photon migration signals. A 10-in. Fresnel lens collects about a 7° to 10° solid angle from the subject's forehead and focuses it on a PMT, which is then coupled to a boxcar detector or to an intensified CCD gated at different times (2 to 5 ns, 5 to 10 ns, etc.) to measure μ*a*, calculated from the rate of decay in ΔOD per nanosecond (where *a* stands for the absorption coefficient of the photon tissue [see fig. 7 on pg 5]).

The larger the absorption coefficient, the more rapid the decay according to the Patterson-Chance-Wilson equation $\mu_a c$, where c is the velocity of light (cm/ns). One can thus distinguish the absorption of migrating photons absorbed by oxy- or deoxyhemoglobin. These relationships have been verified in detail via Monte Carlo simulation and TRS studies of a model of the brain using appropriate absorption and scattering coefficients.

The time scale is relatively long. It may take 5 ns for photons to travel to the subject and back again, so high time resolution is not necessary and 0.5 ns is adequate for the pulsed light source duration.

It is unusual to afford optical imaging of the brain or breast for patients inside the MRI chamber. Because nothing metallic can be placed in the magnet's field, such studies have required the use of 20 or 30 optical fibers 10-m long for excitation and emission. Our remote sensing system only requires articulated mirrors, made from optical micro-electro-mechanical systems, to scan the excitation beam over the forehead or pendant breast (see figure 8). The 90° mirror in the MRI machine projects light onto the forehead. One can get signals from a gated, intensified CCD, as Eva Marie Sevick-Muraca of Texas A&M University (College Station, TX) has shown in her research. If the subject moves, it is possible to track their forehead with standard video techniques. We have shown that this idea is feasible, and now we are trying to build the electronic package to set it up efficiently.

NIR imaging is a useful tool for studying brain function. Indeed, the possibilities include not only the study of problem solving but of other less-easily quantified phenomena. The sensitivity of brain-functional imaging to perturbations suggests that it could eventually be used to monitor emotional stress and fatigue. Our current studies suggest that these techniques may lead to an effective lie detector. As we continue to shrink the equipment, develop telemetry, and build non-contact optoelectronic systems, we'll obtain better information about what is going on within the human brain or breast. **oe**

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SPIE member

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For additional figures and a list of references for further reading, go to www.oemagazine.com.

Figure 2
The optical detector of brain function is easily held in place over forehead Photo credit: University of Pennsylvania

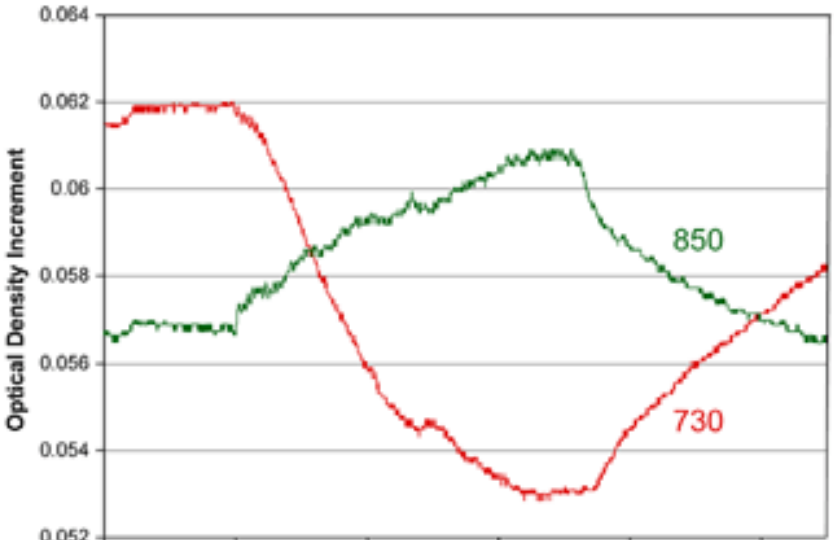

Figure 6
Plot of optical density as a function of time shows decrease of NIR signal at 730 nm (red) due to increased deoxyhemoglobin, and an increase of NIR signal at 850 nm (green) due to decreased oxyhemoglobin. On cessation of exercise, reoxygenation occurs and continues for a further 50 s.

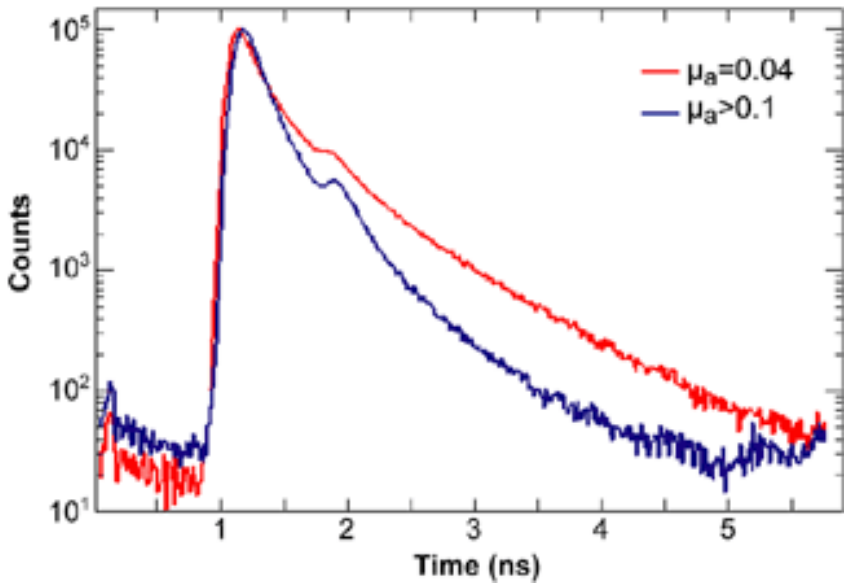

Figure 7
Typical photon signals for a non-contact test taken at 1 m. The slope is steeper because of the larger absorption coefficient, showing that the reflected photons are time resolved from the photons that have gone into the model and have come out again; the bump around 2 s is an artifact of our PMT structure.