Functional near-infrared spectroscopy: current status and future prospects

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Abstract. Near-infrared spectroscopy (NIRS), which was originally designed for clinical monitoring of tissue oxygenation, has been developing into a useful tool for neuroimaging studies (functional near-infrared spectroscopy). This technique, which is completely noninvasive, does not require strict motion restriction and can be used in a daily life environment. It is expected that NIRS will provide a new direction for cognitive neuroscience research, more so than other neuroimaging techniques, although several problems with NIRS remain to be explored. This review demonstrates the strengths and the advantages of NIRS, clarifies the problems, and identifies the limitations of NIRS measurements. Finally, its future prospects are described.
[DOI: 10.1117/1.2804911]

Keywords: CW; TRS; wearable system; quantification; neurovascular coupling.

Paper 07082SSR received Mar. 1, 2007; revised manuscript received Jun. 22, 2007; accepted for publication Jul. 3, 2007; published online Nov. 13, 2007.

1 Introduction

In 1977, Jöbsis first described the *in vivo* application of near-infrared spectroscopy (NIRS);[1] this technique was originally designed for clinical monitoring of tissue oxygenation.[2–4] Since the early 1990s, it has also been developing as a useful tool for neuroimaging studies [functional near-infrared spectroscopy (fNIRS)].[5–8] Over the past 30 years, the technology has advanced and a wide range of NIRS instruments have been developed. Among them, the instruments for continuous wave (CW) measurements based on the modified Beer-Lambert law (CW-type instruments), which include the earliest NIRS instruments, are the most readily available commercially. Instruments of this type allow us to observe dynamic changes in regional cerebral blood flow (rCBF) in real time by measuring concentration changes in cerebral hemoglobin (Hb). Using fNIRS, various types of brain activities, such as motor and cognitive activities have been assessed.[9–13] The recent advent of multichannel CW-type instruments has greatly increased the use of NIRS in a variety of fields.

At the same time, however, the accuracy and reliability of NIRS have not yet been widely accepted. This is mainly attributable to incomplete knowledge of which region in the brain is sampled by near-infrared (NIR) light, difficulty in selective detection of NIRS signals arising from the cerebral tissue, and the problem of quantification. Despite a number of theoretical and experimental investigations, NIR light propagation in the human head remains to be fully understood. Because the detected light on the scalp carries information about not only the cerebral tissue but also the extracerebral tissue, and changes in extracerebral blood flow influence the determination of cerebral Hb concentration changes, it is necessary to separate signals originating in the cerebral tissue from those coming from the extracerebral tissue. For this purpose, a multidetector system consisting of CW-type instruments has been developed.[14,15] However, separation of NIR signals was incomplete, and other methods are being explored.

The major problem with NIRS is that concentration changes in Hb cannot be quantified with CW-type instruments, which has hindered NIRS from being widely employed in clinical medicine and research. Over the past 30 years, work in the field of NIRS has concentrated on solving this problem. Many different approaches to quantification have been tried, and the quantitative accuracy of time-resolved spectroscopy (TRS) and of phase-resolved spectroscopy (PRS) has been established. However, the difficulty of quantification has not yet been completely overcome (see Sec. 4.1).

In this review, I first outline the basic theory of NIRS, which will aid in the understanding of the potential and limitations of the technique. Then, focusing mainly on CW measurements, I give specific examples of the strengths and advantages of NIRS measurements over other neuroimaging modalities, and I also clarify the problems and identify the limitations of NIRS measurements. Finally, I describe its future prospects. Optical imaging is omitted because it is described in detail by other authors.

2 Basic Theory of NIRS

2.1 *NIR Light Propagation in the Head*

Knowledge about which regions in the brain are sampled by NIRS light is still incomplete, although a number of theoretical and experimental investigations on NIR light propagation in the human head have been performed.[16–19] Light propaga-

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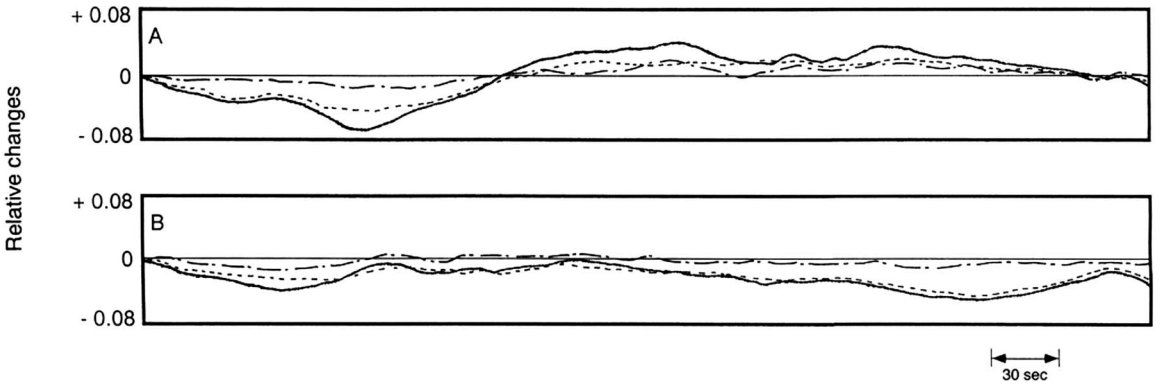


Fig. 1 Fluctuations in concentrations of oxygenated (dotted line), deoxygenated (broken line), and total hemoglobin (solid line) in the frontal (A) and occipital (B) regions during the resting state. The two regions were measured simultaneously. (Reprinted from Ref. 96 with permission.)

tion is generally approximated by diffusion equation, which is not valid on non- or low-scattering regions, and can be predicted by Monte Carlo simulation. Theoretical analyses of the head models consisting of three- or four-layered slabs, the latter incorporating a clear cerebrospinal fluid (CSF) layer, have demonstrated that light propagation in the adult head is highly affected by the presence of a low-scattering CSF layer.[20] This indicated that the light penetration in the adult brain might be limited to the outer cortical gray matter, which has been confirmed by their later studies, in which light propagation in head models generated from a magnetic resonance imaging (MRI) scan was predicted by Monte Carlo simulation.[17] A more recent study has reported that a large source-detector spacing only broadens the sampling region on the brain surface and affects the penetration depth in the adult head to a lesser degree, whereas the intensely sensitive region in the neonatal head is confined in the gray matter; however, the deeper region of the white matter is sampled with a large source-detector spacing.[19] In theoretical analysis, optical properties in each layer of the head are critical for prediction of the light propagation, though absorption (μ_a) and reduced scattering coefficients (μ_s') in each layer used for analysis are different from study to study. This is attributable to the fact that *in situ* measurements of the optical properties are not feasible. Thus, further investigation is required to confirm the validity of the theoretically predicted light propagation.

2.2 *NIRS Signals in Activated Areas*

Regional brain activation is accompanied by increases in rCBF and the regional cerebral oxygen metabolic rate ($rCMRO_2$). It is widely accepted that the degree of the increase in rCBF exceeds that of the increase in $rCMRO_2$,[21] which results in a decrease in deoxyhemoglobin (deoxy-Hb) in venous blood. Thus, increases in total hemoglobin (t-Hb) and oxyhemoglobin (oxy-Hb) with a decrease in deoxy-Hb are expected to be observed in activated areas in NIRS measurements. However, deoxy-Hb and t-Hb do not necessarily show these changes: studies have observed both no change in t-Hb with an increase in oxy-Hb and a reciprocal decrease in deoxy-Hb, and an increase or no change in deoxy-Hb accompanying increases in t-Hb and oxy-Hb.[6,22,23] Using a newly developed perfused rat brain model, we examined the direct effects of each change in CBF and $CMRO_2$ on cerebral hemoglobin oxygenation to interpret NIRS signals.[24] We confirmed that the directions of changes in oxy-Hb are always the same as those of rCBF, whereas the direction of changes in deoxy-Hb is determined by changes in venous blood oxygenation and volume. It has also been confirmed that small changes in CBF are not accompanied by those in t-Hb. Thus, oxy-Hb is the most sensitive indicator of changes in rCBF in NIRS measurements.

2.3 *Fluctuations in NIRS Signals at Rest*

CW measurements have revealed that even under resting conditions, the Hb oxygenation state fluctuates,[25–27] These fluctuations are divided into two types. One is the fluctuation whose general patterns are systemic and that are related to physiological activities such as the systemic arterial pulse oscillations ($\sim$1 Hz) and respiration (0.2 to 0.3 Hz). The other is the slower Hb wave fluctuation (frequency $<$0.05 Hz), of which the temporal pattern varies with each brain region (Fig. 1). It is well known that the cerebral blood flow velocity (CBFV) measured by transcranial Doppler ultrasound shows slow oscillation, which is thought to be attributed to small pial artery oscillations.[28,29] The frequency and characteristics of fluctuations in the Hb oxygenation state are similar to those of the CBFV oscillations. It is thus likely that the fluctuations in the Hb oxygenation state also originate from small artery oscillations. Our simultaneous measurements with NIRS and electroencephalography (EEG) have suggested the possibility that these oscillations are a result of vasomotor responses to spontaneous neuronal activity.[30] Both the faster and slower fluctuations of the Hb oxygenation state sometimes have amplitudes comparable with those of the signals evoked by functional activity. Thus, taking into account these fluctuations is critical for interpretation of NIRS signals.

3 Functional Near-Infrared Spectroscopy (fNIRS)

3.1 *Neuroimaging Studies with CW-Type Instruments*

The strengths and advantages of CW-type instruments are as follows: (1) temporal resolution is high (less than 1 sec) and completely noninvasive, which allow long-time continuous measurements in real time and repeating measurements within short intervals, and (2) measurements can be performed with

less motion restriction and in natural environments. Such strengths and advantages of NIRS enable neuroimaging studies on subjects who have not been fully examined until now, such as children, the elderly, and patients with psychoneurological problems, as they are difficult to measure by other neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

In neonates and infants, NIRS has been mostly applied to investigate evoked responses to stimuli such as visual,[31,32] olfactory,[33] and auditory stimulation,[34,35] and passive knee movement.[36] These studies have shown that unlike measurements on adult subjects, deoxy-Hb often increases accompanying increases in oxy-Hb and t-Hb, which corresponds to an inverse blood oxygen level–dependent (BOLD) signal.[37] This stimulus-related increase in deoxy-Hb was explained by a lower increase in rCBF compared with an increase in the $rCMRO_2$.[31] However, our study has demonstrated that the direction of activation-related changes in deoxy-Hb in neonates varies with each measurement even in the same subject during photic stimulation,[32] which has given another possible explanation for the increase in deoxy-Hb. That is, it might be attributed to venous dilation caused by activation-related increases in rCBF. Even more recently, higher order functions, such as response to language, have been investigated in neonates.[38–40] Although only a few NIRS studies on cognitive and socioemotional development have been so far reported,[41–43] the importance of NIRS will soon increase in developmental psychology.

Okada et al.[44] first applied NIRS to evaluating the frontal function in chronic schizophrenics. In the few years following this study, only a few psychiatric applications were reported.[45,46] Lately, however, NIRS has become an increasingly popular method in psychiatry.[47–50] Several research groups have examined task-related hemodynamic changes in psychiatric patients and found task-dependent abnormalities in frontal hemodynamics in schizophrenia[45,48] and depression.[47,49] Such task-dependent abnormalities were also found in patients with Alzheimer's disease.[51,52] These results underline the usefulness of NIRS in investigating frontal lobe dysfunction and evaluating psychopathologic conditions in psychiatric patients.

Measurements with less motion restriction in the daily life environment open new dimensions in neuroimaging studies. Using a 30-channel CW-type instrument, Miyai et al.[53] succeed in visualizing cortical activation patterns associated with human gait. This indicated that NIRS was useful for evaluating cerebral activation patterns during pathological movements and rehabilitation intervention. Furthermore, a portable single-channel NIRS instrument combined with a wireless telemetry system (the wearable NIRS system) allows subjects to move during measurements as with portable electrocardiogram (ECG) and EEG instruments. The details of the portable NIRS instrument (HEO 200, Omron Ltd. Inc., Kyoto, Japan) have been reported elsewhere.[54] This instrument is connected to the transmitter of a wireless system, and these are packed in a small bag that a subject carries (Fig. 2). NIRS signals are then sent by the wireless system to the receiver, which is connected to a laptop computer, on which data are displayed in real time. NIRS signals can be transmitted to a place at a maximum distance of 30 m in an open field, but about 10 m inside a building. This NIRS system makes it possible to monitor brain activity of freely moving subjects outside of laboratories.[55]

Fig. 2 Measurement being performed using the wearable NIRS system.

Using a multichannel CW-type instrument, we can examine spatiotemporal characteristics in hemodynamic changes associated with brain activity. Furthermore, multichannel NIRS instruments have the potential for imaging the sequence of brain activation.[56,57] In Fig. 3, for an example, three brain regions (the left dorsolateral prefrontal cortex, left BA 8, and right ventrolateral prefrontal cortex) were independently activated during performance of the *n*-back task, in which the time course of changes in oxy-Hb was different and it appeared that these regions had worked in a complementary manner.[57] This also implies that the results obtained in PET and fMRI studies can vary by measurement points. Examining the time course of hemodynamic changes is crucial for understanding the brain function.

3.2 *Multimodal Measurements*

There are various functional neuroimaging modalities, such as fMRI, PET, and magnetoencepahlography (MEG). Each modality detects a different aspect of brain function and has different merits and demerits. Thus, combined measurements with multiple modalities are expected to be complementary and synergistic. Because NIRS can easily be combined with any of the other modalities, a number of combined studies with NIRS and other modalities have already been reported. Simultaneous measurements with PET[52,58] and fMRI[23,59] have also contributed to confirming the validity of NIRS, but the correspondence between the NIRS and the BOLD-fMRI recorded hemodynamic responses is still controversial.[60–62]

Neurovascular coupling is the physiological basis of such neuroimaging techniques to measure signals attributed to hemodynamic changes (e.g., PET, fMRI, and NIRS), whereas its mechanisms remain to be elucidated. To investigate the neurovascular coupling in the human brain, NIRS is appropriate because its temporal resolution is high, and it can be combined with electrophysiological methods, such as EEG and MEG.[63–66] Simultaneous measurements with NIRS and electrophysiological methods have also been employed for studies of higher brain functions.[67]

Transcranial magnetic stimulation (TMS) is becoming popular as a therapeutic tool for neuropsychological diseases, such as depression and cerebellospinal degeneration, as well as for neurological examination. However, because therapeu-

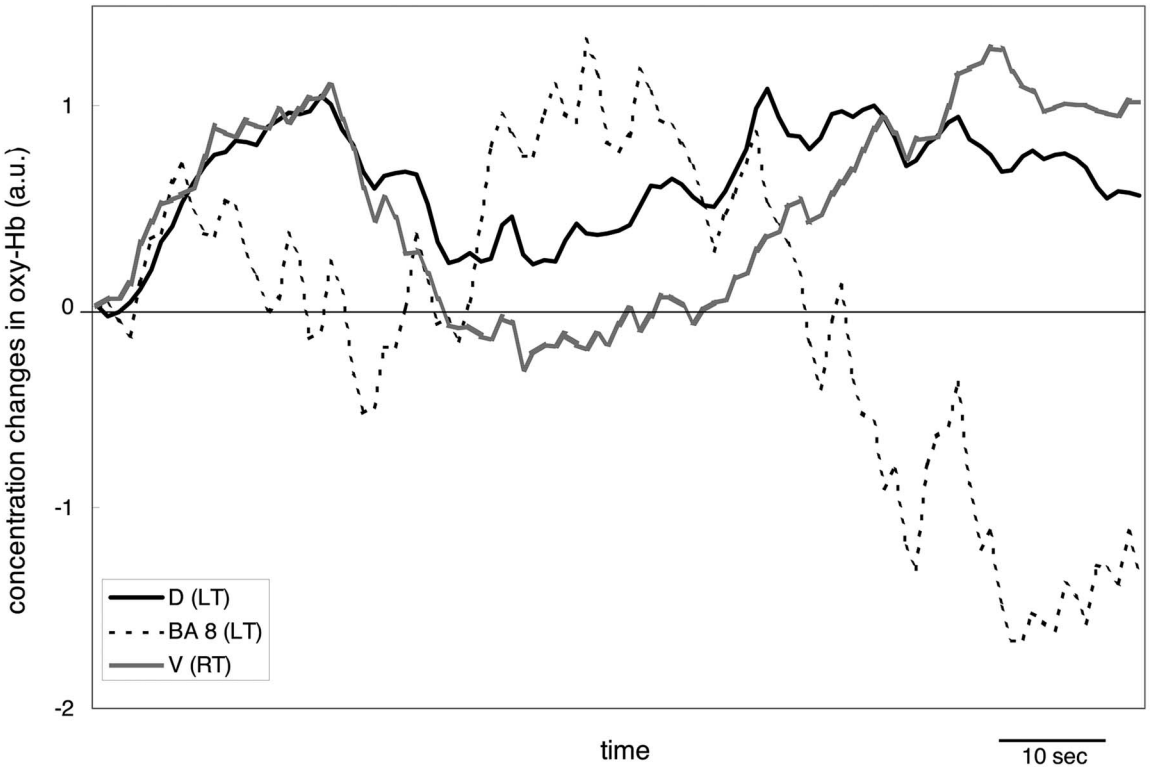


Fig. 3 Dynamic oxygenated Hb changes during the 3-0 back task in different brain regions. The start and end of the horizontal axis denotes the start and end point of the task, respectively. D, dolsorateral prefrontal cortex; BA 8, Brodmann area 8; V, ventrolateral prefrontal cortex; LT, left; RT, right. (Reprinted from Ref. 57 with permission.)

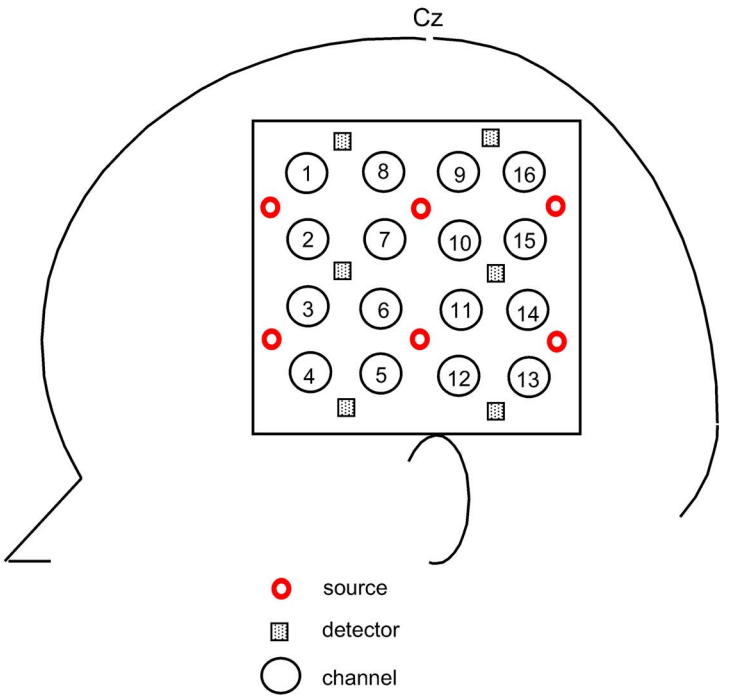
tic effects of TMS vary with its stimulation conditions, it is required to examine the relationship between stimulation conditions and changes in brain activity, CBF, and cerebral metabolisms. NIRS can be combined much more easily with TMS than PET or fMRI and has recently been employed for this aim.[68,69]

4 Problems of NIRS

4.1 *Selective and Quantitative Detection of NIRS Signals*

Quantification of NIRS data has been a central issue in the NIRS field. When Hb concentration changes are global within the tissue, quantification is possible with TRS and PRS, which can determine optical path length. In the case where Hb concentration changes are localized, such as functional brain activation, however, those changes cannot be quantified accurately. The optical path length determined by TRS and PRS is the mean total path length (t-PL) but not the mean partial path length (p-PL) in the cerebral tissue. Because the t-PL is much longer than the p-PL,[17,19] Hb concentration changes are underestimated when the t-PL is substituted for the modified Beer-Lambert law (partial volume reduction). However, measurement of the p-PL is not feasible. To quantify NIRS data obtained from CW-type instruments without measuring the t-PL, the assumption that the ratio of the source-detector separation to the t-PL is constant has often been made.[70] Arranging the source-detector separation for each pair at equal distance, in which the t-PL can be considered a constant if the assumption is correct, multichannel CW-type instruments generate topographical images of relative concentration changes in Hb. However, this assumption is not correct. As shown in Fig. 4, the ratio of the source-detector separation to the t-PL [differential path length factor (DPF)][70] varies with each position. Furthermore, the p-PL is negatively related to the t-PL at a fixed source-detector spacing (Fig. 5), and the ratio of the p-PL to the t-PL varies with each wavelength and each measurement position.[71] This means that substitution of the t-PL for the Beer-Lambert law provides not only underestimated but also inaccurate results. Thus, for quantification, we have to come up with methods to measure the p-PL or other approaches to quantitative and selective detection of signals arising from the brain that are not based on the modified Beer-Lambert law. In addition to the issue of quantification, amplitudes of NIRS signals vary with the source-detector position.[72,73] Thus, comparing amplitudes across subjects and/or regions within a subject is not valid.

Diffuse optical tomography (DOT), which reconstructs images of Hb concentration changes using multiple light sources and detectors, is a potential technique for quantitative detection of focal changes in cerebral hemodynamics.[74] DOT is not based on the modified Beer-Lambert law and can be performed with TRS,[75] PRS,[76] and CW-type instruments.[77] TRS is also a potential tool for this purpose. It provides the temporal point spread function, which carries information about depth-dependent attenuation even for a measurement with a single source-detector distance. Even though several time domain approaches[78–81] and a multidistance frequency domain approach[82] have been proposed, further investigation must



Channel	DPF (759nm)
1	7.44
2	5.47
3	4.88
4	3.76
5	4.33
6	4.61
7	5.57
8	6.91
9	5.29
10	4.90
11	4.36
12	4.39
13	4.15
14	4.82
15	6.03
16	7.56

Fig. 4 Different path length factors measured on the left scalp adjacent to the somatosensorimotor cortex in a 23-year-old healthy adult. The wavelength is 759 nm.

be continued to apply these methods to human head measurements.

4.2 *NIRS Data Analysis*

Unlike PET and fMRI, there are no standard methods of NIRS data analysis, and various analyses have been performed so far. This is not in itself a problem; however, the validity and reliability of each method should be confirmed. Until recently, to examine whether task-related changes in NIRS signals in an individual are significant or not, comparison of NIRS signals between the resting and activation states has commonly been performed by using a paired *t*-test. However, because NIRS data are time series data, *t*-statistics cannot be used for this aim, although they can be used for comparing means of NIRS signal changes between two states within subjects. Autoregressive models are commonly used to analyze time series data, though it is very difficult to derive an autoregressive model for NIRS data. Model-based, event-related, and both combined analyses have recently been tried in some research groups.[60,83–85] Although the model-based analysis is widely used for data analysis in fMRI and PET studies, it is unclear whether this analytical method can be applied to NIRS data, because the pattern of hemodynamic changes varies with each measurement and it is difficult to derive proper hemodynamic response functions, which might be also true of PET and fMRI. In the case that the same task can repeatedly be performed without habituation, however, an event-related analysis is available.

As mentioned in Sec. 2.3, NIRS signals are not constant during the resting state, which possibly reflects physiological phenomena,[26,30] and it is often observed that these signals do not return to the original levels immediately after the activation state. In such cases, baseline correction has been performed in some studies. However, it should be noted that the baseline correction could distort actual cerebral hemodynamic changes.

4.3 *Cross Talk*

Recently, cross talk between the estimated oxy-Hb and deoxy-Hb concentrations has been intensively studied.[72,86] The estimated concentration change ($\Delta[]_{estim}$) is expressed by Eq. (1)

$$\Delta[A]_{estim} = P\Delta[A]_{real} + C[B]_{real}, \tag{1}$$

where A represents either oxy-Hb or deoxy-Hb, and B represents the other chromophores deoxy-Hb or oxy-Hb, respectively. $\Delta[]_{real}$ indicates the real concentration change. P denotes the partial volume reduction in the estimated chromophore concentration, and C denotes the cross talk from the other chromophore.

When two wavelengths (λ_1, λ_2) are used, the cross talk is expressed by Eq. (2)

$$C = EL,$$

$$E = \frac{-\varepsilon_R(\lambda_1)\varepsilon_R(\lambda_2)}{\varepsilon_B(\lambda_1)\varepsilon_A(\lambda_2) - \varepsilon_A(\lambda_1)\varepsilon_B(\lambda_2)},$$

$$L = \frac{\text{p-PL}(\lambda_2)}{\text{t-PL}(\lambda_2)} - \frac{\text{p-PL}(\lambda_1)}{\text{t-PL}(\lambda_1)}, \tag{2}$$

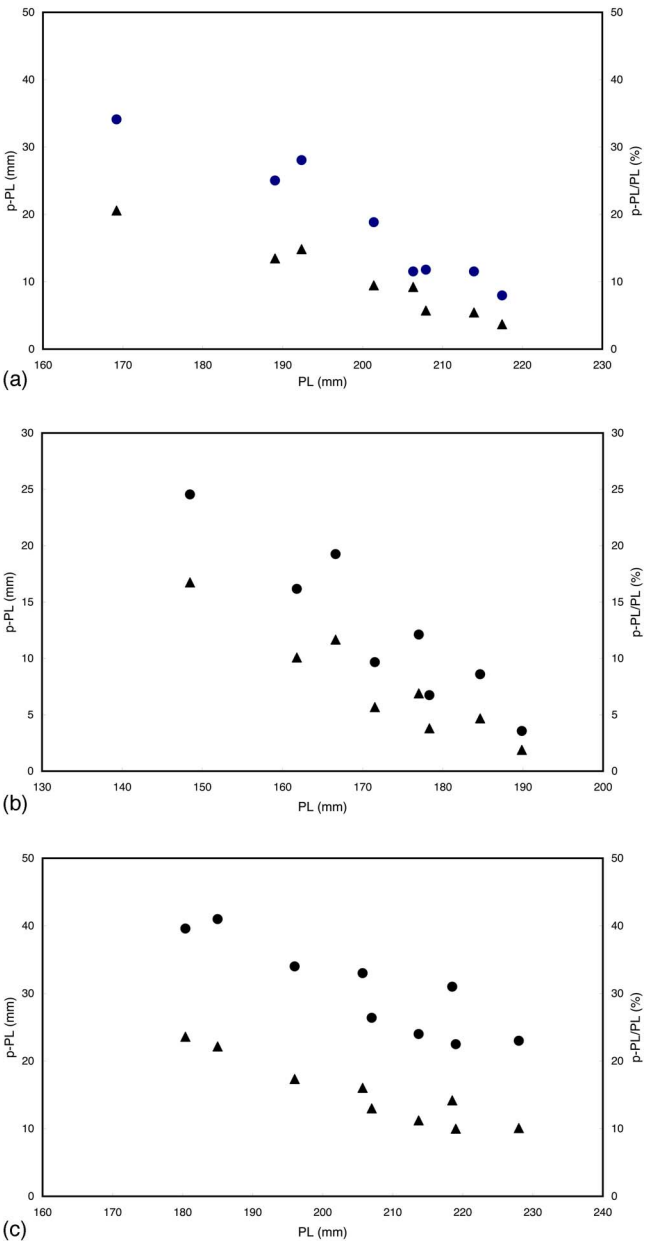


Fig. 5 Relationship between the PL (t-PL) and the p-PL (closed circle) and the ratio of the p-PL to the PL (closed triangle) in the three head models. (Reprinted from Ref. 71 with permission.)

where ε_A and ε_B are the extinction coefficients of the two chromophores, A and B. To eliminate the cross talk, a wavelength pair that minimizes E is required. Some research groups have recommended to use the 830- to 690-nm pair and reported that the 780- to 830-nm pair, which has traditionally been used, increases E.[77,86,87] However, L has not been considered. Even though E is minimized in the 830- to 690-nm pair, L might be larger at this wavelength pair than at the 780- to 830-nm pair. In addition, it is unclear whether light propagation between the source and detector at 690 nm is the same as that at 830 nm and whether scattering changes at 690 nm can be ignored. Further investigations are required before the new wavelength pair is employed.

4.4 *Practical Issues*

Except for neonates, it is not feasible for NIRS to noninvasively measure deep brain structures such as the diencephalons. It is also difficult to identify the exact brain areas that are beneath the NIRS probes without three-dimensional MRI measurements. However, it has been reported that there is an appropriate relationship between the international 10-20 system of electrode positioning in electroencephalogram and the cortical anatomy.[88,89] Thus, the measured brain area can be roughly deduced by using the location of the 10-20 system as a landmark.

Advances in NIRS technology have enabled simultaneous measurements at multiple brain regions with high temporal resolution, which is desirable not only to investigate regional differences in brain activation but also to detect localized brain activation. To improve spatial resolution, various arrangements of source-detector positions are being designed. However, fundamental problems remain to be solved: it takes time and skill to place many source-detector pairs on the hairy scalp and on the head of neonates and infants. Improvement of NIRS probes is vital for dissemination of NIRS in various fields of medicine and research. In addition, although less motion restriction during measurements is the strength of NIRS, head motion easily causes artifacts. Such artifacts cannot be eliminated automatically with a computer because of difficulty in distinguishing between signals and artifacts and require inspection by the naked eye.

5 Future Prospects

As is mentioned in Sec. 4, there remain a number of technical issues to be explored and practical difficulties to be solved. Nevertheless, NIRS is a tool distinct from other neuroimaging techniques for the study of brain functions and for the diagnosis, assessment, and treatment of psychoneurological diseases. Thus, a variety of novel applications of NIRS, such as NIRS-based brain-computer interface (BCI), are being tried. BCI provides users with an alternative output channel rather than the normal output path of the brain (i.e., the efferent nervous system and muscles).[90] BCI has been given much attention recently as an alternate mode of communication and control for the disabled, such as patients suffering from amyotrophic lateral sclerosis and "locked-in" patients. Most of the current BCI systems rely on the brain's electrical activity producing scalp EEG signals. Because the scalp EEG signals, however, are inherently noisy and nonlinear, a more accessible interface that uses a more direct measurement of brain function to control an output device is being explored. NIRS is considered as a possible alternative to electrical signals.[91]

Another optical approach to detect brain activation is also being tried. Conventional NIRS instruments detect signals corresponding to relatively slow hemodynamic responses. In contrast, a much faster signal occurring over a period of tens of milliseconds has been detected by both a frequency-domain system[92,93] and a CW system.[94] These fast signals, which are thought to be attributable to scattering changes in neurons, are much weaker than those of hemodynamic origin, and high temporal resolution is required for their detection. The instrumentation and data analysis of the techniques have remarkably improved over the last few years, making it feasible to

detect neuronal activity. This new approach is becoming a powerful clinical tool.

In the last few years the development of the multichannel NIRS system, which has abandoned handiness, one of the most characteristic features of NIRS, has been focused on in the NIRS field, the miniaturization of the NIRS system has also been tried. We have been extending the wearable system mentioned in Sec. 3.1 to the multichannel system. Wolf's group has recently succeeded in miniaturizing near-infrared optical imaging and creating a wireless sensor.[95] Such miniaturized NIRS systems will contribute not only to neuroscience research but also to monitoring tissue oxygenation, which was the original aim of NIRS development.

The development of NIRS has taken a long time. Over the last 30 years, however, NIRS has been making steady progress and its strengths and advantages are expected to provide a new direction for functional mapping studies that other neuroimaging techniques have not been able to achieve. Thus, NIRS shows great promise for providing further insight into brain function and as a clinical tool. Lastly, I must say that I am greatly indebted to the profound pioneering research of Dr. Jöbsis, and I would like to pay him all due respects.

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