REVIEW

Non-Invasive Neuroimaging Using Near-Infrared Light

Gary Strangman, David A. Boas, and Jeffrey P. Sutton

This article reviews diffuse optical brain imaging, a technique that employs near-infrared light to non-invasively probe the brain for changes in parameters relating to brain function. We describe the general methodology, including types of measurements and instrumentation (including the tradeoffs inherent in the various instrument components), and the basic theory required to interpret the recorded data. A brief review of diffuse optical applications is included, with an emphasis on research that has been done with psychiatric populations. Finally, we discuss some practical issues and limitations that are relevant when conducting diffuse optical experiments. We find that, while diffuse optics can provide substantial advantages to the psychiatric researcher relative to the alternative brain imaging methods, the method remains substantially underutilized in this field. Biol Psychiatry 2002;52:679–693 *© 2002 Society of Biological Psychiatry*

Key Words: NIRS, non-invasive, functional brain activity, diffuse optical tomography, optical imaging

Introduction

Neuroimaging Methods

Several non- or minimally-invasive neuromonitoring techniques for examining functional brain activity are currently available to the psychiatric researcher and clinician. Historically, electroencephalography (EEG) was the first to appear on the scene, followed by other technologies including positron emission tomography (PET) and single-positron emission computed tomography (SPECT), magnetoencephalography (MEG), and most recently functional magnetic resonance imaging (fMRI). These methods are often categorized in terms of whether they provide direct or indirect information about brain function. Direct methods include MEG, EEG, and event-triggered EEG (also called event related potentials; ERPs), each of which monitors a direct consequence of brain electromagnetic activity. In particular, EEG and ERP record the electrical fields generated by neuronal activity, while MEG records the magnetic fields induced by such activity. PET, SPECT and fMRI, on the other hand, are indirect methods in that they generally monitor hemodynamic changes consequent to brain electrical activity. PET and SPECT brain imaging operate by monitoring the decay of blood-borne radioactive isotopes as they pass through the brain. FMRI, in contrast, detects changes in the local concentration of deoxyhemoglobin via its effect on imposed magnetic fields. While each of these techniques has its own distinct advantages, at present the direct methods tend to have limited spatial resolution, whereas the indirect methods can only detect neuronal activity after it has been filtered by a complex and poorly-understood neurovascular coupling function.

Diffuse Optical Methods

A lesser-known technology for monitoring brain function capitalizes on the absorption and scattering properties of near-infrared light to provide information about brain activity. It was long thought that the scattering of light by tissue made it impossible to recover information from anything but the most superficial layers of tissue (e.g., microscopy). Indeed, most long-standing optical techniques in use in the neurosciences are for superficial tissues only (Villringer and Chance 1997). Some 25 years ago, however, it was discovered that useful information could be obtained from thick tissue samples, including brain monitoring using light applied to and detected from the scalp (Jobsis 1977). This finding spurred the development of diffuse optics as a technique for human brain monitoring. The technique goes variously by the names of near-infrared spectroscopy (NIRS), diffuse optical tomography (or topography; DOT) and/or near-infrared imaging (NIRI). All of the techniques are based on essentially the same concept—shine light onto the scalp, detect it as it exits the head, and use the absorption spectra of the light absorbing molecules (chromophores) present in tissue to interpret the detected light levels as changes in chromophore concentrations.

To compare the spatial and temporal sensitivity of these various brain imaging techniques, we present Figure 1, modeled after a similar figure by (Churchland and Sejnowski 1988). It is clear that MEG and ERPs are strong in temporal sensitivity but relatively weak in terms of

From the Neural Systems Group, Massachusetts General Hospital, Harvard Medical School and Harvard-MIT Division of Health Sciences and Technology (GS, JPS), Charlestown, MA; Athinoula M. Martinos Center, Department of Radiology, Massachusetts General Hospital, Harvard Medical School (GS, DAB), Charlestown, MA.

Address reprint requests to Gary Strangman, Ph.D., Neural Systems Group, 149 13th Street, Room 10018, Charlestown MA 02129.

Received February 20, 2002; revised July 8, 2002; accepted July 16, 2002.

© 2002 Society of Biological Psychiatry

0006-3223/02/$22.00
PII S0006-3223(02)01550-0

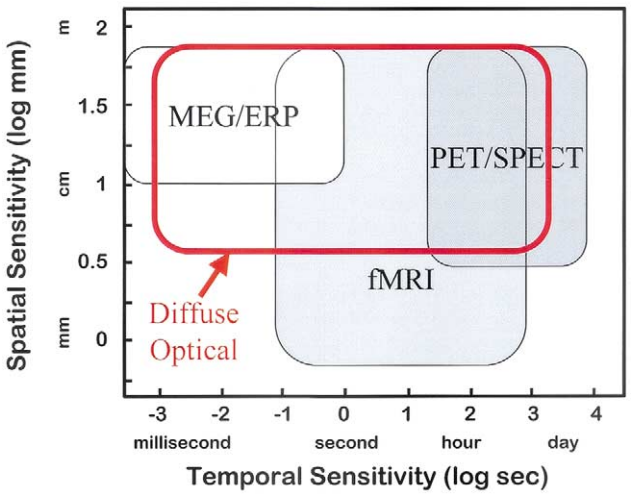

Figure 1. Comparison of the spatial and temporal sensitivities of six non- or minimally-invasive neuroimaging methods.

spatial sensitivity. In contrast, fMRI, PET and SPECT are stronger in spatial sensitivity but weak in terms of temporal resolution. Diffuse optical techniques, in comparison, can provide excellent temporal sensitivity as well as reasonable spatial sensitivity. When multiple colors of light are used, moreover, spectroscopic information about the sampled tissue also becomes available, thereby affording the promise of quantifying the concentrations of the various hemoglobin species-oxyhemoglobin, deoxyhemoglobin, and the sum of these (total hemoglobin, which is proportional to blood volume).

In addition to hemoglobin-based measures of brain activity, diffuse optical techniques also make non-hemoglobin-based measures feasible. For example, by recording data from several wavelengths simultaneously, one can measure other tissue chromophores, including cytochrome oxidase. As a marker of metabolic demands, cytochrome oxidase measurements can provide more direct information about neuronal activity than hemoglobin changes (Heekeren et al 1999; Jobsis et al 1977). There is also evidence to suggest that diffuse optical methods can detect cell swelling that occurs in the 50–200 milliseconds following neuronal firing, which would be an even more direct measure of neuronal activity than the hemodynamic or metabolic markers (Gratton and Fabiani 2001; Steinbrink et al 2000; Stepnoski et al 1991). This type of "fast" signal appears to be significantly smaller than the hemodynamic signals (on the order of a .01% signal change). With sufficiently fast and sensitive electronics, however, such signals could be feasibly recorded by the same equipment as the hemodynamic signals. (The spatial correspondences between these various signals remain to be investigated.) Thus, diffuse optical techniques may be simultaneously capable of providing both indirect and more direct methods of neuronal activity monitoring-complementary sources of information about brain function.

The primary advantages of the optical approach, however, lie in areas not explicitly represented by Figure 1. In particular, the instrumentation—which is completely non-invasive—can be made portable, unobtrusive, low-cost, low-power, and can even be made robust to motion artifacts (e.g., Totaro et al 1998). For the psychiatric researcher, these additional strengths can bring otherwise previously unthinkable projects into the realm of possibility. For example, with proper fiber coupling, extensive movement can be tolerated, opening up the possibility of studying infants, small children, patients with severe movement disorders, or other highly animated subjects, without sedation. The portability and near-zero run-time cost of the instrument affords bedside (or home) monitoring for extended periods, which could be useful for monitoring the effects of slowly acting drugs, or slowly evolving pathologies. And, the fact that near infrared light is non-ionizing means that there is no limit to the number of scans one can undergo.

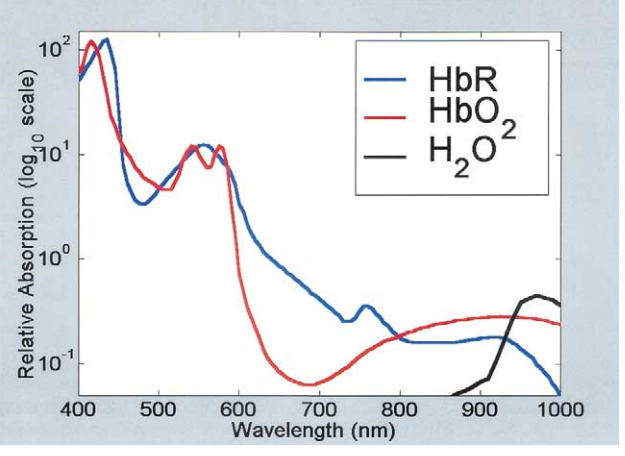

Figure 2. Absorption factors for the primary light absorbers (chromophores) in biological tissue in the near-infrared wavelength range (HbR, deoxyhemoglobin, HbO_2, oxyhemoglobin). The relatively low absorption factors between roughly 650 and 950 nm provide an "optical window" in tissue through which one is able to see changes in oxy- and deoxyhemoglobin deep within tissue, including the head.

BIOL PSYCHIATRY
2002;52:679–693

The "Optical Window"

Diffuse optical recordings depend on two critical characteristics of the electromagnetic spectrum as it interacts with biological tissue. First, while biological tissue is relatively opaque to visible light, it is not totally opaque, as demonstrated by a simple experiment. Darken a room, shine a flashlight through your hand and notice that the white light from the flashlight exits with a red hue, indicating that the tissue least absorbs the redder wavelengths. Near-infrared (NIR) light—from approximately 650–950 nm—is even more weakly absorbed by tissue than the red wavelengths (Figure 2). As a result, this range of wavelengths is often called an "optical window" into biological tissue. This property allows light of these wavelengths to penetrate several centimeters through tissue and still be detected.

The second critical characteristic of NIR light as it interacts with biological tissue is also apparent in Figure 2. The two dominant chromophores for the NIR wavelength range just happen to be two biologically relevant markers for brain activity: oxyhemoglobin (HbO_2) and deoxyhemoglobin (HbR). Thus, NIR wavelengths pass relatively easily through tissue, and their absorption can provide information relevant to brain function.

Having described what makes the technique possible, we next discuss the methodology details, including the types of measurements one can make, the nature of diffuse optical monitoring equipment, and the basic underlying theory necessary for data interpretation. We will then review brain research applications of diffuse optical techniques—with an emphasis on psychiatric patient groups—and will finally discuss the practical issues presently faced by optical researchers.

Methods and Materials

Types of Diffuse Optical Measurements

The amplitude of the recorded signal in a diffuse optical measurement is determined by two factors: (i) absorption of light by the tissue, and (ii) light scattering within the tissue. An increase in either factor results in a decrease in detected light levels, and a corresponding decrease in signal. The goal of diffuse optical measurements is to detect such changes and, in some cases, determine whether the change was due to a change in absorption or scattering by the tissue under investigation. As mentioned, absorption changes are predominantly driven by changes in hemoglobin concentrations. When a diffuse optical probe is placed on the head, the observed hemoglobin changes reflect underlying brain activity (Kleinschmidt et al 1996; Villringer et al 1997). Scattering changes, in contrast, have a less clear relevance to the psychiatric researcher in large part because the sources of scattering changes within the head are only partly understood. For example, scattering may be higher in regions with dense fiber tracts (differences thereby being observable across subjects or evolving over time). However, the importance of scattering changes to normal and diseased brain activity and baseline states remains to be investigated in detail. Presently, most optical brain monitoring experiments simply assume scattering remains essentially constant during the experiment and that all observed signal fluctuations are due to changes in absorption.

Three main categories of diffuse optical measurements have been developed: time domain, frequency domain and continuous wave measurements (Table 1). Time domain, or time-resolved, systems introduce into tissue extremely short (picosecond) incident pulses of light, which are broadened and attenuated by the various tissue layers (e.g., skin, skull, cerebrospinal fluid and brain). A time domain system detects the temporal distribution of photons as they leave the tissue, and the shape of this distribution provides information about tissue absorption and scattering. In frequency domain systems, the light source shines continuously but is amplitude-modulated at frequencies on the order of tens to hundreds of megahertz. Information about the absorption and scattering properties of tissue are obtained by recording the amplitude decay and phase shift (delay) of the detected signal with respect to the incident signal (Chance et al 1998). In continuous-wave (CW) systems, light sources emit light continuously, like frequency domain systems, but at constant amplitude, or modulated at frequencies not higher than a few tens of kilohertz (which provides stray-light rejection). CW systems measure only the amplitude decay of the incident light.

Each of these techniques has intrinsic advantages and drawbacks, the characteristics of which are outlined in Table 1. The choice of measurement mode is basically determined by the type of information one needs to collect. For the psychiatric researcher interested in monitoring brain function changes over time, a frequency domain or continuous wave instrument would typically be sufficient; the added spatial specificity of time domain instruments and the ability to separate absorption and scattering effects is not clearly necessary for such measurements.

Point Measurements vs. Imaging

Each of the three instrument types can in theory be deployed in either point measurement or imaging configurations. Fundamentally, the difference between a point-measurement instrument and an imaging instrument lies merely in the number and geometrical arrangement of sources and detectors. In particular, a point-measurement

Table 1. Characteristics of the Three Main Types of Diffuse Optical Measurements

Measurement Type	Advantages	Disadvantages	Example Uses	References
Time domain	Spatial resolution Penetration depth Most accurate separation of absorption and scattering	Sampling rate Instrument size/weight Stabilization/cooling Cost	Imaging cerebral oxygenation and hemorrhage in neonates, breast imaging	(Benaron and Stevenson 1993; Chance et al 1988; Hebden et al 1997)
Frequency domain	Sampling rate Relatively accurate separation of absorption and scattering	Penetration depth	Cerebral and muscle oximetry, breast imaging	(Franceschini et al 2000; Gratton et al 1997; Jiang et al 1995; Pogue and Patterson 1994)
Continuous wave	Sampling rate Instrument size, weight and simplicity Cost	Penetration depth Difficult to separate absorption and scattering	Finger pulse oximeter Functional brain experiments (as per fMRI)	(Nioka et al 1997; Schmitz et al 2000; Siegel et al 1999)

fMRI, functional magnetic resonance imaging.

instrument requires only one source location and one or more detector locations. In contrast, a true imaging instrument requires that each detector be able to detect light from two or more source locations.

Consider first the spectroscopy (NIRS), or point measurement, instrument (Figure 3A). As seen in Figure 2, the two dominant absorbers in tissue for the NIR wavelength range are HbO_2 and HbR. Because the absorption coefficients of these two species are always roughly the same order of magnitude in the NIR range, any measurement at a single wavelength will be significantly affected by changes in the concentration of either of the two species, confounding the interpretation of any single measurement. However, as alluded to earlier, simultaneous measurements made at two wavelengths can be used to separate the two types of changes, resulting in simultaneously acquired concentration changes for both HbO_2 and HbR. A NIRS instrument for brain recordings will therefore emit light at two (or more) wavelengths through a source optical fiber into the head, and measure the exiting light for *each* wavelength at a detector location some distance away. Three or more wavelengths can be used either to (i) improve the measures of HbO_2 and HbR, or (ii) extract changes in other, less-absorbing species such as water, and/or cytochrome oxidase (Heekeren et al 1999; Matcher et al 1994). All of this can be accomplished with just one (multi-color) source location and one detector location.

An imaging instrument, in contrast, requires multiple source and detector locations arranged in such a way so as to provide overlapping measurement sensitivities (Figure 3B). The overlapping measurements can be mathematically combined, in a self-consistent way, to generate a spatial image of changes in remitted light over time beneath the probe (Arridge 1999; Arridge and Schweiger 1997). If data from multiple colors are simultaneously gathered at every detector location, spectroscopic images (images of both HbO_2 and HbR) can be generated.

Instrumentation Components

To evaluate the appropriateness of optical instrumentation for a given application requires some understanding of the components that comprise such an instrument. Any diffuse optical instrument will require, at a minimum, three

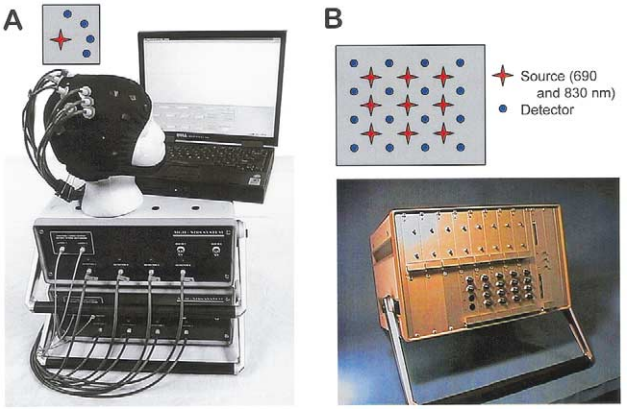

Figure 3. Two example continuous-wave optical instruments. (**A**) An example NIRS experimental setup, including 2 instruments, optical fibers for conducting light to and from the head, and a recording computer. Each instrument provides two light colors (690 and 830 nm) and four avalanche photodiode detectors, affording four separate spectroscopic point-measurements. (**B**) An example DOT instrument, consisting of sixteen detectors (top two rows of connectors), and eighteen laser sources (bottom four rows of connectors). Sources are modular, but typically consist of nine 690 nm lasers and nine 830 nm laser diodes. With an appropriate geometrical arrangement of sources and detectors (top), image reconstruction becomes possible. NIRS, near–infrared spectroscopy; DOT, diffuse optical tomography.

BIOL PSYCHIATRY
2002;52:679–693

Table 2. Types of Light Sources Used in Diffuse Optical Measurements

Source Type	Power Range	Available Colors	Comments
Filtered white light (e.g. tungsten lamp with NIR filter)	Low (<5 mW)	Flexible and variable color resolution	Better color resolution means less power per color
Light emitting diodes (LEDs)	Low to Medium (<1 to 30 mW)	30 nm band surrounding nominal color	Inexpensive
Laser diodes (e.g. in a laser pointer)	Low to High (<1 to >500 mW)	Discrete colors (±1 nm) Limited color choices	More expensive

NIR, near-infrared; LEDs, light emitting diodes.

primary components: a NIR light source, a detector, and electronics for the two. The ideal light source provides multiple discrete NIR wavelengths each at relatively high, tunable power—a type of light source that does not presently exist. Instead, one of three types of light sources is typically used to provide sufficient NIR light for diffuse optical monitoring of brain, as shown in Table 2. Generally speaking, the source tradeoffs depend on two factors: the need for discrete wavelengths and the need for more power. Power is important because detected signals are typically on the order of 10 pW for a source-detector separation of 4 cm, or a loss of 7–9 orders of magnitude in light power. Increasing power can help compensate for this loss, within the safe exposure limits (see Safety Considerations, below).

Detectors form the next critical component of a diffuse optical instrument. Fundamentally, the detection of the extremely low light levels leaving the head requires sensitive detectors, and the four broad classes of optical detectors that are presently in use are outlined in Table 3. The choice of detector is dependent on the particulars of the application. In neuroimaging, as with optical imaging of deep tissue in general, highly sensitive detectors are essential and speed is often highly valued. This suggests the use of PMTs or APDs, respectively. (Though SPDs have been used effectively and are better for use in applications requiring a wide range of incident flux.) Where many wavelengths are desired, CCDs are often used in conjunction with a white light source. The remitted light can be dispersed by a prism onto the CCD, which allows the simultaneous detection of many wavelengths and easily varied spectral resolution.

The final component in a diffuse optical device is the electronic hardware. While the details of the electronics will be of minimal importance to the psychiatric researcher, an understanding of what the electronics must achieve is useful for instrument evaluation. Any given detector is sensitive to all wavelengths of light, and there usually are many source colors and/or source locations to be monitored by any given detector. The electronics must therefore be engineered to allow separation of the various colors and locations. This is achieved in multiple ways. With a CCD camera, separation is achieved spatially, by dispersing light colors across the surface of the detector. The other detectors require modulating and/or multiplexing the sources and then decoding the detector signal so that the colors and locations can be monitored without generating so-called "cross-talk" interference with one another, whereby light from one source is actually interpreted as coming from another source. Minimizing cross-talk can be achieved by time-sharing sources (turn only one on at a time), or various multiplexing schemes (I-Q modulation (Siegel et al 1999); or frequency modulation or time-division multiplexing (Boas et al 2002)). Generally speaking, the electronic needs for an optical instrument are minimal and could easily be loaded onto a single digital signal-processing chip. The overall instrument size, therefore, is determined predominantly by the size of the detectors plus the light sources, as well as the power supply required to stably drive the sources and electronics.

Table 3. Types of Detectors Used in Diffuse Optical Measurements

Detector Type	Speed	Sensitivity	Dynamic Range	Example Application
Silicon photodiodes (SPDs)	Medium (up to 10 kHz)	Low	High (~100 dB)	Multi-use instrument where light levels span many orders of magnitude
Avalanche photodiodes (APDs)	Fast (>100 MHz)	High	Medium (~60 dB)	Adult human measurements
Photomultiplier tubes (PMTs)	Fast (>100 MHz)	Very high below 820 nm, then drops rapidly	Medium (~60 dB)	Adult human measurements
Charge-coupled devices (CCDs)	Slow (up to 1 kHz)	Variable	Up to 60 dB	Simultaneous detection of many wavelengths (e.g., from tungsten lamp)

There are a wide variety of instruments currently in use, both commercial (Colier et al 1997; Cope and Delpy 1988; Franceschini et al 2000; Gomersall et al 1998; Kawaguchi et al 2001; Quaresima et al 2000) and custom-built (Grosenick et al 1999; Konishi et al 2000; Ntziachristos et al 1999; Pogue et al 1997; Schmitz et al 2000; Siegel et al 1999) reflecting the possible tradeoffs when engineering such instruments. The tradeoffs can be made in all three areas just discussed: detectors, light sources, and instrument electronics. The detector choice largely determines the instrument sensitivity, maximum sampling rate and dynamic range. The type of light source determines the amount of spectroscopic data and, in part, the penetration depth (based on the power available). Light modulation/demodulation schemes determine the number of colors and locations that can simultaneously be "seen" by a detector, and they also affect the maximum possible sampling rate for each instrument. The remaining post-detector recording electronics ultimately determine the instrumentation bandwidth, sample rate, total number of samples, the options for post-recording filtering and processing, and occasionally the instrument's dynamic range. All existing instruments handle these tradeoffs differently. Again, for research questions involving changes in functional brain activation within and across subjects (including patient populations), an instrument using APD photodetectors and emitting at least 2–4 colors of light per source location would typically be sufficient. The required number of sources and detectors—and hence the nature of the electronics—is determined by the spatial nature of the question at hand (few needed for hemispheric comparisons, and many for more precise spatial localization).

Safety Considerations

Whenever considering the use of a novel, in-vivo monitoring technology, the issue of safety must be addressed. Unlike MEG and EEG which are passive recording techniques, diffuse optical techniques—like MRI and PET—operate by depositing energy into the subject and recording changes in that energy when remitted. For diffuse optical recordings, safety considerations revolve around maximum safe exposure durations and power densities for near-infrared light, which are defined by the American National Standards Institute (2000). NIR light is nonionizing (unlike, for example, ultraviolet and shorter light wavelengths), so the primary concern has been with tissue heating. For brain monitoring, heating is most relevant for the skin of the scalp, as the vast majority (>95%) of the NIR power is deposited in this layer. The exact limit depends on many factors, including the wavelength, coherence (lasers vs. other light sources), duration and area of exposure, but the power required for diffuse optical measurements—even for relatively large source-detector separations (and hence 7–9 orders of magnitude in total signal loss)—remains well below the level where tissue damage from heating might occur (Ito et al 2000). That limit, the maximum permissible exposure for skin (assuming incoherent light and continuous illumination), ranges from .2 W/cm^2 at 630 nm to .4 W/cm^2 at 850 nm. The limits are substantially lower for eye exposure, particularly for coherent sources, and hence caution must always be exercised with respect to inadvertent eye exposure to the light sources. At present, there is little information on the direct effects of NIR light on brain tissue. On the positive side, there is evidence that the NIR wavelength range can provide therapeutic benefits via photodynamic therapy (Schmidt et al 1996) and can even promote wound healing (Whelan et al 2001), though the mechanism by which this latter effect occurs is still under investigation.

Basic Theory

Modified Beer-Lambert Law (MBLL)

To quantify changes in concentrations of absorbing species, a model of light diffusing through tissue is required. A traditional approximation to the full photon migration theory is called the modified Beer-Lambert Law (MBLL), which is an empirical description of optical attenuation in a highly scattering medium (Cope et al 1987). A change in the concentration of an absorbing species causes the detected light intensity to change and, according to the MBLL, the concentration change is proportional to the logarithm of the detected light intensity during the change divided by the light intensity before the change. The proportionality constant is comprised of two, simple conceptual pieces: (1) a measure of the path length the scattered light actually traveled through the tissue (decomposed as the source-detector separation times a quantity called the differential pathlength factor), and (2) the extinction coefficient of the absorbing species. The source-detector separation is easily measured along the surface of the head, and the extinction coefficient for a given species can be looked up in tables. The differential pathlength factor is either measured (with a time-domain or frequency domain instrument) or it is estimated (for a continuous wave measurement).

As already mentioned, in order to determine the contribution of multiple chromophores (e.g., oxy- and deoxyhemoglobin), we must take measurements at one or more wavelengths per chromophore to be resolved. For example, by measuring the change in light intensity at two wavelengths, and using the known extinction coefficients of oxyhemoglobin (ε_{HbO_2}) and deoxyhemoglobin (ε_{HbR}) at those wavelengths (from Figure 2), one can then sepa-

BIOL PSYCHIATRY
2002;52:679–693

rately determine the concentration changes of oxyhemoglobin and deoxyhemoglobin by solving the two equations with two unknowns for Δ[HbR] and Δ[HbO_2]. This approach can be generalized to more than two wavelengths (Cope et al 1991).

Beyond MBLL

The MBLL method provides a reasonable first approximation to calculating concentration changes. However, this model is dependent on knowledge about the precise spatial location and extent of any change in [HbR] and/or [HbO_2] relative to the location of the source and detector (Boas et al 2001). Without such knowledge, a simplifying assumption is typically made wherein any concentration changes are assumed to be uniform throughout the entire sampling region (Cope and Delpy 1988; Cope et al 1991). For measurements in settings such as functional brain activity, this assumption is violated. In an adult human, the scalp and skull range from approximately 1 to 2 cm thick, depending on the subject and the region on the head (Figure 4). Moreover, a lack of significant findings in these layers from whole-head functional MRI scanning suggest that these layers generally exhibit little or no change in hemodynamic variables during task performance. Thus, the region of hemoglobin change will typically be focal relative to the entire sampling region for a given source-detector pair. The consequences of violating the global-change assumption are only beginning to be characterized (Uludag et al 2002). Thus far, however, the validity of the technique has tested favorably against several other monitoring modalities (Kleinschmidt et al 1996; Terborg et al 2000; Villringer et al 1997) and theoretical studies suggest that any resulting errors can be limited to less than 10% (Strangman et al., unpublished). One way to further reduce such focal-change errors is to use an imaging instrument and associated image reconstruction algorithms. Imaging, by definition, accounts for the focal nature of changes by replacing the MBLL with reconstruction algorithms that find a self-consistent spatial "explanation" for the observed multiple overlapping measurements. This will be discussed further in Image Reconstruction, below.

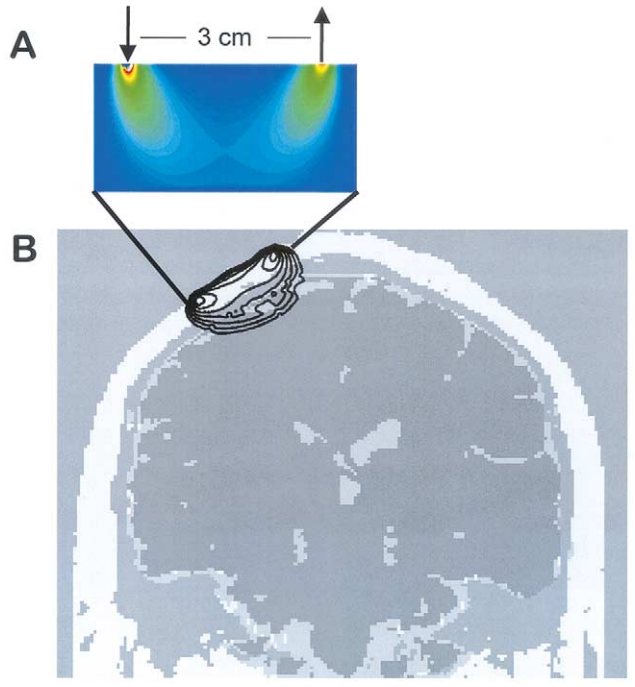

Figure 4. (**A**) An example sensitivity plot for light traveling in a homogeneous, highly scattering medium for a continuous-wave or frequency-domain measurement. Arrows indicate the location of a source (left) and detector (right), and colors indicate the number of detected photons that reached any given point in the homogeneous medium. White, reds and yellows indicate the highest numbers (and hence the highest sensitivities), blues and purples indicate progressively lower sensitivities. (**B**) A similar plot for light traveling through the head of an example subject. Contour lines appear every half-order of magnitude and end at the sensitivity limit of our NIRS instrument. Anatomical MRI scans were performed and segmented into 1 mm voxels labeled as air, scalp, skull, CSF or brain. Simulations of light propagation through both media were performed in 3D—using different optical properties for each tissue type—to determine the spatial distribution of light flux through the head based on the source-detector positioning shown. NIRS, near–infrared spectroscopy; MRI, magnetic resonance spectroscopy; CSF, cerebral spinal fluid.

Neuromonitoring Applications

Physiology

An example time series from a CW NIRS instrument appears in Figure 5, obtained from probe located over position C3 in the International 10/20 system (approximately over left primary motor cortex) on a subject sitting upright, quietly resting with eyes open. The high-frequency oscillations correspond to the cardiac cycle, whereas the low frequency oscillations likely correspond to Mayer wave oscillations (Obrig et al 2000). Simple measures such as these can provide useful physiological information, but for functional monitoring such baseline signals can confound data interpretation. With sufficient temporal resolution, as is available in the data in Figure 5, it becomes possible to model and remove some such physiological changes (e.g., heart rate), resulting in a cleaner signal and substantially increased signal-to-noise ratio for functional changes (Gratton and Corballis 1995).

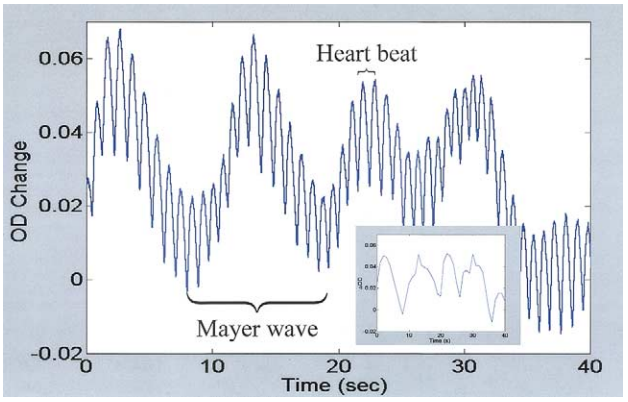

Figure 5. Optical density change [$OD = -\log(I_{final}/I_{baseline})$, where I is the measured light intensity] recorded from position C3 (i.e., over primary motor cortex) in a seated subject during quiet rest. Several physiological oscillations are evident including the cardiac cycle and Mayer waves. Inset shows the same signal sampled at 1 Hz, illustrating the loss of information that can occur with slower sampling, as is the case with fMRI. The relatively high speed of optical instruments allows more complete interpretation of collected data, which can in turn increase the signal-to-noise ratio for changes due to functional brain activity. fMRI, functional magnetic resonance imaging.

The inset in Figure 5 shows the same signal when sampled at 1 Hz—a typical recording rate for fMRI—wherein there is insufficient information for such modeling, making signal interpretation for this subsampled signal more difficult than with the higher sampling rate. Fast recordings not only improve temporal signals, but they can also enhance spatial localization by detecting the temporal properties of structures (e.g., localizing an artery by looking for pulsations in the signal; Barbour et al 2001). Slow physiological changes—ones that evolve on a timescale similar to that of the hemodynamic response to brain activation (such as Mayer waves)—must be reduced or eliminated by other techniques, such as the use of event related experimental paradigms (Rosen et al 1998).

Basic Research

In the functional brain imaging arena, diffuse optical techniques are not as widespread as other methods, but they have been applied in a variety of fields in both basic and clinical neuroscience and neuroimaging. Figure 6 shows example responses recorded in a simple motor task, as compared to the simultaneously acquired, spatially co-registered fMRI signal from primary motor cortex in a human volunteer. To summarize the procedure: after consent to a protocol approved by the Massachusetts General Hospital review board, we fitted a subject with a continuous-wave diffuse optical apparatus (Figure 3A), positioned over the left sensorimotor area. The subject was then positioned for scanning in a Siemens Sonata 1.5T scanner, and anatomical SPGR images were collected to enable the identification of fiducial markers near the fiber tips. This allowed post-scanning co-localization of the optical probes in the MR imaging space. The subject performed eight 16 sec blocks of a right-hand tapping task (onsets indicated by vertical bars in Figure 6), interleaved with 16 sec periods of rest. Statistical maps of the fMRI were used to select activated voxels near the surface of the cortex, four of which were averaged to produce the fMRI timeseries in the figure. Once the optical fibers were identified in the MR imaging space, we selected the source-detector pair closest to the identified region of fMR activation, converted the data to HbO_2 and HbR concentrations, and plotted the results. The decrease in [HbR] mirrors the observed increase in the blood-oxygenation level dependent fMRI signal, with good correspondence between the two recording modalities. The inset shows the signal obtained from a source-detector pair several cm from the activated region.

The diffuse optical results for this motor task are typical of brain activation, and hence similar findings have been

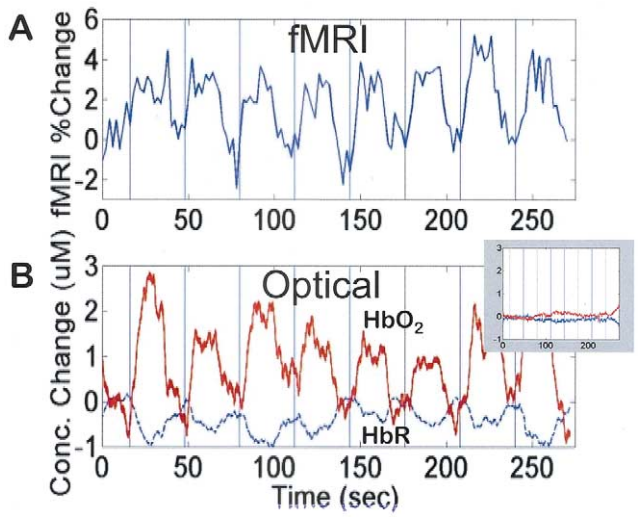

Figure 6. Raw time courses for a single run of a simple motor task, consisting of eight 16 sec periods of finger tapping alternating with 16 sec periods of rest. Vertical bars indicate onset of motor activity. (**A**) fMRI time course for left primary motor cortex during right finger tapping, averaged over four significantly activated voxels. (**B**) Changes in [HbO_2] and [HbR] as determined from the source-detector pair closest to the fMRI activation. Inset shows control HbR and HbO_2 timecourses from a measurement several centimeters away from the activated region (same y-axis scaling). fMRI, functional magnetic resonance imaging.

BIOL PSYCHIATRY
2002;52:679–693

demonstrated in the visual system (Villringer et al 1993; Wobst et al 2001), the somatosensory system (Beese et al 1998; Obrig et al 1996; Steinbrink et al 2000), the auditory system (Sakatani et al 1999a; Sato et al 1999), and with language stimuli (Sato et al 1999; Watanabe et al 1998) and other cognitive tasks (Hoshi and Tamura 1993; LaBar et al 1999; Villringer et al 1994). In general, these studies find spatially localized increases in [HbO_2] and corresponding decreases in [HbR] in response to functional challenge, with onsets around 2 sec following task onset and times-to-peak in the 5–9 sec range. All such findings are as expected from fMRI studies. Moreover, the particular brain regions exhibiting such changes are typically concordant with the findings from other neuroimaging modalities, at least in those cases where similar paradigms have been investigated. Interestingly, the HbR changes appear to be somewhat more spatially localized than the HbO_2 changes (Hirth et al 1996), although the reason for this is still under investigation.

The potential basic research questions that remain and can be addressed with diffuse optical techniques are numerous. One possibility is to examine hemodynamic responses as a function of task or disease—not only in terms of amplitude and onset times, but also the relative contributions by HbO_2 and HbR, and the timing relationships between these hemodynamic components. Some initial steps in this direction specifically for psychiatric populations are mentioned in the following section. Another possibility is the investigation of spatial distributions of activity (and how such distributions evolve over time) as a function of task, subject population or even, in a more clinical setting, as a function of treatment for a given disease. In general, a research question for which one of the other brain monitoring modalities might be considered, particularly if it involves more superficial cortical regions, will likely be amenable to diffuse optical techniques.

Clinical Applications

One of the first clinical applications of diffuse optical techniques for functional brain monitoring was the investigation of fetal, neonatal and infant cerebral oxygenation and functional activation. This population was of interest because other neuroimaging methods were (and are) not feasible given the high activity level of such subjects. In this domain, the diffuse optical approach has helped uncover developmental alterations in the cerebral hemodynamic response to auditory and visual stimulation (Meek et al 1998; Zaramella et al 2001), has helped characterize changes in cerebral perfusion as a function of surgical events such as bypass and reperfusion (Kurth et al 1995), and has provided measures of fetal brain oxygen supply during labor (Aldrich et al 1995) and post birth-asphyxia (van Bel et al 1993). In another major effort, several groups are working towards employing diffuse optics in monitoring adults with ischaemic and hemorrhagic stroke, although this effort is still in its early stages (Kirkpatrick et al 1998; McKinley et al 1996; Stankovic et al 1999; Stankovic et al 2000; Vernieri et al 1999; Wolf et al 1997).

Relatively few psychiatric applications of diffuse optical techniques have thus far been reported. Hock and colleagues have examined Alzheimer's patients during verbal fluency and other cognitive tasks, finding decreases in HbO_2 and total hemoglobin ($HbT = HbO_2 + HbR$) relative to baseline in the parietal lobe (Hock et al 1996; Hock et al 1997). Both young and elderly controls demonstrate increases in both parameters in the same region, supporting the idea that Alzheimer's may result in damage to the parietal lobe itself, or to regions with significant inputs to the parietal lobe. Two groups have looked at schizophrenia patients. The first found unusual, "dysregulated" patterns of HbO_2 and HbR change—i.e., increases in HbO_2 were not necessarily paralleled by decreases in HbR, and vice versa—in frontal regions of schizophrenic patients as compared to healthy subjects during a mirror drawing task (Okada et al 1994). The second group showed that the typical pattern of right-lateralized activation during a continuous performance test was absent in schizophrenic patients (Fallgatter and Strik 2000). A third psychiatric population, namely depressed patients, have also been examined with diffuse optical techniques, finding reduced frontal activation during a verbal fluency test relative to controls (Matsuo et al 2000), and atypical lateralization of frontal activation responses (more strongly favoring the non-dominant hemisphere) during a mirror drawing test (Okada et al 1996).

In addition to cognitive studies, evaluations of the hemodynamic response have also been completed during deep brain stimulation in Parkinson's patients (Murata et al 2000; Sakatani et al 1999b), during induced seizures in patients with intractable epilepsy (Watanabe et al 2000), and during magnetic brain stimulation for the treatment of depression (Eschweiler et al 2000). For the Parkinson's patients, frontally recorded oxygenation varied dramatically depending on the rate and location of stimulation. The study of epilepsy patients suggested that NIRS could be a useful non-invasive probe for localizing seizure foci. And, in the case of magnetic brain stimulation for depression, NIRS-derived total hemoglobin concentrations actually predicted the patient's response to treatment.

Clearly, such work only begins to address questions about the nature of functional circuit disruption in psychiatric populations. It does, however, suggest that (i) diffuse optical techniques are sufficiently sensitive to detect such

changes, and (ii) that the information provided about both HbR and HbO_2—unavailable from other brain imaging methods—may be important in certain psychiatric disorders. The discovery of substantial "dysregulation" of hemodynamic parameters in patient populations is likely to become important in the interpretation of other psychiatric brain imaging data. Moreover, it would appear that diffuse optical techniques have considerable potential not only in characterization and ongoing evaluation of psychiatric diseases, but also in diagnosis and outcomes prediction.

The fact that relatively few such papers have appeared—certainly in comparison to PET and fMRI studies—and the broad applicability of the technique across populations and research questions, suggests that psychiatric research is still wide open for the application of diffuse optical techniques. As just one example, there has been surprisingly little cortical activation testing of patient groups with motor dysfunction—e.g., Huntington's, obsessive compulsive, and Parkinson's patients—for which diffuse optical methods are particularly well suited. Other opportunities await the proper combination of research interest, study population and instrument selection.

Current Issues

The advantages that diffuse optical techniques can provide brain researchers are substantial. These include portability, unobtrusiveness and low cost. As with any technique, however, these advantages come with some limitations, and so we consider here the issues that need to be considered when designing diffuse optics experiments.

Non-invasive Spatial Localization

As with EEG, MEG and PET, diffuse optical methods cannot provide anatomical images or other direct measures of anatomy—at least not of the sort people have come to expect with the availability of MRI. To afford between-subject comparisons for functional brain changes in a diffuse optical setting, therefore, an extrinsic frame of reference is required. With over 50 years of experience, EEG researchers have developed an external-referential system—the International 10-20 system—which provides 21 standardized electrode placement positions (Harner and Sannit 1974), and has been expanded to dense sensor grids of 256 detectors (Suarez et al 2000). While such a system is technically only self-consistent, efforts have been made to determine the location of various major anatomical landmarks relative to the standard 10-20 system locations (Homan et al 1987; Steinmetz et al 1989). Between-subject variability is still substantial, but such references can be of considerable help in orienting the optical researcher by standardizing placement positions and easing the challenge of communicating to others the placements on the surface of an irregularly shaped object such as the head. Again, precise positioning is only important for situations where functional changes are confined to known, small regions of the brain, which (arguably) tends to be less true for many psychiatric diseases.

Another aspect of localization in optical studies arises from fiber placement. A single ("point") measurement with optical techniques is slightly more complicated than, for example, an EEG electrode placement, because an optical measurement requires two fibers (a source and detector); an EEG point measurement requires only a single electrode location. An example sensitivity profile of a source-detector pair on an adult human head appeared in Figure 4. Each contour corresponds to the absorption of half an order of magnitude in light levels. One can therefore see that the sensitivity to changes in brain tissue will be maximal below and between the source and detector. As an approximate rule of thumb—for frequency domain and continuous wave measurements—the depth of maximum brain sensitivity is approximately half the source-detector separation distance. Thus, for a source-detector separation of 3 cm, the region of maximum brain sensitivity will be found between the source and detector fiber tip locations, and roughly 1.5 cm below the surface of the scalp, though banana-shaped region of sensitivity extends both above and below this depth. The maximum overall sensitivity, as evident in Figure 4, is actually at each fiber tip. It is typically assumed, however, that the scalp and skull produce little or no change in hemoglobin concentrations, which implies that observed changes localize to brain tissue (Firbank et al 1998). The sensitivity pattern for time domain measurements, on the other hand, is variable, affording deeper sensitivities by selectively rejecting light that travels exclusively through these superficial tissue layers.

Regardless of the measurement type, however, the fact that tissue strongly scatters light means spatial resolution decreases with depth. Localizing activation to the amygdala, for example, is not feasible, and cingulate cortex would be difficult (see also the discussion on penetration depth in the following section). Superficial cortex, including (but not limited to) dorsolateral prefrontal cortex, superior parietal cortex, and language and primary sensorimotor areas, on the other hand, are all within detectable limits of the current diffuse optical tools.

Coupling, Light Levels, and Penetration Depth

Another challenge for optical methods can be achieving good, stable optical contact and sufficient light levels

BIOL PSYCHIATRY
2002;52:679–693

detected from the subject. Several issues affect coupling: hair (absorption and instability), hair follicles (follicles strongly absorb near infrared wavelengths), skin color or variations (darker skin regions are typically more absorbing of NIR wavelengths), and general fiber stability against the head (a function of rigidity, strain relief, torque and subject comfort). Such variables make a generalized solution to the coupling problem challenging for in vivo diffuse optics experiments. Many solutions have been implemented for holding the optical fibers—with a goal of rigidity, plus flexibility with respect to head shape. A few examples include: fibers inserted through modified motorcycle helmets, thermoplastic molded to the contours of each subject's head, spring-loaded fibers attached to semi-rigid plastic forms, and fibers embedded in neoprene rubber forms. New and improved coupling methods are continuously being developed.

Once fibers are relatively stable, and properly coupled to the head (i.e., no extra-cranial light leakage from source to detector), the remaining determinants of detected light levels are tissue optical properties and instrument properties. Instrument properties, including the instrument speed/sensitivity tradeoffs, were discussed earlier. As for subjects, since both hair and hair follicles are strongly absorbing at the wavelengths of interest, hair-free portions of the head (or subjects with thinner or lighter colored hair) usually provide improved signal strength and penetration depth for optical recordings. It is nevertheless possible to record through the hair with many instruments. The thickness of the subject's scalp and skull are also relevant to monitoring brain function, as thicker scalps and skulls will both absorb more light and will require larger separations to achieve sensitivity to brain chromophores. The parameters vary not only between subjects, but also around the head within a given subject, and are unknowns unless an MRI scan is available. Geometrical factors (e.g., source-detector separations, whether sources and detectors point towards or away from one another, etc.) are additional signal-level determinants, but work is underway to help quantify these effects.

While there are clearly a substantial number of factors contributing to signal detection, it is important to remember that penetration depth is fundamentally a function of contrast. A very large change (e.g., a hemorrhage) in the thalamus of an adult human may be detectable by a diffuse optical instrument, though with poor spatial resolution. In comparison, a small change—as found with functional activation—may only be detectable 1–2 cm below the surface of the cortex. As mentioned, while penetration depth increases with source-detector separation, current diffuse optical instruments can only detect light with maximum source-detector separations of up to 5 or 6 cm on an adult head. This contrasts with an infant head, where light may well be detectable when transmitted straight through from one side of the head to the other, due to a thinner skull, smaller head, less hair and smaller follicles.

In sum, there is an abundance of factors that can influence signal levels aside from the instrumentation hardware. The practical consequence of these factors is straightforward: some initial trial and error is typically required to maximize signal quality for a given combination of instrument, study population, and probed brain area. In general, these factors affect healthy and patient populations equally and in many cases, such empirical work has already been completed (e.g., the initial work discussed under Neuromonitoring Applications, above). In our experience, the signals from diffuse optical recordings are inadequate in fewer than 10% of volunteers.

Absolute Quantification of Hemoglobin Species

Presently, most non-invasive diffuse optical brain measurements are capable of only detecting changes, much like blood oxygenation level dependent fMRI. Removing an optical probe and replacing it, even if placed in the "exact" same position on the head, will inevitably result in different coupling efficiencies between the fibers and the head. As a result, *absolute* oxy- and deoxyhemoglobin concentration measurements taken on separate days cannot yet be reliably compared. This would preclude studies where, for example, it is necessary to compare baseline oxygenation states during the temporal evolution of a disease state. The use of relative measures, however, can go a long way (as shown by the extensive application of fMRI and non-catheterized PET studies); for example, functional modulation (i.e., *changes* from baseline) can be monitored and compared over the evolution of a disease. Moreover, the diffuse optical method retains the potential for providing such absolute measures (see below).

Image Reconstruction

Imaging provides one potential—though as yet not fully realized—solution to the absolute quantification problem. By recording from many source-detector pairs simultaneously, (i) the coupling efficiencies can be accounted for, and (ii) the overlapping measurements can be combined to generate self-consistent measurements across regions in a way that is impossible with point measurements. The resulting image therefore provides more accurate, absolute and quantitative measures of hemoglobin concentrations. The present limitation for this procedure is the theory of image reconstruction. In the case of brain imaging, the activation regions and optical probes are both distributed in three dimensions, with non-uniformly varying incidence orientations of the probes. Moreover, the tissues consist of highly non-uniform, undulating layers of optically distinct

types. Image reconstruction investigations generally concentrate on reconstructions from either flat or circular, semi-infinite, uniform media (Arridge and Schweiger 1997; Paulsen and Jiang 1995; Pogue et al 1999), although a few more complicated geometries have been considered (Schweiger and Arridge 1999). Present research is beginning to focus on algorithms that can generate 3D images from measurements made on a curved, layered structure such as the head (Bluestone et al 2001). The advances hold great promise for using optical methods to detect functionally localized activity in the brain, and to eventually provide absolute measures of HbR and HbO_2 concentrations, thereby allowing comparison of single measurements across days or even years.

Summary and Conclusions

Diffuse optical methods have several advantages over existing technologies for brain monitoring, including excellent temporal resolution coupled to reasonable spatial resolution, spectroscopic information for hemodynamic events, portability, unobtrusiveness, and the ability to be achieved by low-power and low-cost instruments that are robust to motion artifacts. The technology is also completely non-invasive, unlike PET and SPECT. For the psychiatric researcher, these strengths facilitate the investigation of several difficult populations such as infants, small children, and patients with claustrophobia and severe movement disorders. The portability and low runtime cost of the instrument affords bedside or home telemetry and monitoring for extended periods of time. This in turn can be useful for monitoring the time course of pathologies and associated behaviors, as well as the effects of various interventions, including drugs. Tradeoffs include difficulty with precise anatomical localization with respect to the brain (as with all other non-invasive technologies except MRI), and relatively poor penetration and localization in depth. For investigations of cortical activation, however, and especially when referenced to an external landmark system (e.g., the international 10/20 system), diffuse optical methods can provide opportunities unavailable with any other existing technology.

GS and JPS acknowledge support from the National Space Biomedical Research Institute through NASA Cooperative Agreement NCC 9-58 and the McDonnell-Pew Foundation (97-33). GS was also supported by the NIH-NINDS (F32-NS10567-01). DAB acknowledges financial support from NIH R29-NS38842, NIH P41-RR14075 and from the Center for Innovative Minimally Invasive Therapies.

References

American National Standards Institute (2000): *American National Standard for Safe Use of Lasers.* New York, New York: American National Standards Institute, pp 130.

Aldrich CJ, D'Antona D, Spencer JAD, et al (1995): The effect of maternal posture on fetal cerebral oxygenation during labour. *Br J Obstet Gynaecol* 102:14–19.

Arridge SR (1999): Optical Tomography in medical imaging. *Inverse Problems* 15:R41–R93.

Arridge SR, Schweiger M (1997): Image reconstruction in optical tomography. *Philos Trans R Soc Lond B Biol Sci* 352:717–726.

Barbour RL, Graber HL, Pei Y, Zhong S, Schmitz CH (2001): Optical tomographic imaging of dynamic features of dense-scattering media. *J Opt Soc Am A Opt Image Sci Vis* 18:3018–3036.

Beese U, Langer H, Lang W, Dinkel M (1998): Comparison of near-infrared spectroscopy and somatosensory evoked potentials for the detection of cerebral ischemia during carotid endarterectomy. *Stroke* 29:2032–2037.

Benaron DA, Stevenson DK (1993): Optical time-of-flight and absorbance imaging of biologic media. *Science* 259:1463–1466.

Bluestone AY, Abdoulaev G, Schmitz CH, Barbour RL, Hielscher AH (2001): Three-dimensional optical tomography of hemodynamics in the human head. *Optics Express* 9:272–286.

Boas DA, Franceschini MA, Dunn AK, Strangman G (2002): Non-Invasive imaging of cerebral activation with diffuse optical tomography. In Frostig R, (ed), *In-Vivo Optical Imaging of Brain Function.* Boca Raton: CRC Press, pp 193–221.

Boas DA, Gaudette T, Strangman G, Cheng X, Marota JJA, Mandeville JB (2001): The accuracy of near infrared spectroscopy and imaging during focal changes in cerebral hemodynamics. *NeuroImage* 13:76–90.

Chance B, Cope M, Gratton E, Ramanujam N, Tromberg B (1998): Phase measurement of light absorption and scattering in human tissues. *Rev Sci Instru* 689:3457–3481.

Chance B, Leigh JS, Miyake H, et al (1988): Comparison of time-resolved and -unresolved measurements of deoxyhemoglobin in brain. *Proc Natl Acad Sci USA* 85:4971–4975.

Churchland PS, Sejnowski TJ (1988): Perspectives on cognitive neuroscience. *Science* 242:741–745.

Colier WNJM, van Haaren NJCW, van de Ven MJT, Folgering HTM, Oeseburg B (1997): Age dependency of cerebral oxygenation assessed with near infrared spectroscopy. *J Biomed Optics* 2:162–170.

Cope M, Delpy DT (1988): System for long-term measurement of cerebral blood flow and tissue oxygenation on newborn infants by infra-red transillumination. *Med Biol Eng Comput* 26:289–294.

Cope M, Delpy DT, Reynolds EOR, Wray S, Wyatt J, Van der Zee P (1987): Methods of quantitating cerebral near infrared spectroscopy data. *Adv Exp Med Biol* 222:183–189.

Cope M, van der Zee P, Essenpreis M, Arridge SR, Delpy DT (1991): Data analysis methods for near infrared spectroscopy

of tissue: problems in determining the relative cytochrome aa3 concentration. *SPIE* 1431:251–262.

Eschweiler GW, Wegerer C, Schlotter W, Spandl C, Stevens A, Bartels M, et al (2000): Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychiatry Res* 99:161–172.

Fallgatter AJ, Strik WK (2000): Reduced frontal functional asymmetry in schizophrenia during a cued continuous performance test assessed with near-infrared spectroscopy. *Schizophr Bull* 26:913–919.

Firbank M, Okada E, Delpy DT (1998): A theoretical study of the signal contribution of regions of the adult head to near-infrared spectroscopy studies of visual evoked responses. *Neuroimage* 8:69–78.

Franceschini MA, Toronov V, Filiaci ME, Gratton E, Fantini S (2000): On-line optical imaging of the human brain with 160-ms temporal resolution. *Optics Express* 6:49–57.

Gomersall CD, Leung PL, Gin T, Joynt GM, Young RJ, Poon WS, et al (1998): A comparison of the Hamamatsu NIRO 500 and the INVOS 3100 near-infrared spectrophotometers. *Anaesth Intensive Care* 26:548–557.

Gratton E, Fantini S, Franceschini MA, Gratton G, Fabiani M (1997): Measurements of scattering and absorption changes in muscle and brain. *Philos Trans R Soc Lond B Biol Sci* 352:727–735.

Gratton G, Corballis PM (1995): Removing the heart from the brain: compensation for the pulse artifact in the photon migration signal. *Psychophysiology* 32:292–299.

Gratton G, Fabiani M (2001): Shedding light on brain function: the event-related optical signal. *Trends Cogn Sci* 5:357–363.

Grosenick D, Wabritz H, Rinneberg HH, Moesta KT, Schlag PM (1999): Development of a time-domain optical mammograph and first *in vivo* applications. *App Optics* 38:2927–2943.

Harner PF, Sannit T (1974): *A review of the international ten-twenty system of electrode placement.* West Warwick, RI: Astro-Med, Inc.

Hebden JC, Arridge SR, Delpy DT (1997): Optical imaging in medicine: I. Experimental techniques. *Physics Med Biol* 42:825–840.

Heekeren HR, Kohl M, Obrig H, Wenzel R, von Pannwitz W, Matcher SJ, et al (1999): Noninvasive assessment of changes in cytochrome-c oxidase oxidation in human subjects during visual stimulation. *J Cereb Blood Flow Metab* 19:592–603.

Hirth C, Obrig H, Villringer K, Thiel A, Bernarding J, Muhlnickel W, et al (1996): Non-invasive functional mapping of the human motor cortex using near-infrared spectroscopy. *Neuroreport* 7:1977–1981.

Hock C, Villringer K, Muller-Spahn F, Hofmann H, Heekeren H, Schuh-Hofer S, et al (1996): Near infrared spectroscopy in the diagnosis of Alzheimer's disease. *Ann N Y Acad Sci* 777:22–29.

Hock C, Villringer K, Muller-Spahn F, Wenzel R, Heekeren H, Schuh-Hofer S, et al (1997): Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by means of near-infrared spectroscopy (NIRS)—correlation with simultaneous rCBF-PET measurements. *Brain Res* 755:293–303.

Homan RW, Herman J, Purdy P (1987): Cerebral location of international 10-20 system electrode placement. *Electroencephalogr Clin Neurophysiol* 66:376–382.

Hoshi Y, Tamura M (1993): Dynamic multichannel near-infrared optical imaging of human brain activity. *J Appl Physiol* 75:1842–1846.

Ito Y, Kennan RP, Watanabe E, Koizumi H (2000): Assessment of heating effects in skin during continuous wave near infrared spectroscopy. *J Biomed Opt* 5:383–390.

Jiang H, Paulsen KD, Osterberg UL, Pogue BW, Patterson MS (1995): Simultaneous reconstruction of optical absorption and scattering maps in turbid media from near-infrared frequency-domain data. *Opt Lett* 20:2128–2130.

Jobsis FF (1977): Noninvasive infrared monitoring of cerebral and myocardial sufficiency and circulatory parameters. *Science* 198:1264–1267.

Jobsis FF, Keizer JH, LaManna JC, Rosenthal M (1977): Reflectance spectrophotometry of cytochrome aa3 in vivo. *J Appl Physiol* 43:858–872.

Kawaguchi F, Ichikawa N, Fujiwara N, Yamashita Y, Kawasaki S (2001): Clinically available optical topography system. *Hitachi Rev* 50:18–22.

Kirkpatrick PJ, Lam J, Al-Rawi P, Smielewski P, Czosnyka M (1998): Defining thresholds for critical ischemia by using near-infrared spectroscopy in the adult brain. *J Neurosurg* 89:389–394.

Kleinschmidt A, Obrig H, Requardt M, Merboldt KD, Dirnagl U, Villringer A, et al (1996): Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. *J Cereb Blood Flow Metab* 16:817–826.

Konishi I, Takeuchi S, Oikawa Y, Nishimoto T (2000): Development of OMM-2000 optical multichannel monitor. *Shimadzu Rev* 57:141–151.

Kurth CD, Steven JM, Nicolson SC (1995): Cerebral oxygenation during pediatric cardiac surgery using deep hypothermic circulatory arrest. *Anesthesiology* 82:74–82.

LaBar KS, Gitelman DR, Parrish TB, Mesulam M (1999): Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *Neuroimage* 10:695–704.

Matcher SJ, Cope M, Delpy DT (1994): Use of the water absorption spectrum to quantify tissue chromophore concentration changes in near-infrared spectroscopy. *Phys Med Biol* 39:177–196.

Matsuo K, Kato T, Fukuda M, Kato N (2000): Alteration of hemoglobin oxygenation in the frontal region in elderly depressed patients as measured by near-infrared spectroscopy. *J Neuropsychiatry Clin Neurosci* 12:465–471.

McKinley BA, Morris WP, Parmley CL, Butler BD (1996): Brain parenchyma PO2, PCO2, and pH during and after hypoxic, ischemic brain insult in dogs. *Crit Care Med* 24:1858–1868.

Meek JH, Firbank M, Elwell CE, Atkinson J, Braddick O, Wyatt JS (1998): Regional hemodynamic responses to visual stimulation in awake infants. *Pediatr Res* 43:840–843.

Murata Y, Katayama Y, Oshima H, Kawamata T, Yamamoto T, Sakatani K, et al (2000): Changes in cerebral blood oxygenation induced by deep brain stimulation: study by near-

infrared spectroscopy (NIRS). *Keio J Med* 49(Suppl 1):A61–A63.

Nioka S, Luo Q, Chance B (1997): Human brain functional imaging with reflectance CWS. *Adv Exp Med Biol* 428:237–242.

Ntziachristos V, Ma XH, Yodh AG, Chance B (1999): Multichannel photon counting instrument for spatially resolved near infrared spectroscopy. *Review of Scientific Instruments* 70:193–201.

Obrig H, Neufang M, Wenzel R, Kohl M, Steinbrink J, Einhaupl K, et al (2000): Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults. *Neuroimage* 12:623–639.

Obrig H, Wolf T, Doge C, Hulsing JJ, Dirnagl U, Villringer A (1996): Cerebral oxygenation changes during motor and somatosensory stimulation in humans, as measured by near-infrared spectroscopy. *Adv Exp Med Biol* 388:219–224.

Okada F, Takahashi N, Tokumitsu Y (1996): Dominance of the 'nondominant' hemisphere in depression. *J Affect Disord* 37:13–21.

Okada F, Tokumitsu Y, Hoshi Y, Tamura M (1994): Impaired interhemispheric integration in brain oxygenation and hemodynamics in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 244:17–25.

Paulsen KD, Jiang H (1995): Spatially varying optical property reconstruction using a finite element diffusion equation approximation. *Med Phy* 22:691–701.

Pogue BW, McBride TO, Osterberg UL, Paulsen KD (1999): Comparison of imaging geometries for diffuse optical tomography of tissue. *Optics Express* 4:270–286.

Pogue BW, Patterson MS (1994): Frequency-domain optical-absorption spectroscopy of finite tissue volumes using diffusion-theory. *Phys Med Biol* 39:1157–1180.

Pogue BW, Testorf M, McBride T, Osterberg U, Paulsen K (1997): Instrumentation and design of a frequency-domain diffuse optical tomography imager for breast cancer detection. *Optics Express* 1:391–403.

Quaresima V, Sacco S, Totaro R, Ferrari M (2000): Noninvasive measurement of cerebral hemoglobin oxygen saturation using two near infrared spectroscopy approaches. *J Biomed Opt* 5:201–205.

Rosen BR, Buckner RL, Dale AM (1998): Event-related functional MRI: past, present, and future. *Proc Natl Acad Sci USA* 95:773–780.

Sakatani K, Chen S, Lichty W, Zuo H, Wang YP (1999a): Cerebral blood oxygenation changes induced by auditory stimulation in newborn infants measured by near infrared spectroscopy. *Early Hum Dev* 55:229–236.

Sakatani K, Katayama Y, Yamamoto T, Suzuki S (1999b): Changes in cerebral blood oxygenation of the frontal lobe induced by direct electrical stimulation of thalamus and globus pallidus: a near infrared spectroscopy study. *J Neurol Neurosurg Psychiatry* 67:769–773.

Sato H, Takeuchi T, Sakai KL (1999): Temporal cortex activation during speech recognition: an optical topography study. *Cognition* 73:B55–B66.

Schmidt MH, Bajic DM, Reichert KW, Martin TS, Meyer GA, Whelan HT (1996): Light-emitting diodes as a light source for intraoperative photodynamic therapy. *Neurosurgery* 38:552–556; discussion 556–557.

Schmitz CH, Graber HL, Luo H, Barbour RL, Pei Y, Zhong S, et al (2000): Instrumentation and calibration protocol for imaging dynamic features in dense-scattering media by optical tomography. *Appl Optics* 39:6466–6486.

Schweiger M, Arridge SR (1999): Optical tomographic reconstruction in a complex head model using a priori region boundary information. *Physics in Medicine and Biology* 44:2703–2721.

Siegel AM, Marota JJA, Boas DA (1999): Design and evaluation of a continuous-wave diffuse optical tomography system. *Optics Express* 4:287–298.

Stankovic MR, Maulik D, Rosenfeld W, Stubblefield PG, Kofinas AD, Gratton E, et al (2000): Role of frequency domain optical spectroscopy in the detection of neonatal brain hemorrhage—a newborn piglet study. *J Matern Fetal Med* 9:142–149.

Stankovic MR, Maulik D, Rosenfeld W, Stubblefield PG, Kofinas AD, Drexler S, et al (1999): Real-time optical imaging of experimental brain ischemia and hemorrhage in neonatal piglets. *J Perinat Med* 27:279–286.

Steinbrink J, Kohl M, Obrig H, Curio G, Syre F, Thomas F, et al (2000): Somatosensory evoked fast optical intensity changes detected non-invasively in the adult human head. *Neurosci Lett* 291:105–108.

Steinmetz H, Furst G, Meyer BU (1989): Craniocerebral topography within the international 10-20 system. *Electroencephalogr Clin Neurophysiol* 72:499–506.

Stepnoski RA, LaPorta A, Raccuia-Behling F, Blonder GE, Slusher RE, Kleinfeld D (1991): Noninvasive detection of changes in membrane potential in cultured neurons by light scattering. *Proc Natl Acad Sci USA* 88:9382–9386.

Suarez E, Viegas MD, Adjouadi M, Barreto A (2000): Relating induced changes in EEG signals to orientation of visual stimuli using the ESI-256 machine. *Biomed Sci Instrum* 36:33–38.

Terborg C, Gora F, Weiller C, Rother J (2000): Reduced vasomotor reactivity in cerebral microangiopathy: a study with near-infrared spectroscopy and transcranial Doppler sonography. *Stroke* 31:924–929.

Totaro R, Barattelli G, Quaresima V, Carolei A, Ferrari M (1998): Evaluation of potential factors affecting the measurement of cerebrovascular reactivity by near-infrared spectroscopy. *Clin Sci (Colch)* 95:497–504.

Uludag K, Kohl M, Steinbrink J, Obrig H, Villringer A (2002): Crosstalk in the Lambert-Beer calculation for near-infrared wavelengths estimated by Monte simulations. *J Biomed Optics* 7:51–59.

van Bel F, Dorrepaal CA, Benders MJ, Zeeuwe PE, van de Bor M, Berger HM (1993): Changes in cerebral hemodynamics and oxygenation in the first 24 hours after birth asphyxia. *Pediatrics* 92:365–372.

Vernieri F, Rosato N, Pauri F, Tibuzzi F, Passarelli F, Rossini PM (1999): Near infrared spectroscopy and transcranial Doppler in monohemispheric stroke. *Eur Neurol* 41:159–162.

Villringer A, Chance B (1997): Non-invasive optical spectroscopy and imaging of human brain function. *Trends Neurosci* 20:435–442.

Villringer A, Planck J, Hock C, Schleinkofer L, Dirnagl U (1993): Near infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults. *Neurosci Lett* 154:101–104.

Villringer A, Planck J, Stodieck S, Botzel K, Schleinkofer L, Dirnagl U (1994): Noninvasive assessment of cerebral hemodynamics and tissue oxygenation during activation of brain cell function in human adults using near infrared spectroscopy. *Adv Exp Med Biol* 345:559–565.

Villringer K, Minoshima S, Hock C, Obrig H, Ziegler S, Dirnagl U, et al (1997): Assessment of local brain activation. A simultaneous PET and near-infrared spectroscopy study. *Adv Exp Med Biol* 413:149–153.

Watanabe E, Maki A, Kawaguchi F, Takashiro K, Yamashita Y, Koizumi H, et al (1998): Non-invasive assessment of language dominance with near-infrared spectroscopic mapping. *Neurosci Lett* 256:49–52.

Watanabe E, Maki A, Kawaguchi F, Yamashita Y, Koizumi H, Mayanagi Y (2000): Noninvasive cerebral blood volume measurement during seizures using multichannel near infrared spectroscopic topography. *J Biomed Optics* 5:287–290.

Whelan HT, Buchmann EV, Whelan NT, Turner SG, Cevenini V, Stinson H, et al (2001): NASA light emitting diode medical applications from deep space to deep sea. *Space Tech Appl Int Forum* CP552:35–37.

Wobst P, Wenzel R, Kohl M, Obrig H, Villringer A (2001): Linear aspects of changes in deoxygenated hemoglobin concentration and cytochrome oxidase oxidation during brain activation. *Neuroimage* 13:520–530.

Wolf T, Lindauer U, Reuter U, Back T, Villringer A, Einhaupl K, et al (1997): Noninvasive near infrared spectroscopy monitoring of regional cerebral blood oxygenation changes during peri-infarct depolarizations in focal cerebral ischemia in the rat. *J Cereb Blood Flow Metab* 17:950–954.

Zaramella P, Freato F, Amigoni A, Salvadori S, Marangoni P, Suppjei A, et al (2001): Brain auditory activation measured by near-infrared spectroscopy (NIRS) in neonates. *Pediatr Res* 49:213–219.