Optical Imaging of Infants' Neurocognitive Development: Recent Advances and Perspectives

Yasuyo Minagawa-Kawai,[1] Koichi Mori,[2] Jeremy C. Hebden,[3] Emmanuel Dupoux[1,4]

[1] Laboratoire de Sciences Cognitives et Psycholinguistique, EHESS-DEC-ENS-CNRS, 29 rue d'Ulm, Paris 75005, France

[2] Department of Rehabilitation for Sensory Functions, Research Institute, National Rehabilitation Center for Persons with Disabilities, Saitama 359-8555, Japan

[3] Department of Medical Physics and Bioengineering, University College London, London WC1E 6BT, United Kingdom

[4] Maternité Port-Royal Hôpital Cochin, AP-HP Université René Descartes, 123 Blvd Port Royal, Paris 75014, France

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ABSTRACT: Near-infrared spectroscopy (NIRS) provides a unique method of monitoring infant brain function by measuring the changes in the concentrations of oxygenated and deoxygenated hemoglobin. During the past 10 years, NIRS measurement of the developing brain has rapidly expanded. In this article, a brief discussion of the general principles of NIRS, including its technical advantages and limitations, is followed by a detailed review of the role played so far by NIRS in the study of infant perception and cognition, including language, and visual and auditory functions. Results have highlighted, in particular, the developmental changes of cerebral asymmetry associated with speech acquisition. Finally, suggestions for future studies of neurocognitive development using NIRS are presented. Although NIRS studies of the infant brain have yet to fulfill their potential, a review of the work done so far indicates that NIRS is likely to provide many unique insights in the field of developmental neuroscience. © 2008 Wiley Periodicals, Inc. Develop Neurobiol 68: 712–728, 2008

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INTRODUCTION

Since Jöbsis (1977) first demonstrated that measurements of near-infrared (NIR) absorption could be used to monitor the level of oxygenation of certain chromophores *in vivo,* near-infrared spectroscopy (NIRS) has evolved into an effective method for noninvasive study of blood volume and oxygenation in the brain. The introduction of multichannel NIRS in the early 1990s led to the development of the technique as a means of measuring human cognitive functions, sometimes referred to as functional NIRS (Hoshi and Tamura, 1993; Kato et al., 1993; Villringer et al., 1993). NIRS has recently helped to reveal the neurocognitive functions of the infant brain (e.g. Peña et al., 2004; Taga et al., 2004), and researchers in developmental cognitive neuroscience, language acquisition, social cognition, and other functional aspects of the brain development during early childhood have become increasingly interested

Correspondence to: Y. Minagawa-Kawai (myasuyo@ens.fr).
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in this technique for its significant potential as a neuroimaging method. In this article, we review the current role of NIRS and the discoveries made so far in this rapidly expanding research field. We begin with an overview of the general principles of NIRS, with comments on its technical advantages and limitations, and then discuss recent NIRS studies on infant cognition, including language, visual, and auditory functions. We highlight, in particular, the progress made of the study of cerebral lateralization during speech processing.

GENERAL PRINCIPLES OF NIRS

It is well known that brain activity is associated with regional changes in blood flow and oxygenation (Fox and Raichle, 1986). Although the relationship between neuronal activity and the vascular response is not straightforward (Logothetis et al., 2001) and not yet fully understood (see the Advantages and Limitations of CW Optical Topography of the Brain section), studies of hemodynamic behavior in the brain are based on the assumption that an increase in blood flow, which in turn increases the mean local oxygenation, reflects an increase in neuronal activity. Blood flow and blood volumes are correlated and mostly interchangeable when estimating neural activity with some reasonable assumptions (Villringer et al., 1997; Hoshi et al., 2001; Strangman et al., 2002).

The *in vivo* NIRS technique discussed here assesses brain function by determining changes in the concentrations of oxygenated [HbO_2] and deoxygenated hemoglobin [Hb] in the circulating red blood cells by measuring changes in the diffuse transmittance of NIR light at an appropriate combination of wavelengths. Their specific absorption coefficients are illustrated in Figure 1. Because water is so prevalent in tissue, constituting around 80% of the human brain for example, increasingly dominant absorption by water at longer wavelengths limits practical *in vivo* NIRS to shorter than about 1000 nm. The lower limit on the wavelength is dictated by the overwhelming absorption by hemoglobin below about 650 nm. Hemoglobin is the dominant and clinically most interesting chromophore in the 650–1000 nm wavelength range (van der Zee et al., 1992). The isobestic point, where the specific absorption coefficients of the two forms of hemoglobin are equal, is at around 800 nm. Simultaneous monitoring of the transmittance changes at multiple wavelengths allows changes in concentrations of [HbO_2] and [Hb] to be estimated. Increasing the number of measurement wavelengths enables more accurate estimations of changes in hemoglobin concentrations, with smaller contributions from other chromophores such as cytochrome also taken into account (Heekeren et al., 1999). Further details of the principles of NIRS are described elsewhere (Ferrari et al., 2004).

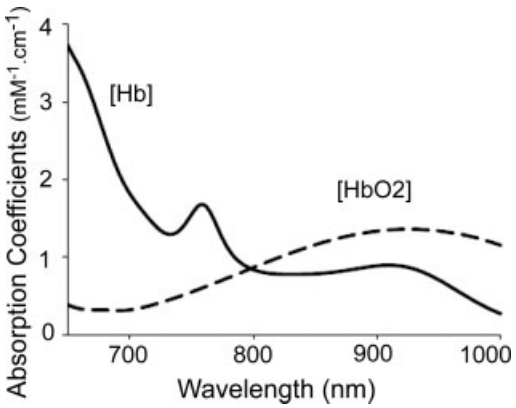

Figure 1 The NIR absorption spectra of oxygenated hemoglobin [HbO_2] and deoxygenated hemoglobin [Hb].

CONTINUOUS WAVE SYSTEMS

A variety of methods and instruments have been proposed for NIRS on the intact brain. The most common and simplest method involves measuring the intensity of diffusely reflected light with continuously emitting sources. Instruments which acquire such measurements are referred to as continuous wave (CW) systems. Typically, NIR light is emitted at a specific location on the surface of the scalp, while the intensity of the highly scattered and attenuated light that has passed through tissues close to the surface (including the cerebral cortex, skull and scalp) is measured at another location a few centimetres away [Fig. 2(A)]. It has been shown that with sufficient separation of source and detector fibers on the scalp, a significant proportion of the detected signal interrogates the cortical regions of the brain (Okada and Delpy, 2003). Changes in the intensity at two or more wavelengths can then be converted into changes in concentrations of [HbO_2] and [Hb] using the modified Beer–Lambert law (Reynolds et al., 1988; Delpy and Cope, 1997). If a single chromophore is uniformly distributed within the interrogated medium, the modified Beer–Lambert law can be expressed as

$$A = \log_e(I_0/I) = (\varepsilon \cdot c \cdot d \cdot B) + G \qquad (1)$$

where A is the attenuation, I_0 and I are the initial and final intensities, ε is the specific extinction coefficient

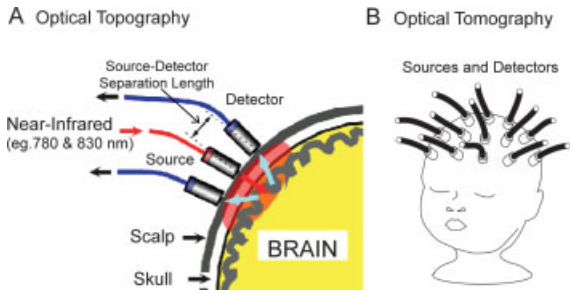

Figure 2 (A) Optical topography using an array of sources and detectors. Near-infrared light illuminates the brain through the skin and skull, and is diffusely reflected back toward the detectors. (B) Optical tomography using sources and detectors distributed over the entire scalp. Diffusely transmitted light, which has penetrated across the entire thickness of the brain, is detected.

of the chromophore (μmol^{-1} cm^{-1}), c is the concentration of the chromophore (μmol), d is the distance between the source and detector fibers, B is a differential pathlength factor (DPF), and G is an unknown term due to scattering losses. The DPF is the ratio of the mean path traveled in the tissue by detected photons and the minimum path d. Although the DPF can be measured using either a time- or frequency-domain system, as described in the following section (van der Zee et al., 1992), the DPF cannot be determined by a CW system. Nevertheless, a reasonable estimate of B can be made, which is sufficient for some applications (Ferrari et al., 1992). But even if B is known or can be estimated accurately, G is still unknown, and therefore absolute chromophore concentrations cannot be derived. However, if we consider the changes in attenuation due to the changes in the concentrations of [HbO_2] and [Hb], we can eliminate G as follows:

$$\Delta A = \{\Delta c[\mathrm{HbO_2}] \cdot \varepsilon[\mathrm{HbO_2}] + \Delta c[\mathrm{Hb}] \cdot \varepsilon[\mathrm{Hb}]\} \cdot d \cdot B \quad (2)$$

If measurements of ΔA are made at two wavelengths (e.g. 780 and 830 nm), then simultaneous equations can be obtained which can be solved for Δc[HbO_2] and Δc[Hb], assuming an appropriate value for B. These values can then be used to estimate changes in blood volume and oxygenation. The limitations of this approach are described by Obrig and Villringer (2003).

Until the early 1990s, almost all NIRS systems employed one or two measurement channels, which were sufficient for acquiring global measurements. The determination of spatial variations in tissue properties was facilitated by the development of the technique known as "optical topography" (Watanabe et al., 1996) which uses arrays of multiple NIR sources (e.g. laser diodes) and detectors arranged over the scalp surface [Figs. 2(A) and 3(A,B)]. The arrays enable a broad area of the cortical surface to be sampled with a minimal numbers of optical fibers, and a two-dimensional map of surface brain activity to be generated. To identify the source associated with a given detected signal it is necessary to either illuminate each source sequentially, or modulate each source at a unique frequency, and then distinguish the signals using lock-in amplifiers or a Fourier transform in software. Measurements on all detectors can be recorded at a rate of several Hz, enabling the time-course of the typical hemodynamic response to functional activation to be adequately sampled. Several

Figure 3 The NIRS measurements of (A) frontal activation in a 3-month-old infant using a Hitachi CW optical topography system, (B) temporal activation in a newborn infant using the UCL CW optical topography system, and (C) 3D optical properties of a newborn infant brain with the UCL time-resolved optical tomography system.

CW optical topography systems have been produced and employed for the study of infant brain function (Chance et al., 1998; Hintz et al., 2001; Koizumi et al., 2003).

TIME-DOMAIN AND FREQUENCY-DOMAIN SPECTROSCOPY

Because NIR light does not travel through tissue in straight lines, the exact volume of tissue interrogated by detected light using a CW system is not known, and thus it is not possible to derive absolute values of chromophore concentrations. To evaluate the changes in chromophore concentration in nonarbitrary units, it is necessary to determine the average pathlength of the diffusely reflected light [i.e. to determine an average value of $d \cdot B$ in Eq. (2)]. The pathlength of light can be recorded directly with a time-domain system, which employs a source of short (picosecond) laser pulses and a fast time-resolved detector. The average flight time multiplied by the speed of light in the tissue gives the mean pathlength. A time-domain system was first demonstrated for measurements on biological tissue by Delpy et al. (1988), using a device known as a streak camera. During the past decade, time-correlated single-photon counting hardware has become the technology of choice for time-domain systems. This requires a fast photon counting detector, and a histogram of photon flight times across the interrogated medium is acquired. The necessity to detect individual photons inherently limits the speed and dynamic range of time-domain systems, which consequently require longer data acquisition times than CW systems to attain a comparable signal to noise ratio (SNR). Nevertheless, the availability of time-of-flight information provides greater information about the distribution of photons within tissue (leading to superior depth resolution), and also enables changes in absorption to be distinguished from changes in scatter (Arridge and Lionheart, 1998).

Alternatively, frequency-domain systems enable the average pathlength to be determined using an intensity modulated source and a device which measures the phase delay of the transmitted signal, as demonstrated by Chance et al. (1990). Such systems do not rely on photon counting, and therefore offer greater SNR and dynamic range than time-domain methods. However, they provide less equivalent temporal information unless multiple frequencies are employed, and operate less efficiently at very low intensities (Nissilä et al., 2006). Optical topography systems have been built based on both time-domain (Quaresima et al., 2005) and frequency-domain (Danen et al., 1998; Choi et al., 2004; Kotilahti et al., 2005) technologies. Their disadvantage compared to CW systems is their comparatively high cost, and slower sampling rates (particularly for photon-counting systems).

As well as identifying hemodynamic changes in the brain, optical techniques have also observed signals varying over much smaller time intervals which are considered to have a neuronal origin. The neuronal signal exhibits a latency of around 10–100 ms, and changes in scattering in neuronal tissue have been proposed as a likely cause (Gratton et al., 2000; Gratton and Fabiani, 2001; Sable et al., 2007; Franceschini and Boas, 2004). A commercial frequency-domain optical topography system developed by ISS (USA), called the Imagent^{TM}, has been designed specifically to monitor these fast changes in optical properties in the brain associated with neuronal activity as well as the much slower changes due to hemodynamic activity (Choi et al., 2004).

OPTICAL TOMOGRAPHY

If a sufficient number of sources and detectors are placed around the head it is feasible to generate cross-sectional or three-dimensional (3D) images of the optical properties of the brain [Figs. 2(B) and 3(C)] (see review by Gibson et al., 2005b). This approach, known as optical tomography, requires sophisticated image reconstruction algorithms to convert the transmittance measurements into 3D images. A 32-channel time-domain system at UCL has been used to reconstruct 3D images of the whole infant brain, which has revealed an incidence of intraventricular hemorrhage (Hebden et al., 2002), changes in blood volume, and oxygenation induced by small alterations in ventilator settings (Hebden et al., 2004), and the first 3D optical images of the entire neonatal head during motor evoked response (Gibson et al., 2005a). However, optical tomography is far from routine use, mainly because of its slow acquisition and reconstruction speed, and high cost. Optical tomography of the entire brain is also limited to newborn infants, since the attenuation of light across a larger head is too great to sample the inner regions of the brain. Because of the high attenuation, data acquisition is relatively slow, and imaging of evoked response requires averaging over several activations (Gibson et al., 2005a).

In the remaining sections, we particularly focus on the optical topography (surface recording) studies

using CW, because of its advantages as mentioned earlier, and because most of the developmental studies with NIRS have so far been conducted with CW.

ADVANTAGES AND LIMITATIONS OF CW OPTICAL TOPOGRAPHY OF THE BRAIN

Spatial and Temporal Resolution

The typical temporal resolution of optical topography systems is technically a few Hz. However, because of the slow hemodynamic response to neural activation, the temporal resolution is effectively around 0.3–0.5 Hz. Spatial resolution can be characterized in terms of lateral (parallel to the brain surface) and depth resolutions. Both are strongly dependent on the arrangement of source and detector fibers on the scalp. Finer sampling of the surface obviously can be achieved by increasing the density of sources and detectors, although the resolution below the surface will be limited ultimately by the spread of photons within the tissue (Yamamoto et al., 2002). Sensitivity to activation occurring deeper below the surface can be increased by acquiring measurements with greater source-detector separation. Good depth resolution can therefore be achieved by acquiring data with a range of source-detector separations over the same surface area. Using simple linear back-projection schemes, spatial resolution for optical topography would depend on the size and shape of the so-called photon measurement density function (Arridge, 1995), which is the shape of a probabilistic photon-sampling volume. The use of model-based algorithms incorporating *a priori* structural information may significantly enhance spatial resolution. However, it has been suggested that the diffuse light reflection between white and gray matters limits the depth resolution even if source-detector distance is increased in adults, while the lower density of the white matter in neonates enables information from deeper regions to be obtained (Fukui et al., 2003). Overall the spatial resolution of CW NIRS is better than electroencephalography (EEG) but inferior to functional magnetic resonance imaging (fMRI).

A method has been developed for probabilistically registering NIRS data onto the Montreal Neurological Institute coordinate space without using anatomical MR images (Okamoto et al., 2004; Tsuzuki et al., 2007). It enables recorded brain regions to be identified by employing the landmarks of the international 10–20 system. Currently it is only applicable to adult brains.

Hemodynamic Information

NIRS provides sensitivity to both [HbO_2] and [Hb] (and consequently also to total hemoglobin), whereas BOLD fMRI is only sensitive to changes in [Hb]. In fact, *in vivo* NIRS has revealed that an absence of a BOLD signal does not always indicate a lack of brain activation (Fujiwara et al., 2004; Seiyama et al., 2004). An increase in the local arterial blood flow causes an increase in [HbO_2] and a decrease in [Hb], whereas an increase in oxygen consumption produces a decrease in [HbO_2] and an increase in [Hb]. Previous NIRS studies have indicated that the overall effect of these opposing mechanisms is different in infants from that in adults, possibly because of the immaturity of the vascular regulation. Whereas brain activation in adults in many cases leads to a localized increase in [HbO_2] and a decrease in [Hb] (Villringer et al., 1993; but see also Sakatani et al., 1998), some infant data are consistent with a net increase in both [HbO_2] and [Hb] (e.g. Meek et al., 1998; Sakatani et al., 1999). One study on awake infants suggests that this variation in response may be attributable to differences in attention and level of consciousness (Taga et al., 2003). Another contributing factor is the higher sensitivity of NIRS to capillary signals than to larger deeper vessels. NIRS measures Hb in capillaries, venules, and arterioles (Yamamoto and Kato, 2002) smaller than 1 mm in diameter (Liu et al., 1995), unless larger vessels are directly beneath one or more of the optical fiber probe pairs. Thus the downstream signals in larger draining vessels in areas remote from the activation do not show up in the NIRS signal while they do in BOLD, especially in a block-design paradigm.

Comparison with Other Methods

NIRS methods offer several significant advantages over fMRI. The SNR and temporal resolution of NIRS is considerably better than fMRI (Strangman et al., 2002). Optical topography using flexible optical fibers can accommodate almost any head position and posture, and can tolerate a degree of head movement. However, fMRI requires the infant head to be held stationary for long periods so that infants are often sedated. Consequently fMRI is not normally the primary choice for studies on the developing brain (but see also Dehaene-Lambertz et al., 2002, 2006). Whereas optical techniques can be conducted in silence, an MRI scanner is a very noisy environment, which makes fMRI studies of language or auditory responses very difficult, and may even present a risk of inducing hearing loss with the repeated exposure

to the loud scanner noise unless ears are properly protected. Other advantages of NIRS over fMRI include its portability, lower cost and compatibility with other electrical or magnetic monitoring systems and therapeutic devices (e.g. hearing aids and cochlear implants).

Although EEG shares some of the same advantages as optical methods over fMRI, such as portability, silent operation, and tolerance of posture, its ability to localize the focus of activity is generally poorer than NIRS. Magnetoencephalography (MEG) is far superior to EEG in this respect. However, its requirement for strict fixation of the subject's head relative to the sensor assembly often necessitates sedation of the infant. Both EEG and MEG are so good at resolving millisecond neural events, that only well-synchronized responses in a predetermined latency range can be detected. NIRS as well as fMRI, on the other hand, can be used when no clear synchrony is assumed, as in a block-design paradigm in which brain activation is recorded under two or more distinct conditions, each lasting more than several seconds. Depending on the stimuli, these two groups of methods may generate different results. For example, in a change detection task, the evoked response to phonemic changes was left-lateralized both with MEG and NIRS (Mori et al., 2004). However, the response to intonational changes was lateralized to the right with NIRS, whereas that observed with MEG was not, suggesting that while the early ($\sim$200 ms latency) mismatch response is bilateral, the later, less-synchronized response phase is more correlated with function (detection of prosodic change rather than physical frequency change).

Limitations of Optical Topography

Although NIRS represents a potentially powerful tool for infant developmental studies, it has several significant limitations. It offers poorer spatial resolution and depth sensitivity than either fMRI or MEG. Typical depth sensitivity of most optical topography systems is about 25–30 mm, although this depends on many factors including the source-detector separation, the source power, detector sensitivity, the optical properties of the skin/skull layers, and the degree of white matter myelination (Fukui et al., 2003). Optical topography is unsuited for probing deeper regions of the brain. This is a considerable disadvantage for some cognitive studies which involve deep regions such as the basal ganglia in relation to language/grammar, or amygdala in relation to emotion and memory processing. These regions may be accessed via 3D optical tomography for young infants, although with a much reduced temporal resolution. Lateral localization of signals also involves a high degree of uncertainty. For a single CW measurement with a given source-detector pair, it is impossible to distinguish between a moderate change in a localized small volume and a smaller change occurring in a larger volume of tissue. However, CW measurements made with an array of fibers with a combination of different source-detector separations improves the differentiation to a certain degree (Kawaguchi et al., 2004).

Because hemodynamic changes measured from the scalp surface include systemic vascular effects not only from inside but also from outside the brain, it is important to use experimental tasks that do not evoke any large systemic vascular changes, unless they are monitored independently (e.g. heart rate, blood pressure, and skin circulation). Another potential problem is blood volume changes in the scalp and within the muscles beneath the optical probes. Vocalization, for instance, affects the state of temporal muscles, and it is necessary to avoid a vocal production task during measurement of the anterior temporal area (Watanabe et al., 1998).

There are additional problems to be solved, such as development of an optimal means of attaching arrays of optical fibers to the infant head. NIRS also suffers from a lack of a standard method for data analysis. Infant hemodynamic physiology in the brain is poorly understood and one should be cautious about applying the same model established from adult fMRI analyses to infant NIRS (Schroeter et al., 2004). Discussions of further technological or methodological issues related to NIRS of infants can be found elsewhere (Hebden, 2003; Aslin and Mehler, 2005).

FUNCTIONAL CEREBRAL LATERALIZATION IN SPEECH PROCESSING

Language enables humans to convey complex and abstract meanings through a linear sequence of speech sounds. It has been debated whether this ability is based on particular brain ''modules'' for language (Fodor, 1985). Although strict modularity for language does not seem plausible, it is evident that language and speech processing largely rely on specialized neuronal networks in the perisylvian area, especially in the left hemisphere.

Speech processing in adults involves a series of steps starting from acoustic analysis and integration

of segmental (phonemic) and suprasegmental (prosodic) features (e.g. intonation, stress), followed by lexical access and syntactic integration, right up to semantic interpretation. Certain acoustic properties of speech (e.g. temporal vs. spectral information) as well as language properties (e.g. native vs. nonnative speech patterns) determine the pattern of neural recruitment, including left vs. right dominance (Best and Avery, 1999; Dehaene-Lambertz et al., 2005; Gandour et al., 2002; Poeppel, 2003; Shtyrov et al., 2005). In general, phonemes of one's native language are processed predominantly in the left side of the auditory area, whereas suprasegments (nonlexical prosody) are preferentially processed in the right side. NIRS allows the functional lateralization in response to auditory speech stimuli to be assessed in children as well as in adults (Minagawa-Kawai et al., 2002; Furuya and Mori, 2003; Sato et al., 2003). In their change detection paradigm, stimulus A (e.g. word or syllable) is repeatedly presented for 10–20 s as a baseline habituation block, followed by a target block where contrast stimulus B and baseline stimulus A are pseudo-randomly presented for 10–20 s. By alternating these blocks in tandem several times, the responses that are evoked by the stimulus changes in the target block can be detected in the temporal auditory area including Wernicke's area. Employing this paradigm, Furuya and Mori (2003) measured changes in total-Hb in response to phonemic contrast /itt**a**/ vs. /itt**e**/ and prosodic contrast /itt**a**/ vs. /itt**a?**/. The results for the right-handed subjects showed that peak values of total-Hb changes in the auditory area for the phonemic contrast were higher on the left side, whereas those for the prosodic contrast were higher on the right side (see Fig. 4). Individual assessment revealed that 85% of the right-handed subjects showed leftward dominance for the phonemic contrast. The non-right handers showed no significant lateralization differences as a group (see Fig. 5). These results were consistent with previous imaging studies using fMRI, positron emission tomography (PET), and MEG (Näätänen et al., 1997; Tervaniemi et al., 2000; Zevin and McCandliss, 2005). Note that the side of the language dominant hemisphere thus assessed for receptive speech may not always correspond to the Wada test, especially in non–right-handed subjects. This is probably due to the larger demand for the speech production function (or Broca's area) by the Wada test, and to the lateralization difference between Broca's and Wernicke's areas in some of the subjects, as suggested by Binder et al. (1996). Since the assessment of the hemispheric laterality depends on various experimental factors such as task design, stimulus properties, attentional demands, and the component of the brain responses being examined (Rinne et al., 1999; Hertrich et al., 2002; Shtyrov et al., 2005), the neuroimaging literature is sometimes contradictory in terms of the left-side superiority in speech processing (for review, see Dehaene-Lambertz & Gliga, 2004; Scott and Johnsrude, 2003; Tervaniemi and Hugdahl, 2003). Other reported paradigms for assessing hemispheric dominance for language with NIRS include word fluency (Watanabe et al., 1998; Matsuo et al., 2000; Watson et al., 2004; Quaresima et al., 2005) and word presentation tasks (Kennan et al., 2002). These active tasks, in contrast to the passive auditory task, are obviously not applicable to infants.

Whether or not particular phonemes are analyzed as part of language in the left auditory area depends if they are in the repertoire of the listener's native language (Näätänen et al., 1997). Using Japanese long and short vowel contrast as stimuli, Minagawa-Kawai et al. (2005b) showed that phoneme-specific responses were predominantly observed in the left auditory area for native Japanese participants (see Fig. 6) but not for late-bilingual Korean subjects, although their behavioral scores for identification and discrimination tests were almost indistinguishable. This finding shows that neurophysiological measures have a high potential for detecting cortical activities specific to language. In addition to the phonetic level of speech processing, semantic and syntactic levels have also been examined (see Sato et al., 1999; Noguchi et al., 2002; Horovitz and Gore, 2004). In the auditory studies related to cerebral lateralization, total-Hb has been used as the indicator of local cerebral activation. However, as discussed in Minagawa-Kawai et al. (2007), the choice of indicator may depend on various factors such as the cortex areas studied, age, task demand, and individual vascular responsiveness.

LANGUAGE DISCRIMINATION CAPACITY IN INFANTS

Newborn infants are able to discriminate between speech and backward speech, and also between their mother tongue (L1) and foreign languages (L2) if these languages possess different language rhythm (i.e. stress-timed as in English and German; syllable-timed as in French and Spanish) (Mehler et al., 1988). After 4 months of exposure to their L1, infants can discriminate L1 from any other L2 (Bosch and Sebastian-Galles, 1997; Nazzi et al., 2000). In discriminating these languages, infants seem to use

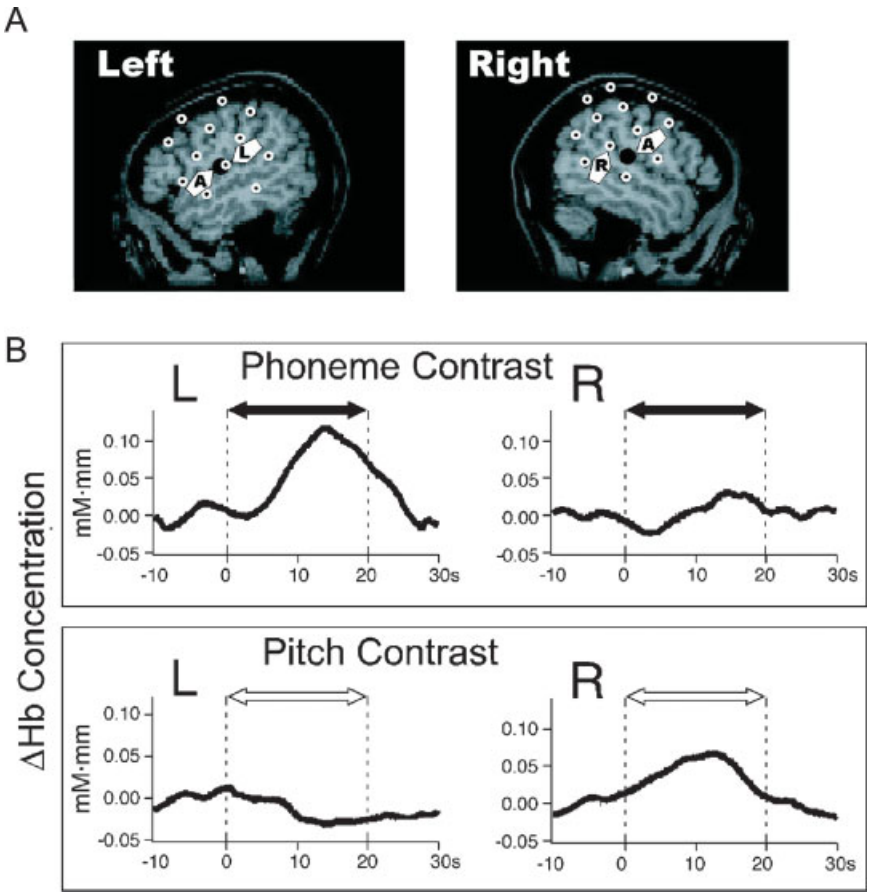

Figure 4 (A) The estimated locations of the sampled regions on an adult subject. The positions of the optical probes were measured with a 3D digitizer arm. The recording sites were identified by superimposing the above coordinate onto the left and right parasagittal MRI images for each subject. Posterior is to the center of the two images. The lateral posterior borders of the Heschl gyri are indicated by the filled circles labeled "A." Channels labeled "L" and "R" are the left and right auditory channels, respectively, whose recordings are shown in the lower panels. (B) The averaged Hb concentration changes in response to the phonemic contrast and pitch (prosodic) contrasts. The target blocks are indicated by arrows. Data were adopted from Furuya and Mori (2003).

prosodic cues, because they can still discriminate even if the stimuli are low-pass filtered at 400 Hz (Mehler et al., 1988).

For almost a decade after the discovery of newborns' ability to discriminate language (Mehler et al., 1988), there had been no easy method to monitor infants' cortical activities associated with this. Peña et al. (2003) added a new and important line of evidence for the earliest functional lateralization of the brain in response to receptive speech. They presented forward L1 speech and its backward version to neonates who were less than 5 days old. Neonates showed larger neural activations (total-Hb changes) in the left temporal area in response to the forward speech than to the backward speech and silence. Because the backward speech included exactly the same long-term spectral properties as those of the

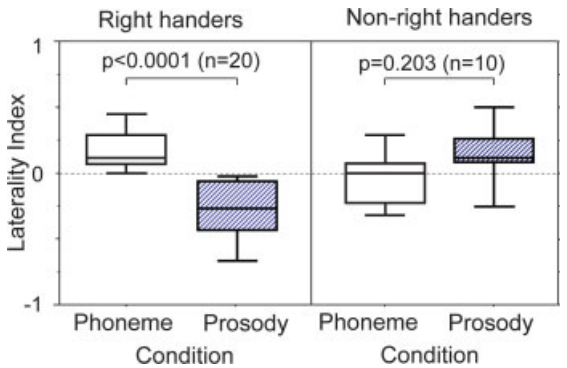

Figure 5 Laterality indices in phonemic and prosodic conditions for right handers and non-right handers. Laterality index (LI) was calculated by the formula $LI = (L - R)/(L + R)$, where L and R is the maximum values of total Hb changes in the left and right auditory area. Data were adopted from Furuya and Mori (2003).

forward speech, it can be concluded that newborn infants already have sensitivity to some temporal characteristics of the speech stimuli. The differential responses of the left temporal area to certain properties of speech a few days after birth could be related to the language faculty unique to humans. An fMRI study performed on 3-month-olds showed similar results (Dehaene-Lambertz et al., 2002). However, as has already been mentioned elsewhere (Minagawa-Kawai and Mori, 2004), one should be careful in interpreting these results as entirely linguistic, because the specific properties that activated the left temporal area have not been fully elucidated. They may not be specific to language processing, at least not in their entirety, for three reasons. First, young infants seem to discriminate language differences or prosodic structures of languages by using general auditory mechanisms shared by other animals. Tamarin monkeys and rodents discriminate language differences and forward vs. backward speech as young infants do (Ramus et al., 2000; Toro et al., 2003). Second, in both NIRS and fMRI studies, activations observed during reversed speech were weak but they were also left-dominant. Third, sentences including segmental features (i.e. rapidly changing segments) are more likely to be processed dominantly on the left, whereas prosodic sentences without segments are on the right (Poeppel, 2003; Perkins et al., 1996). The second and the third points may suggest that the laterality of infants' brain activation could be determined chiefly by the acoustic properties of stimuli, irrespective of their linguistic content. Namely, rapidly or temporally changing sounds could induce a left-dominant response, and slowly or spectrally changing sounds could evoke a right-dominant response. This hypothesis is partly supported by a NIRS study (Homae et al., 2006), which shows relative right dominant responses to prosodic speech compared to flattened speech with the same segment information in 3-month-old infants. Other factors such as familiarity and attention may also contribute to the lateralized pattern of activations in newborns.

Language processing in the first year of life comprises various cognitive aspects including analysis of acoustic features, perception of phonemic and prosodic units, and rule extraction. Only by untangling these interdependent factors with appropriate analytical approaches can one elucidate the cerebral bases of language. In fact, recently there has been a sudden growth of interest in infant/child NIRS studies related to speech development (e.g. Sato et al., 2003; Gervain and Mehler, 2006; Homae et al., 2006, 2007; Bortfeld et al., 2007; Minagawa-Kawai et al., 2007; Taga and Asakawa, 2007; Wartenburger et al., 2007), some of which examine phonemic and prosodic factors as discussed in the next section.

DEVELOPMENTAL CEREBRAL LATERALIZATION AND SPEECH PROCESSING IN INFANTS

Behavioral studies have consistently shown that newborn infants can discriminate between almost any of the phonemic contrasts in the world languages, but lose this initial ability within the first year of life, while their phoneme discrimination becomes attuned to the phonemic repertoires of their mother tongue (Werker and Tees, 1984). Does the same language network persistently underlie this developmental process before and after the attunement? Although functional laterality in speech processing in infants has been examined by dichotic listening tests with high intensity sucking and EEG, the results were not consistent (Molfese and Hess, 1978; Novak et al., 1989; Simos et al., 1997). By measuring localized Hb increases in the temporal auditory area, NIRS has detected functional lateralization associated with speech. Sato et al. (2003) assessed lateralization for speech in infants and children from 7-month-old to 5-year-old by using a phonemic contrast (/iit**a**/ vs. /itt**e**/) and a prosodic contrast (/itt**a**/ vs. /itt**a?**/) in the change detection paradigm used in an adult study (Furuya and Mori, 2003). While infants in the youngest age groups (7–10-month-old) did not show any significant differences in the response laterality between the two conditions, 11–12-month-olds showed a significant lateralization similar to adults, i.e., the phonemic change evoked a left-dominant response and the prosodic contrast a right-dominant response.

Using a similar change detection paradigm, Minagawa-Kawai et al. (2007) further extended these results by comparing neural responses to Japanese long and short vowels. A pseudo-word /mama/ was contrasted with another whose second syllable either carried a linguistically significant difference in vowel length (across-category condition) or a nonlinguistic difference (within-category condition), yet with the same physical durational difference. Infants showed different patterns of activation in the course of development depending on the linguistic nature of the contrasts. A larger response to the across-category changes than to the within-category changes occurred transiently in the 6- to 7-month-old group, which disappeared afterwards, and then reappeared for final stabilization after 12 months [Fig. 7(A)]. In contrast, left-dominant responses appeared only after 12 months, as shown in Figure 7(B). In other words, the

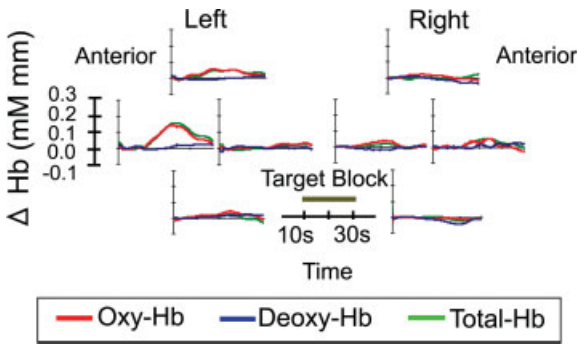

Figure 6 The averaged Hb concentration changes in response to across-category condition in an adult. Four channels around the temporal areas (left and right) are shown. Data were adopted from Minagawa-Kawai et al. (2007).

combination of the phoneme specificity and the left dominance typical of the native adult responses appeared only in the groups older than 12 months. Because the earlier transient phoneme sensitivity was not lateralized, it must be sustained by a different neural network than the one that develops later. During the first year of life, infants may resort to general auditory mechanisms for linguistic discrimination in the brain. However, as they continue to be exposed to their L1, the neural processing of the contrast is then switched over to a more linguistic circuit, which presumably is more attuned to L1 after 12 months. It is assumed that this timing of leftward lateralization reflects the neural process where certain linguistic sounds are integrated into phonological frameworks.

One question raised by the above finding is how neural recruitment changes for L2 phoneme processing. Infant ERP revealed that the sensitivity of 12-month-olds to a L2 vowel is weaker than that of 6-month-olds (Cheour et al., 1998). However no consistent results were reported with regards to cerebral lateralization. In a longitudinal NIRS study comparing the total-Hb changes to the L1 Japanese phonemic contrast [i] vs. [□] and the L2 Korean contrast [□] vs. [u] in pseudo-word contexts, it was revealed that the responses from the temporal area at the age of 8 months were lateralized to the left-side only for the L1 phonemic contrast (Minagawa-Kawai et al., 2005c), while the same subjects at the age of 4 months did not show any lateralized responses. This finding in addition to that on the durational contrasts, suggests that the development of lateralization differs depending on the phonemic type (i.e. spectral difference vs. durational difference and vowel types). More importantly, this study showed longitudinal developmental changes of functional asymmetries in the temporal cortex specific to the native language.

FRONTAL ACTIVATION IN RESPONSE TO SPEECH

In contrast to the auditory areas described earlier, which involved both lower sensory function and higher cognition, the frontal lobe is chiefly related to higher cognitive processes. It plays a critical role in human executive functions involving memory, attention, language, and in the integration of information from various brain areas. While the auditory system is relatively mature at birth, as revealed by myelination (Ray et al., 2005), NIRS (Zaramella et al., 2001), and MEG (Huotilainen et al., 2003), the maturation of the frontal lobe is slower than any other brain areas (Yakovlev and Lecours, 1967). However, frontal activation in neonates has been observed by NIRS. In

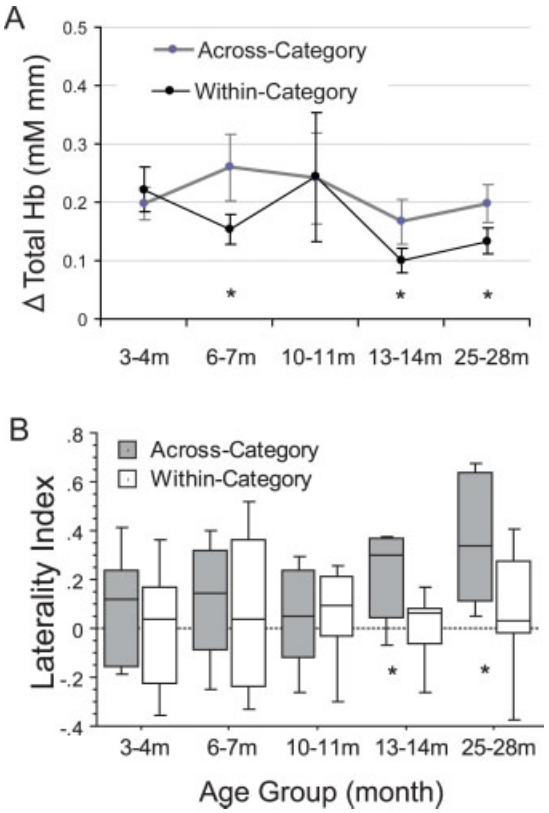

Figure 7 (A) Averaged values of the total Hb changes in the left auditory area (L) in response to the across- and within-phonemic changes of the stimuli. $*p < 0.05$ for the difference between the responses in the across- and within-sessions. (B) Laterality index in different age groups. Left dominance is observed in the older age groups. $*p < 0.05$. Data were adopted from Minagawa-Kawai et al. (2007).

response to music, newborns' frontal lobe showed activation with increased [HbO_2] (Sakatani et al., 1999; Chen et al., 2002). Saito et al. (2007a) found a larger increase in [HbO_2] in the frontal area in response to infant-directed speech than to adult-directed speech. Infant-directed speech tends to have richer prosodic expressions with exaggerated pitch contours, which is presumed to facilitate infants' speech acquisition. The difference in the prosodic feature likely affected the activation level in the frontal area, because the same group (Saito et al., 2007b) reported a larger [HbO_2] response to prosodic speech than to monotonous speech. Richness in the prosodic structure may catch infants' attention, contributing to the enhanced frontal activation.

In the change detection paradigm mentioned in the previous section, activation foci around the frontal area are often observed together with the temporal area in infants as young as 2–3 months or older (Sato et al., 2003; Minagawa-Kawai et al., 2007). This brain response may reflect novelty detection of the stimuli or attention (Näätänen, 2003). However, the frontal activation may also be related to language *per se*, because speech evokes stronger frontal responses than nonspeech for 6-month-olds, as shown in a similar paradigm with MEG (Imada et al., 2006). Infant fMRI studies revealed activation in Broca's area by a passive verbal memory task in infants as young as 3 months of age (Dehaene-Lambertz et al., 2006). Because of the limited time available to study infants during MEG or fMRI, there has been insufficient data so far to reveal the detailed nature of the function of the frontal area in speech development. Since Broca's area is involved in critical language processes such as rule learning and speech production (Friederici, 2006), more work of an analytical nature on the roles of the frontal area is obviously desirable. NIRS provides a potentially powerful tool which should enable suitable investigations of the developing brain to be conducted.

OTHER COGNITIVE STUDIES USING NIRS

Reports on NIRS studies that investigate visual perception and cognition in infants are relatively sparse. This is partly due to the difficulty in presenting stable visual stimuli, and in retaining infants' attention on them during measurement. Localized [HbO_2] changes in the occipital area in young infants (3 days – 12 weeks) have been recorded using checkerboard stimuli (Meek et al., 1998). Simultaneous measurement of the occipital and frontal areas for 2–4-month-olds showed occipital activation accompanied by a slight [HbO_2] increase in the frontal area (Taga et al., 2003). Cortical activations in face processing have also been revealed in the occipital area (Csibra et al., 2004; Blasi et al., 2007). In addition to these neural correlates to lower sensory function, Otsuka et al. (2007) revealed functional cerebral localization during an attempt to explore the effects of face inversion in infants. Meanwhile, 5–8-month-olds exhibited larger responses to upright faces than to inverted faces in [HbO_2] and total-Hb in the right temporal area, showing a similar interhemispheric pattern to adults (Otsuka et al., 2007). In response to video clips of their own and unfamiliar mothers/infants in different emotional states (positive vs. negative), mothers and 9–13-month-olds showed similar patterns of neural recruitment in the prefrontal cortex (Minagawa-Kawai et al., 2005a). In infants, the presentation of their mother's face with a "positive emotion" evoked larger [HbO_2] changes in the anterior part of the orbito frontal cortex than any other conditions. This suggests that infants are able to read emotions based on their social knowledge. In studying face processing with NIRS, careful choice of measurement areas depending on the purpose of the experiment is required, since CW NIRS has difficultly measuring the fusiform gyrus deep in the brain, which are critically involved in face perception. NIRS studies of the prefrontal cortex to examine the effects of eye gaze or emotional faces in the context of social cognition might be promising and would be of great interest.

A large number of behavioral studies have revealed remarkable knowledge about young infants' processing of objects (e.g. Baillargeon et al., 1985; Spelke et al., 1992). Understanding what infants know about objects is valuable, because it tells us about their conceptual knowledge and how they process visual patterns such as shapes and colors. The neuronal activity underlying object processing in infants has begun to be explored recently using EEG (Csibra et al., 2000; Kaufman et al., 2003, 2005). With NIRS, infant object observation and memory (Baird et al., 2002; Wilcox et al., 2005) as well as object vs. action observation (Shimada and Hiraki, 2006) have been examined. One set of EEG studies showed that oscillations in the gamma band ($\sim$40 Hz) appear to be one possible neural marker of object retention (Kaufman et al., 2003, 2005). Since γ-band oscillation was found to correlate with the BOLD responses obtained using fMRI (Foucher et al., 2003; Fiebach et al., 2005), coregistration of NIRS and ERP in exploring γ-band oscillation would provide a rich source of information on object processing in devel-

oping brain. In summary, NIRS provides a powerful complementary tool to existing neuroimaging and behavioral studies in visual cognition, social cognition, and conceptual knowledge (Spelke and Kinzler, 2007), revealing neural development.

Apart from the studies of higher cognitive domains that we have focused on earlier, NIRS has also been used to explore the sensory-motor functions, including the olfactory function (Bartocci et al., 2000, 2001), pain (Slater et al., 2006), passive motor movements (e.g. Hintz et al., 2001; Isobe et al., 2001), and occipital responses to photostimulation during sleep (e.g. Hoshi et al., 2000; Kusaka et al., 2004). Furthermore, a great amount of clinical research has been devoted to investigating cerebral circulation in infants and exploring potential clinical applications (for review, see Nicklin et al., 2003; Greisen, 2006). These include the measurement of the fetal brain (Peebles and Wyatt, 1993; D'Antona et al., 1997), assessment of hypoxia (Brazy et al., 1985), and perinatal asphyxia (Meek et al., 1999). These studies have played a major role in the development of NIRS technology as a tool for understanding the normal and damaged infant brain.

CONCLUSIONS AND FUTURE PERSPECTIVES

Functional optical imaging of the developing brain has rapidly expanded during the past 10 years. Although there is still room for improvement on various technical issues, a considerable amount of new information on the early cerebral developmental processes of cognition has already been acquired. The investigation of cerebral hemodynamic responses with NIRS offers a means of directly comparing infant and adult cognitive brain functions, the latter of which have been studied mostly with fMRI and PET. NIRS can thus fill the knowledge gap for cognitive neuroscience.

In the field of speech acquisition, the significant potential of NIRS has already been demonstrated in studies of the acquisition of phonemic and prosodic contrasts. It would be possible to link these findings to a larger framework of the neural substrates of language development. For this to happen, we consider the following four directions to be of importance.

First, one should be able to estimate the connection or pathways in the brain for particular cognitive processing, in addition to functional localization of the infant brain. An infant fMRI study using presentation of repeated sentences suggests a plausible neural pathway based on an early activation in the Heschl's gyrus, followed by activation in the posterior temporal and the inferior frontal gyrus (Broca's area) (Dehaene-Lambertz et al., 2006). However, to our knowledge no NIRS studies have formally investigated connections or the time course of activations between different areas. In this article, neural responses from the auditory and the frontal cortex were described separately, as many studies examined them independently. However observations of developmental changes in connectivity between the frontal and temporal areas, for instance, would be of great interest for language research. As shown earlier, NIRS provides a powerful tool for early longitudinal measurements (Minagawa-Kawai et al., 2005c).

Second, NIRS would benefit from simultaneous recording with EEG in order to elucidate correlations between optical signals and electrophysiological changes. Although such a relationship is well documented in invasive NIRS with an exposed brain (e.g. Rector et al., 1997), only weak correlation has been found for noninvasive NIRS and cortical EEG (Hoshi et al., 1998; Steinbrink et al., 2001). Adult and infant ERP studies have revealed electrophysiological components or gamma- or theta-band oscillations that are specific to certain perceptual or cognitive processes such as N400 in relation to semantics and familiarity (e.g. face perception) and E-LAN (early left anterior negativity) in relation to syntactic processing. Identification of the brain regions for each EEG component using NIRS would greatly facilitate interpretation of ERP in infants.

Third, performing relevant behavioral measurement compatible with NIRS recording is important. Simultaneous use of an eye tracking camera to facilitate looking time measurements or for behavioral coding, for example, is desirable. In many cases, traditional behavioral measurements of infant speech involve head turning which could cause motion artifacts in NIRS data. Thus a novel experimental paradigm is required in this field. With properly balanced conditions during NIRS sessions, behavioral testing before or after NIRS recording should be also considered. In testing sleeping babies, monitoring their sleep stages such as quiet sleep and active sleep is desirable.

Fourth, it is important to obtain adult data with the same or similar paradigms used for infant studies. NIRS studies of functional neuronal activity show differences between adults and infants in some cases, which may be because of the different hemodynamic physiology resulting from the infant's immature vascular regulation. At present, however, direct comparison of optical signals between infants and adults is not so simple because of the inherent differences in

light scattering and absorbing properties of the brain, due to the immature myelination and/or larger volume of white matter in infants. Nevertheless, adult NIRS and/or fMRI data is in many cases essential in interpreting infant data.

The points raised above are crucial for gaining an understanding of fundamental neural systems from the level of action potentials (electrophysiological activity) to human behavior, and associated developmental changes. Additionally, on-going technological development of time-domain and frequency-domain NIRS is likely to improve the sensitivity and quantitation of infant NIRS measurements. In the past decade, the significant potential of NIRS as a tool to assess infant neuronal development *in vivo* has been demonstrated, and during the next decade it could help to yield unique insights in developmental neuroscience. NIRS studies of infants' cognitive function have just begun. If we consider that most of the research described earlier was not even possible 5 years ago, we can expect that within the next 5 years NIRS should reveal many unique and surprising discoveries about the infant brain, which remains mysterious and elusive at present.

REFERENCES

Arridge SR. 1995. Photon-measurement density functions. Part I: Analytical forms. Appl Opt 34:7395–7409.

Arridge SR, Lionheart WRB. 1998. Non-uniqueness in optical tomography. Opt Lett 23:882–884.

Aslin R, Mehler J. 2005. Near-infrared spectroscopy for functional studies of brain activity in human infants: Promise, prospects, and challenges. J Biomed Opt 10:011009–011003.

Baillargeon R, Spelke ES, Wasserman S. 1985. Object permanence in fivemonth-old infants. Cognition 20:191–208.

Baird AA, Kagan J, Gaudette T, Walz KA, Hershlag N, Boas DA. 2002. Frontal lobe activation during object permanence: data from near-infrared spectroscopy. Neuroimage 16:1120–1125.

Bartocci M, Winberg J, Papendieck G, Mustica T, Serra G, Lagercrantz H. 2001. Cerebral hemodynamic response to unpleasant odors in the preterm newborn measured by near-infrared spectroscopy. Pediatr Res 50:324–330.

Bartocci M, Winberg J, Ruggiero C, Bergqvis LL, Serra G, Lagercrantz H. 2000. Activation of olfactory cortex in newborn infants after odor stimulation: A functional near-infrared spectroscopy study. Pediatr Res 48:18–23.

Best CT, Avery RA. 1999. Left-hemisphere advantage for click consonants is determined by linguistic significance and experience. Psychol Sci 10:65–70.

Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, Benbadis S, et al. 1996. Determination of language dominance using functional MRI: A comparison with the Wada test. Neurology 46:978–984.

Blasi A, Fox S, Everdell N, Volein A, Tucker L, Csibra G, Gibson AP, Hebden JC, Johnson MH, Elwell CE. 2007. Investigation of depth dependent changes in cerebral haemodynamics during face perception in infants. Phys Med Biol 52:6849–6864.

Bortfeld H, Wruck E, Boas DA. 2007. Assessing infants' cortical response to speech using near-infrared spectroscopy. Neuroimage 34:407–415.

Bosch L, Sebastian-Galles N. 1997. Native-language recognition abilities in 4-month-old infants from monolingual and bilingual environments. Cognition 65:33–69.

Brazy JE, Lewis DV, Mitnick MH, Jobsis vander Vliet FF. 1985. Noninvasive monitoring of cerebral oxygenation in preterm infants: preliminary observations. Pediatrics 75: 217–225.

Chance B, Anday E, Nioka S, Zhou S, Hong L, Worden K, Li C, et al. 1998. A novel method for fast imaging of brain function, non-invasively, with light. Opt Exp 2:411–423.

Chance B, Maris M, Sorge J, Zhang MZ. 1990. A phase modulation system for dual wavelength difference spectroscopy of hemoglobin deoxygenation in tissues. Proc SPIE 1204:481–491.

Chen S, Sakatani K, Lichty W, Ning P, Zhao S, Zuo H. 2002. Auditory-evoked cerebral oxygenation changes in hypoxic-ischemic encephalopathy of newborn infants monitored by near infrared spectroscopy. Early Hum Dev 67:113–121.

Cheour M, Ceponiene R, Lehtokovski A, Luuk A, Allik J, Alho K, Näätänen R. 1998. Development of language-specific phoneme representations in the infant brain. Nat Neurosci 1:351–353.

Choi J, Wolf M, Toronov V, Wolf U, Polzonetti C, Hueber D, Safonova LP, et al. 2004. Noninvasive determination of the optical properties of adult brain: Near-infrared spectroscopy approach. J Biomed Opt 9:221–229.

Csibra G, Davis G, Spratling MW, Johnson MH. 2000. Gamma oscillations and object processing in the infant brain. Science 290:1582–1585.

Csibra G, Henty J, Volein A, Elwell C, Tucker L, Meek J, Johnson MH. 2004. Near infrared spectroscopy reveals neural activation during face perception in infants and adults. J Pediatr Neurol 2:85–89.

Danen RM, Wang Y, Li XD, Thayer WS, Yodh AG. 1998. Regional imager for low-resolution functional imaging of the brain with diffusing near-infrared light. Photochem Photobiol 67:33–40.

D'Antona D, Aldrich CJ, O'Brien P, Lawrence S, Delpy DT, Wyatt JS. 1997. Recent advances in fetal near infrared spectroscopy. J Biomed Opt 2:15–21.

Dehaene-Lambertz G, Dehaene S, Hertz-Pannier L. 2002. Functional neuroimaging of speech perception in infants. Science 298:2013–2015.

Dehaene-Lambertz G, Gliga T. 2004. Common neural basis for phoneme processing in infants and adults. J Cogn Neurosci 16:1375–1387.

Dehaene-Lambertz G, Pallier C, Serniclaes W, Sprenger-Charolles L, Jobert A, Dehaene S. 2005. Neural correlates of switching from auditory to speech perception. Neuroimage 24:21–33.

Dehaene-Lambertz G, Hertz-Pannier L, Dubois J, Meriaux S, Roche A, Sigman M, Dehaene S. 2006. Functional organization of perisylvian activation during presentation of sentences in preverbal infants. Proc Natl Acad Sci USA 103:14240–14245.

Delpy DT, Cope M. 1997. Quantification in tissue near-infrared spectroscopy. Philos Trans R Soc Lond B Biol Sci 352:649–659.

Delpy DT, Cope M, van der Zee P, Arridge S, Wray S, Wyatt JS. 1988. Estimation of optical pathlength through tissue from direct time of flight measurement. Phys Med Biol 33:1433–1442.

Ferrari M, Mottola L, Quaresima V. 2004. Principles, techniques, and limitations of near infrared spectroscopy. Can J Appl Physiol 29:463–487.

Ferrari M, Wei Q, Carraresi L, De Blasi RA, Zaccanti G. 1992. Time-resolved spectroscopy of the human forearm. J Photochem Photobiol B 16:141–153.

Fiebach CJ, Gruber T, Supp G. 2005. Neuronal meachanisms of repetition priming inoccipitotemporal cortex: Spatiotemporal evidence from functional magnetic imaging and electroencephalography. J Neurosci 25: 3414–3422.

Fodor J. 1985. Précis of the modularity of mind. Behav Brain Sci 8:1–5.

Foucher JR, Otzenberger H, Gounot D. 2003. The BOLD response and the gamma oscillations respond differently than evoked potentials: an interleaved EEG-fMRI study. BMC Neuroscience 4:22.

Fox PT, Raichle ME. 1986. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci USA 83:1140–1144.

Franceschini MA, Boas DA. 2004. Noninvasive measurement of neuronal activity with NIR optical imaging. Neuroimage 21:372–380.

Friederici AD. 2006. Broca's area and the ventral premotor cortex in language: Functional differentiation and specificity. Cortex 42:472–475.

Fujiwara N, Sakatani K, Katayama Y, Murata Y, Hoshino T, Fukaya C, Yamamoto T. 2004. Evoked-cerebral blood oxygenation changes in false-negative activations in BOLD contrast functional MRI of patients with brain tumors. Neuroimage 21:1464–1471.

Fukui Y, Ajichi Y, Okada E. 2003. Monte Carlo prediction of near-infrared light propagation in realistic adult and neonatal head models. Appl Opt 42:2881–2887.

Furuya I, Mori K. 2003. Cerebral lateralization in spoken language processing measured by multi-channel near-infrared spectroscopy (NIRS). Brain Nerve 55:226–231.

Gandour J, Wong D, Lowe M, Dzemidzic M, Satthamnuwong N, Long Y, Lurito J. 2002. Neural circuitry underlying perception of duration depends on language experience. Brain Lang 83:268–290.

Gervain J, Mehler J. 2006. Neonates' discrimination of structured vs. unstructured linguistic input: An optical topography study. In: Proceeding of the 31th Annual BU Conference on Language Development. p 19.

Gibson AP, Austin T, Everdell NL, Schweiger M, Arridge SR, Meek JH, Wyatt JS, et al. 2005a. Three-dimensional whole-head optical tomography of passive motor evoked responses in the neonate. Neuroimage 30:521–528.

Gibson AP, Hebden JC, Arridge SR. 2005b. Recent advances in diffuse optical imaging. Phys Med Bio 50:R1–R43.

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

Gratton G, Sarno A, Maclin E, Corballis PM, Fabiani M. 2000. Toward noninvasive 3-D imaging of the time course of cortical activity: investigation of the depth of the event-related optical signal. Neuroimage 11:491–504.

Greisen G. 2006. Is near-infrared spectroscopy living up to its promises? Semin Fetal Neonatal Med 11:498–502.

Hebden JC. 2003. Advances in optical imaging of the newborn infant brain. Psychophysiology 40:501–510.

Hebden JC, Gibson A, Austin T, Yusof R, Everdell N, Delpy DT, Arridge SR, et al. 2004. Imaging changes in blood volume and oxygenation in the newborn infant brain using three-dimensional optical tomography. Phys Med Biol 49:1117–1130.

Hebden JC, Gibson A, Yusof R, Everdell N, Hillman EMC, Delpy DT, Arridge SR, et al. 2002. Three-dimensional optical tomography of the premature infant brain. Phys Med Biol 47:4155–4166.

Heekeren HR, Kohl M, Obrig H, Wenzel R, von Pannwitz W, Matcher SJ, Dirnagl U, 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.

Hertrich I, Mathiak K, Lutzenberger W, Ackermann H. 2002. Hemispheric lateralization of the processing of consonant-vowel syllables (formant transitions): Effects of stimulus characteristics and attentional demands on evoked magnetic fields. Neuropsychologia 40:1902–1917.

Hintz SR, Benaron DA, Siegel AM, Zourabian A, Stevenson DK, Boas DA. 2001. Bedside functional imaging of the premature infant brain during passive motor activation. J Perinat Med 29:335–343.

Homae F, Watanabe H, Nakano T, Asakawa K, Taga G. 2006. The right hemisphere of sleeping infant perceives sentential prosody. Neurosci Res 54:276–280.

Homae F, Watanabe H, Nakano T, Taga G. 2007. Prosodic processing in the developing brain. Neurosci Res 59: 29–39.

Horovitz SG, Gore JC. 2004. Simultaneous event-related potential and near-infrared spectroscopic studies of semantic processing. Hum Brain Mapp 22:110–115.

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

Hoshi Y, Kosaka S, Xie Y, Kohri S, Tamura M. 1998. Relationship between fluctuations in the cerebral hemoglobin oxygenation state and neuronal activity under resting conditions in man. Neurosci Lett 245:147–150.

Hoshi Y, Kobayashi N, Tamura M. 2001. Interpretation of near-infrared spectroscopy signals: A study with a newly developed perfused rat brain model. J Appl Physiol 90:1657–1662.

Hoshi Y, Kohri S, Matsumoto Y, Cho K, Matsuda T, Okajima S, Fujimoto S. 2000. Hemodynamic responses to photic stimulation in neonates. Pediatr Neurol 23:323–327.

Huotilainen M, Kujala A, Hotakainen M, Shestakova A, Kushnerenko E, Parkkonen L, Fellman V, et al. 2003. Auditory magnetic responses of healthy newborns. Neuroreport 14:1871–1875.

Imada T, Zhang Y, Cheour M, Taulu S, Ahonen A, Kuhl PK. 2006. Infant speech perception activates Broca's area: A developmental magnetoencephalography study. Neuroreport 17:957–962.

Isobe K, Kusaka T, Nagano K, Okubo K, Yasuda S, Kondo M, Itoh S, et al. 2001. Functional imaging of the brain in sedated newborn infants using near infrared topography during passive knee movement. Neurosci Lett 299:221–224.

Jöbsis FF. 1977. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198:1264–1267.

Kato T, Kamei A, Takashima S, Ozaki T. 1993. Human visual cortical function during photic stimulation monitoring by means of near-infrared spectroscopy. J Cereb Blood Flow Metab 13:516–520.

Kaufman J, Csibra G, Johnson MH. 2003. Representing occluded objects in the human infant brain. Proc Biol Sci 270 (S2):140–143.

Kaufman J, Csibra G, Johnson MH. 2005. Oscillatory activity in the infant brain reflects object maintenance. Proc Natl Acad Sci USA 102:15271–15274.

Kawaguchi H, Hayashi T, Kato T, Okada E. 2004. Theoretical evaluation of accuracy in position and size of brain activity obtained by near-infrared topography. Phys Med Biol 49:2753–2765.

Kennan RP, Kim D, Maki A, Koizumi H, Constable RT. 2002. Non-invasive assessment of language lateralization by transcranial near infrared optical topography and functional MRI. Hum Brain Mapp 16:183–189.

Koizumi H, Yamamoto T, Maki A, Yamashita Y, Sato H, Kawaguchi H, Ichikawa N. 2003. Optical topography: practical problems and new applications. Appl Opt 42:3054–3062.

Kotilahti K, Nissila I, Huotilainen M, Makela R, Gavrielides N, Noponen T, Bjorkman P, et al. 2005. Bilateral hemodynamic responses to auditory stimulation in newborn infants. Neuroreport 16:1373–1377.

Kusaka T, Kawada K, Okubo K, Nagano K, Namba M, Okada H, Imai T, et al. 2004. Noninvasive optical imaging in the visual cortex in young infants. Hum Brain Mapp 22:122–132.

Liu H, Chance B, Hielscher AH, Jacques SL, Tittel FK. 1995. Influence of blood vessels on the measurement of hemoglobin oxygenation as determined by time-resolved reflectance spectroscopy. Med Phys 22:1209–1217.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. 2001. Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150–157.

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.

Meek JH, Elwell CE, McCormick DC, Edwards AD, Townsend JP, Stewart AL, Wyatt JS. 1999. Abnormal cerebral haemodynamics in perinatally asphyxiated neonates related to outcome. Arch Dis Child Fetal Neonatal Ed 81:F110–F115.

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.

Mehler J, Jusczyk P, Lambertz G, Halsted N, Bertoncini J, Amiel-Tison C. 1988. A precursor of language acquisition in young infants. Cognition 29:143–178.

Minagawa-Kawai Y, Matsuoka S, Naoi N, Kojima S. 2005a. Neural correlates of mother-infant attachment and limitations and potential of NIRS measurement. In: Proceedings of the Annual Convention Japan Psychological Association. p S-15.

Minagawa-Kawai Y, Mori K. 2004. Near-infrared spectroscopic measurement of human language function. Jpn J Clin Psychiatr 33:741–748.

Minagawa-Kawai Y, Mori K, Furuya I, Hayashi R, Sato Y. 2002. Assessing cerebral representations of short and long vowel categories by NIRS. Neuroreport 13:581–584.

Minagawa-Kawai Y, Mori K, Naoi N, Kojima S. 2007. Neural attunement processes in infants during the acquisition of a language-specific phonemic contrast. J Neurosci 27:315–321.

Minagawa-Kawai Y, Mori K, Sato Y. 2005b. Different brain strategies underlie the categorical perception of foreign and native phonemes. J Cogn Neurosci 17:1376–1385.

Minagawa-Kawai Y, Nishijima N, Naoi N, Kojima S. 2005c. Developmental changes of cerebral responses to native and non-native phonemic contrast. Neurosci Res 52 (S1):P3–P275.

Molfese DL, Hess TM. 1978. Hemispheric specialization for VOT perception in the preschool child. J Exp Child Psychol 26:71–84.

Mori K, Sato Y, Ozawa E, Imaizumi S. 2004. Cerebral lateralization of speech processing in adult and child stutterers: Near infrared spectroscopy and MEG study. In: Packman A, Meltzer A, Peters HFM, editors. Theory, Research and Therapy in Fluency Disorders (Proceeding of the 4th World Congress on Fluency Disorders). The Netherlands: Nijmegen University Press. pp 323–330.

Näätänen R. 2003. Mismatch negativity: Clinical research and possible applications. Intl J Psychophys 48:179–188.

Näätänen R, Lehtokoski A, Lennes M, Cheour M, Huotilainen M, Iivonen A, Vainio M, et al. 1997. Language-specific phoneme representations revealed by electric and magnetic brain responses. Nature 85:432–434.

Nazzi T, Juscyzk PW, Johnson EK. 2000. Language discrimination by English-learning 5-month-olds: Effects of rhythm and familiality. J Mem Lang 43:1–19.

Nicklin SE, Hassan IA, Wickramasinghe YA, Spencer SA. 2003. The light still shines, but not that brightly? The current status of perinatal near infrared spectroscopy. Arch Dis Child Fetal Neonatal Ed 88:F263–F268.

Nissilä I, Hebden JC, Jennions D, Heino J, Schweiger M, Kotilahti K, Noponen T, et al. 2006. A comparison between a time-domain and a frequency-domain system for optical tomography. J Biomed Opt 11:064015.

Noguchi Y, Takeuchi T, Sakai KL. 2002. Lateralized activation in the inferior frontal cortex during syntactic processing: An event-related optical topography study. Hum Brain Mapp 17:89–99.

Novak G, Kurtzberg PD, Kreuzer JA, Vaughan HG Jr. 1989. Cortical responses to speech sounds and their formants in normal infants: Maturational sequence and spatiotemporal analysis. Clin Electroencephalogr Clin Neurophysiol 73:295–305.

Obrig H, Villringer A. 2003. Beyond the visible-imaging the human brain with light. J Cereb Blood Flow Metab 23:1–18.

Okada E, Delpy DT. 2003. Near-infrared light propagation in an adult head model II. Effect of superficial tissue thickness on the sensitivity of the near-infrared spectroscopy signal. Appl Opt 42:2915–2922.

Okamoto M, Dan H, Sakamoto K, Takeo K, Shimizu K, Kohno S, Oda I, et al. 2004. Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping. Neuroimage 21:99–111.

Otsuka Y, Nakato E, Kanazawa S, Yamaguchi MK, Watanabe S, Kakigi R. 2007. Neural activation to upright and inverted faces in infants measured by near infrared spectroscopy. Neuroimage 34:399–406.

Peebles DM, Wyatt JS. 1993. Near infrared spectroscopy and intrapartum fetal monitoring. Contemp Rev Obstet Gynaecol 5:124–129.

Peña M, Maki A, Kovacic D, Dehaene-Lambertz G, Koizumi H, Bouquet F, Mehler J. 2003. Sounds and silence: An optical topography study of language recognition at birth. Proc Natl Acad Sci USA 100:11702–11705.

Perkins JM, Baran JA, Gandour J. 1996. Hemispheric specialization in processing intonation contours. Aphasiology 10:343–362.

Poeppel, D. 2003. The analysis of speech in different temporal integration windows: Cerebral lateralization as asymmetric sampling in time. Speech Commun 41: 245–255.

Quaresima V, Ferrari M, Torricelli A, Spinelli L, Pifferi A, Cubeddu R. 2005. Bilateral prefrontal cortex oxygenation responses to a verbal fluency task: A multichannel time-resolved near-infrared topography study. J Biomed Opt 10:11012.

Ramus F, Hauser MD, Miller C, Morris D, Mehler J. 2000. Language discrimination by human newborns and by cotton-top tamarin monkeys. Science 288:349–351.

Ray B, Roy TS, Wadhwa S, Roy KK. 2005. Development of the human fetal cochlear nerve: A morphometric study. Hear Res 202:74–86.

Rector DM, Poe GR, Kristensen MP, Harper RM. 1997. Light scattering changes follow evoked potentials from hippocampal Schaeffer collateral stimulation. J Neurophysiol 78:1707–1713.

Reynolds EO, Wyatt JS, Azzopardi D, Delpy DT, Cady EB, Cope M, Wray S. 1988. New non-invasive methods for assessing brain oxygenation and haemodynamics. Br Med Bull 44:1052–1075.

Rinne T, Alho K, Alku P, Holi M, Sinkkonen J, Virtanen J, Bertrand O, et al. 1999. Analysis of speech sounds is left hemisphere predominant at 100–150 ms after sound onset. Neuroreport 10:1113–1117.

Sable JJ, Low KA, Whalen CJ, Maclin EL, Fabiani M, Gratton G. 2007. Optical imaging of temporal integration in human auditory cortex. Eur J Neurosci 25:298–306.

Saito Y, Aoyama S, Kondo T, Fukumoto R, Konishi N, Nakamura K, Kobayashi M, et al. 2007a. Frontal cerebral blood flow change associated with infant-directed speech. Arch Dis Child Fetal Neonatal Ed 92:F113–F116.

Saito Y, Kondo T, Aoyama S, Fukumoto R, Konishi N, Nakamura K, Kobayashi M, et al. 2007b. The function of the frontal lobe in neonates for response to a prosodic voice. Early Hum Dev 83:225–230.

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

Sakatani K, Xie Y, Lichty W, Li S, Zuo H. 1998. Language-activated cerebral blood oxygenation and hemodynamic changes of the left prefrontal cortex in poststroke aphasic patients: A near-infrared spectroscopy study. Stroke 29:1299–1304.

Sato Y, Mori K, Furuya I, Hayashi R, Minagawa-Kawai Y, Koizumi T. 2003. Developmental changes in cerebral lateralization to spoken language in infants: Measured by near-infrared spectroscopy. Jpn J Logoped Phoniatr 44:165–171.

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

Schroeter ML, Bucheler MM, Muller K, Uludag K, Obrig H, Lohmann G, Tittgemeyer M, et al. 2004. Towards a standard analysis for functional near-infrared imaging. Neuroimage 21:283–290.

Scott S, Johnsrude I. 2003. The neuroanatomical and functional organization of speech perception. Trends Neurosci 26:100–107.

Seiyama A, Seki J, Tanabe HC, Sase I, Takatsuki A, Miyauchi S, Eda H, et al. 2004. Circulatory basis of fMRI signals: relationship between changes in the hemodynamic parameters and BOLD signal intensity. Neuroimage 21:1204–1214.

Shimada S, Hiraki K. 2006. Infant's brain responses to live and televised action. Neuroimage 32:930–939.

Shtyrov Y, Pihko E, Pulvermuller F. 2005. Determinants of dominance: Is language laterality explained by physical or linguistic features of speech? NeuroImage 27:37–47.

Simos PG, Molfese DL, Brenden RA. 1997. Behavioral and electrophysiological indices of voicing-cue discrimination: Laterality patterns and development. Brain Lang 57:122–150.

Slater R, Cantarella A, Gallella S, Worley A, Boyd S, Meek J, Fitzgerald M. 2006. Cortical pain responses in human infants. J Neurosci 26:3662–3666.

Spelke ES, Breinlinger K, Macomber J, Jacobson K. 1992. Origins of knowledge. Psychol Rev 99:605–632.

Spelke ES, Kinzler KD. 2007. Core knowledge. Dev Sci 10:89–96.

Steinbrink J, Kohl M, Obrig H, Curio G, Syre F, Thomas F, Wabnitz H, et al. 2001. Somatosensory evoked fast optical intensity changes detected non-invasively in the adult human head. Neurosci Lett 291:105–108.

Strangman G, Culver JP, Thompson JH, Boas DA. 2002. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. Neuroimage 17:719–731.

Taga G, Asakawa K. 2007. Selectivity and localization of cortical response to auditory and visual stimulation in awake infants aged 2 to 4 months. Neuroimage 36:1246–1252.

Taga G, Asakawa K, Maki A, Konishi Y, Koizumi H. 2003. Brain imaging in awake infants by near-infrared optical topography. Proc Natl Acad Sci USA 100:10722–10727.

Tervaniemi M, Hugdahl K. 2003. Lateralization of auditory-cortex functions. Brain Res Rev 43:231–246.

Tervaniemi M, Medvedev SV, Alho K, Pakhomov SV, Roudas MS, Van Zuijen TL, Näätänen R. 2000. Lateralized automatic auditory processing of phonetic versus musical information: A PET study. Hum Brain Mapp 10:74–79.

Toro JM, Trobalon JB, Sebastian-Galles N. 2003. The use of prosodic cues in language discrimination tasks by rats. Anim Cogn 6:131–136.

Tsuzuki D, Jurcak V, Singh AK, Okamoto M, Watanabe E, Dan I. 2007. Virtual spatial registration of stand-alone fNIRS data to MNI space. Neuroimage 34:1506–1518.

van der Zee P, Cope M, Arridge SR, Essenpreis M, Potter LA, Edwards AD, Wyatt JS, et al. 1992. Experimentally measured optical pathlengths for the adult head, calf and forearm and the head of the newborn infant as a function of inter optode spacing. Adv Exp Med Biol 316:143–153.

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

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.

Wartenburger I, Steinbrink J, Telkemeyer S, Friedrich M, Friederici AD, Obrig H. 2007. The processing of prosody: Evidence of interhemispheric specialization at the age of four. Neuroimage 34:416–425.

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

Watanabe E, Yamashita Y, Maki A, Ito Y, Koizumi H. 1996. Non-invasive functional mapping with multi-channel near infra-red spectroscopic topography in humans. Neurosci Lett 205:41–44.

Watson NF, Dodrill C, Farrell D, Holmes MD, Miller JW. 2004. Determination of language dominance with near-infrared spectroscopy: comparison with the intracarotid amobarbital procedure. Seizure 13:399–402.

Werker JF, Tees RC. 1984. Cross-language speech perception: Evidence for perceptual reorganization during the first year of life. Infant Behav Dev 7:49–63.

Wilcox T, Bortfeld H, Woods R, Wruck E, Boas DA. 2005. Using near-infrared spectroscopy to assess neural activation during object processing in infants. J Biomed Opt 10:11010.

Yakovlev PA, Lecours IR. 1967. The myelogenetic cycles of regional maturation of the brain. In: Minkowski A, editor. Regional Development of the Brain in Early Life. Oxford: Blackwell. pp. 3–70.

Yamamoto T, Kato T. 2002. Paradoxical correlation between signal in functional magnetic resonance imaging and deoxygenated haemoglobin content in capillaries: A new theoretical explanation. Phys Med Biol 47:1121–1141.

Yamamoto T, Maki A, Kadoya T, Tanikawa Y, Yamad Y, Okada E, Koizumi H. 2002. Arranging optical fibres for the spatial resolution improvement of topographical images. Phys Med Biol 47:3429–3440.

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

Zevin JD, McCandliss BD. 2005. Dishabituation of the BOLD response to speech sounds. Behav Brain Funct 1:4.