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HIGHER-ORDER BRAIN FUNCTION ANALYSIS BY TRANS-CRANIAL DYNAMIC NEAR-INFRARED SPECTROSCOPY IMAGING

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ABSTRACT

Near-infrared spectroscopy is discussed from the viewpoint of human higher-order brain function analysis. Pioneering work in this field is reviewed; then we describe our concept of noninvasive trans-cranial dynamic optical topography and its instrumentation. Also, the validity of its functional images is assessed from both physical and physiological viewpoints. After confirming the validity of this method, we have applied it to a wide variety of fields such as clinical medicine, cognitive science, and linguistics in collaboration with researchers at several other institutes. Further application possibilities and the future of trans-cranial dynamic optical topography are also discussed. © *1999 Society of Photo-Optical Instrumentation Engineers.* [S1083-3668(99)00804-7]

Keywords optical topography; human brain mapping; brain function; NIRS; fMRI.

1 INTRODUCTION

Throughout the history of analytical science, photons have been frequently used as information carriers to analyze objective systems.[1] A photon is a neutral and weightless elementary particle traveling at the speed of light that can often pass deep into the objective system to be analyzed. As an information carrier, photons (visible light) were used for long-distance telecommunication in the Roman empire to enable rapid communication throughout the empire's far-reaching territory. A more sophisticated telecommunication system using light, based upon the heliograph, was developed by Napoleon who understood the importance of timely information. However, these early telecommunication systems suffered from light scattering caused by dust in the air, rain, or fog. This light scattering, photon migration in other words, remains the essential problem in spectrophotometry since photons are frequently used as information carriers to probe into an objective system such as samples with heavy matrices and human tissues.

Newton studied the nature of color by using the spectrum of light resolved by a prism. Newton's successors vigorously debated the nature of light with Goethe, who wrote *The Theory of Color* from the viewpoint of psychology. The debate between physics and psychology that continues to this day had thus begin. Later, Bunsen and Kilchhoff discovered the atomic-line spectrum, and Zeeman discovered the Zeeman effect that proved the existence of the electron. He shared the second Nobel Prize in physics with H. A. Lorentz in 1902, and atomic spectroscopy became one of the main tools that propelled quantum physics throughout this century.

In the 1930s, however, more practical trials were made by physicist Glen Millikan, the son of Robert Millikan, who measured the unit charge of a single electron by inventing the oil-drop method and received the 1923 Nobel Prize in physics. G. Millikan was the first to apply optical spectroscopy to the biomedical field through his invention of dual-wavelength spectroscopy,[2–4] although this is not widely recognized. Since the most serious problem in the spectroscopic analysis of practical samples, including human tissues, is heavy light scattering—photon migrations—dual-wavelength spectroscopy was an essential technique for metabolite analysis in humans.

This dual-wavelength concept was also applied to atomic absorption spectrophotometry to correct scattering.[5] New concepts enabling further light-scattering correction and discrimination of atomic absorption from molecular absorption resulted from the introduction of magnetic quantum numbers of Koizumi (one of the authors) and Hadeishi in the 1970s.[6–9] Polarized Zeeman-effect atomic absorption spectroscopy, which is widely used in trace-element analysis, enabled correction for light scattering and molecular absorption at exactly the same wavelength as the atomic absorption line,[6] something that was not possible with the dual-wavelength method. Although selectivity based upon the magnetic quantum number has been

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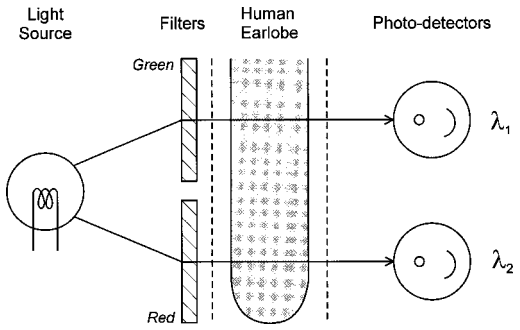

Fig. 1 Dual-wavelength analysis of oxy-Hb and deoxy-Hb *in vivo* by G. Millikan.

widely utilized in magnetic resonance imaging and spectroscopy, it has not yet been introduced into noninvasive optical spectroscopy in medicine.

To correct light scattering in tissues, Delpy and Chance developed time-resolved spectroscopy independently in 1988.[10,11] In 1990 Chance developed phase-modulation spectroscopy,[12] which is mathematically equivalent. Chance is a great pioneer in this field, and has developed significant new spectroscopy techniques, that he applied to physiological fields such as enzyme kinetics throughout the 1950s and 1960s.[13,14]

2 HISTORY OF THE NONINVASIVE SPECTROSCOPIC ANALYSIS OF HUMAN SUBJECTS

2.1 THE ORIGIN OF DUAL-WAVELENGTH SPECTROSCOPY

From a methodological viewpoint, there are two kinds of advances typically achieved in science and technology. The most common type is a linear, or incremental, improvement in, for example, performance such as sensitivity, reproducibility, or temporal and spatial resolution. The other is a nonlinear improvement that gives rise to a new field of study. The invention of dual-wavelength spectrophotometry by Glen Millikan was the latter type, despite its simplicity, since it enabled various practical applications which were impossible with previously existing methods.[2–4]

Figure 1 shows the concept of Millikan's original instrument developed in 1942.[4] In an earlier paper published in 1933,[2] he used the purple line at 436 nm, the green line at 546 nm and the green doublet lines at 577 and 579 nm from a mercury spectral line source to spectroscopically probe biological systems. Both oxy-hemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) have absorption through the UV, visible, and near-infrared regions as shown in Figure 2.[15] There are many isobestic points around the peak of deoxy-Hb at 555 nm (13.04) and around the peaks of oxy-Hb at 542 nm (14.37) and 577 nm (15.37): at 506.5 nm (4.81), 522 nm (6.42), 548.5 nm (12.46), 569 nm (11.27) and 586 nm (7.23) (the numbers in parentheses are the extinction coefficients). Millikan first used the purple line at 436 nm mainly for deoxy-Hb and the green and yellow lines at 546, 577, and 579 nm for total-Hb in his paper on the photoelectric colorimeter in 1933. He further refined this method by using red light between 620 and 680 nm mainly for deoxy-Hb and green/yellow light around the isobestic points for total-Hb by using a continuum light source and filters as described in his paper on the oximeter in 1942. He also applied his technique to the *in vivo* measurement of oxy-myoglobin (oxy-Mb) and deoxy-myoglobin (deoxy-Mb) in muscles.[3]

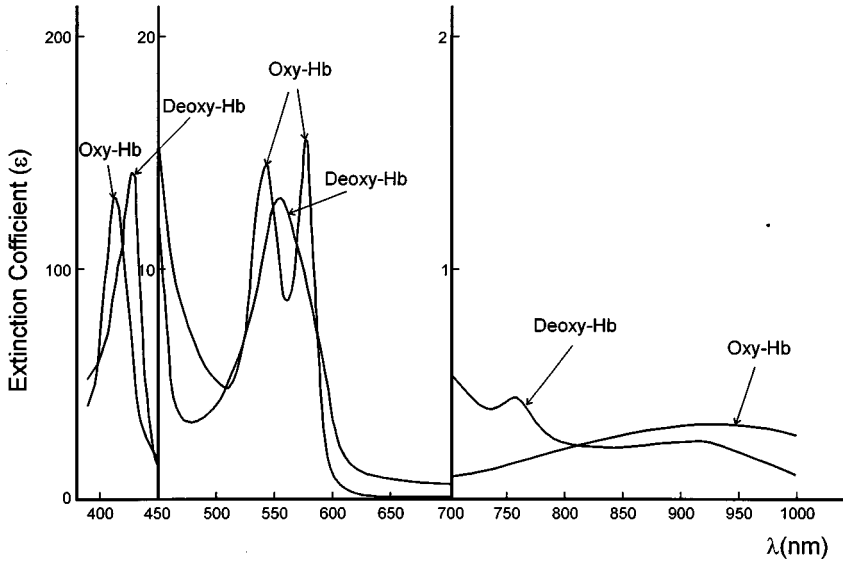

Fig. 2 Absorption spectra of oxy-Hb and deoxy-Hb.

2.2 TRANS-CRANIAL HUMAN BRAIN FUNCTIONAL IMAGING

Since Millikan developed his noninvasive spectroscopic oximeter for human study in 1942, many pioneers, including Chance, have worked in this field. The usable wavelength region was expanded to near infrared, and new methods were developed for light-scattering correction by using time-resolved spectroscopy and phase-modulation spectroscopy.

For human analysis, Jobsis et al. tried to apply near-infrared spectroscopy (NIRS) to brain-oxygenation monitoring.[16] In 1993, four different research groups led by Kato, Hoshi, Villringer and Chance independently reported the possibility of measuring brain function with a NIRS oxygen monitor.[17–20]

In 1995 we reported the first NIRS imaging of human higher-order-brain-function, which we called optical topography.[21] This was a nonlinear advance in methodology from single point analysis to imaging that had much in common with the advance from analytical nuclear magnetic resonance (NMR) to magnetic resonance imaging (MRI). (The first presentation of the images we obtained through optical topography was made in 1994.[22] Chance also reported phased-array optical imaging of phantoms in 1996.[23])

In the next section, we describe the concept of optical topography and explain what made it possible to obtain NIRS functional images.[21,22,24–32]

3 CONCEPT OF NONINVASIVE OPTICAL TOPOGRAPHY

3.1 FUNDAMENTAL PRINCIPLE

In 1980, Koizumi described the concept of optical computed tomography (optical CT) as ''a diagnostic imaging technique to reconstruct spectroscopic data from transmitted light through an objective system to be analyzed.'' [33] Although the tomographic image of a rat brain could be obtained by using time-resolved spectroscopy with a picosecond laser pulse in 1991[34–36] (Benaron also reported an optical CT image in 1993[37]), we found experimentally that its practical application to a human adult brain was extremely difficult within a reasonable imaging time that assured safety. This was because the number of photons that could be transmitted through a human brain was extremely small. Thus, we conceived the concept of optical topography as ''a noninvasive trans-cranial functional imaging technique of the human brain-cortex activity by spectroscopic mapping of internal reflection.'' [38,39]

Noninvasive optical topography is possible largely due to the anatomical and physiological structure of the surface layer of the human brain. The cerebral cortex, which is related to higher-order brain functions, is situated just beneath the skull. In cooperation with Dr. Eiju Watanabe, a neurosurgeon at the Tokyo Metropolitan Police Hospital, we experimentally confirmed that transmittance through the adult human skull was possible over the wavelength range from 400 to 1000 nm.[39] We found that the quasiparallel transmission of light through a human adult skull is on the order of 0.1%. We measured this transmission with an F5.7-aperture spectrophotometer around the isobestic point of oxy-Hb and deoxy-Hb at 815 nm. Figure 3 shows experimentally observed light transmission through an adult human skull. A white-light beam within a diameter of 10 mm from a tungsten lamp was irradiated from behind the skull. We could see the 10 mm core of the light beam followed by scattered and diffused light with a diameter of about 30 mm. The dura, the arachnoid membranes, and the cerebral spinal fluid (CSF) are comparatively transparent at this wavelength. The cerebral cortex—the 2.5-mm-thick surface layer of the cerebrum—contains dense neurons and blood vessels. The structural unit of the arteries and veins coincides with the neuronal structural unit, i.e., the neural column. The regional blood flow is closely associated with neuronal activities, and increases by 10%–60% during activation. The regional blood volume and oxygenation state are also associated with the regional blood-flow change. The change in the oxy-Hb and deoxy-Hb can be measured by a dual-wavelength NIRS technique. (If the light-path length can be determined, the absolute concentration can be determined.) The cortex and substance of the brain are called gray and white matter, respectively, based on their optical characteristics. The layer of gray matter absorbs more light than the white matter underneath due to its high density of blood vessels and neurons. However, the white matter, which contains dense neuron fibers, seems to scatter more incident light. Furthermore, transparent cerebral spinal fluid is likely to work as a light guide in a sulcus. This property represents further potential for the application of optical topography.

Figure 4 shows the optical-topography interface to the human head in the case of a 12-channel instrument. This interface consists of eight flexible optical fibers whose tip surfaces lightly touch the scalp between hairs. Therefore, the measurement coordinates can be fixed on the subject's head, unlike with positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magneto-encephalography (MEG). This makes it possible for a subject to move during the examination, and we are now preparing to study brain functions while the subject is walking.

3.2 THE SIMULTANEOUS POSITION ENCODING METHOD

Figure 5 shows the simultaneous position encoding method developed for our trans-cranial optical topography. The simultaneous position encoding is

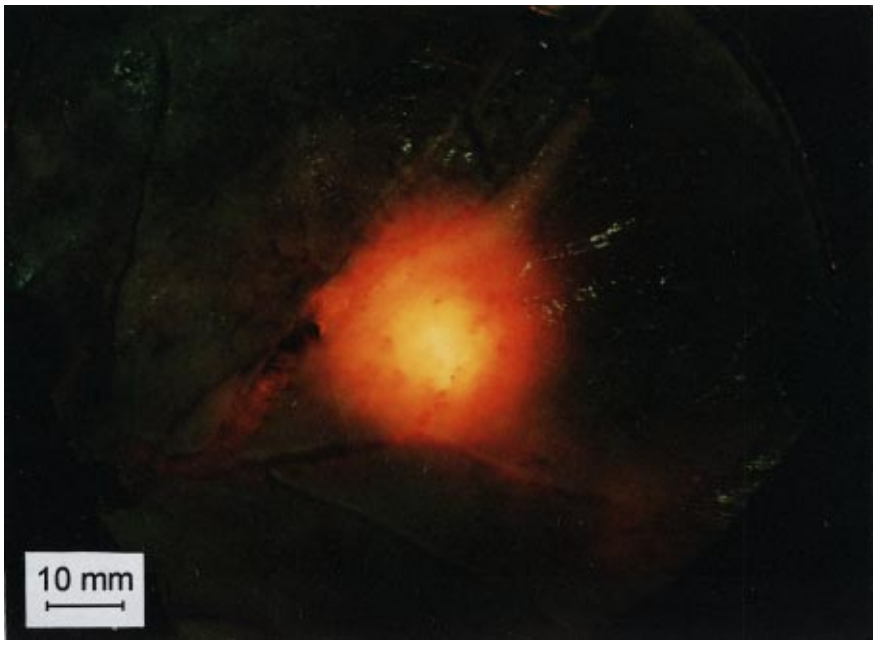

Fig. 3 Experimental observation of light transmission through an adult human skull. A white-light beam with a diameter of 10 mm from a tungsten lamp was irradiated from behind the skull.

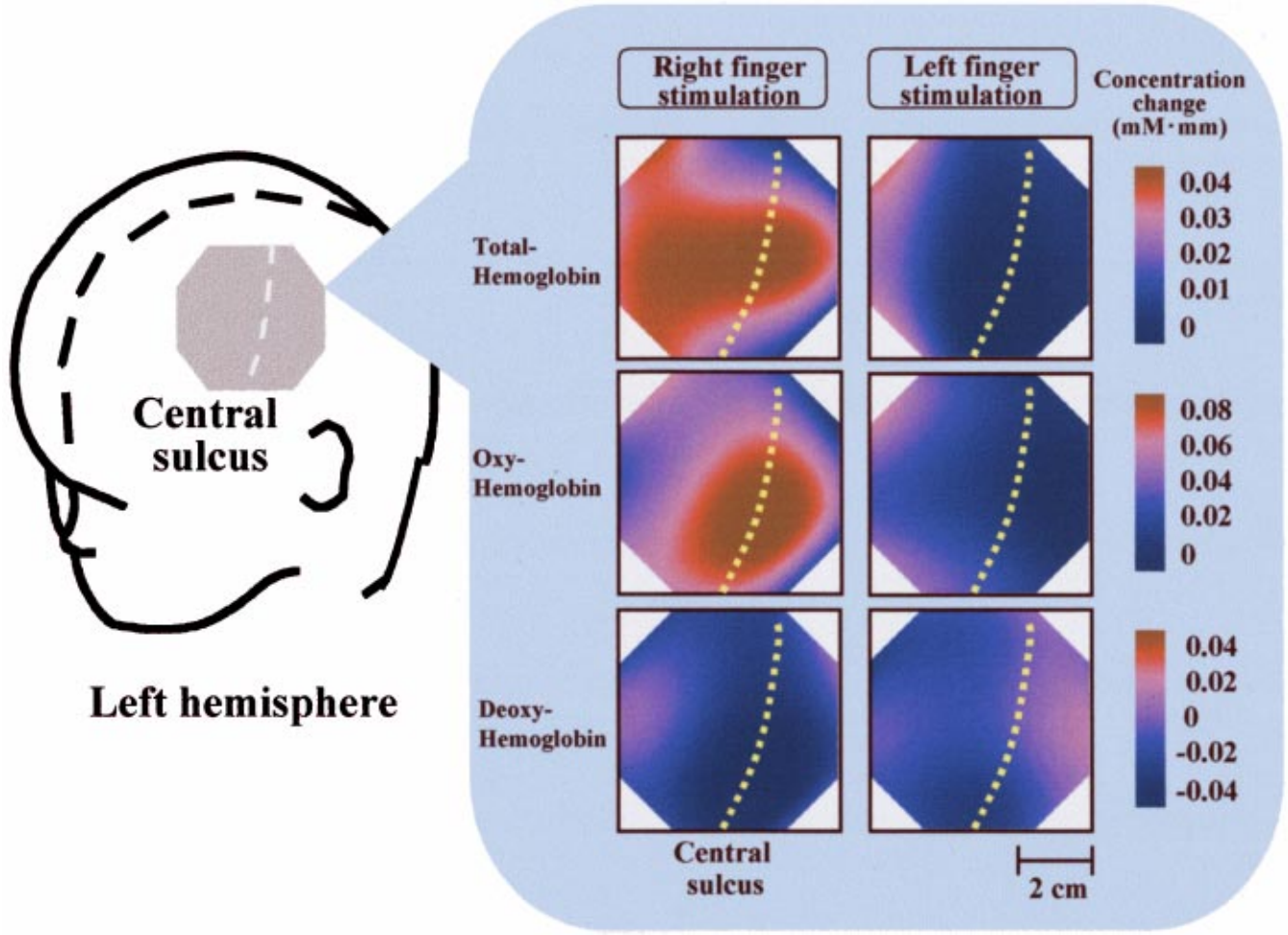

Fig. 8 Functional imaging by optical topography. The motor and somatosensory areas in the left hemisphere of the brain were observed during a finger-tapping task. Clear activation was observed for right-finger tapping (the contra-lateral case), but not for left-finger tapping (the ipso-lateral case). This result agrees with those obtained by fMRI. In the contra-lateral case, an increase of oxy-Hb and a slight decrease of deoxy-Hb were observed during the task.

Fig. 4 The optical topography interface (a 12-channel instrument).

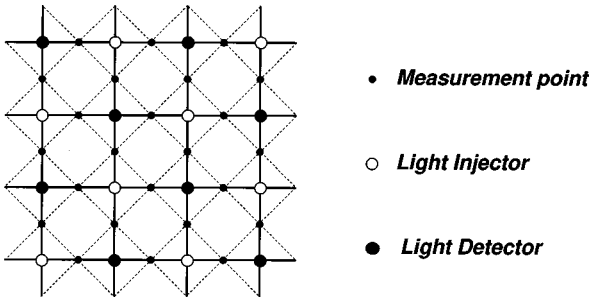

Fig. 6 A typical position arrangement for light injectors and detectors to obtain brain function topograms.

the key to effective imaging, and we have named this method the frequency encoding method. This is analogous to x-ray CT and MRI, where back projection and Fourier zeugmatography methods are used, respectively. In optical topography, each channel has dual-wavelength optics to separately determine the changes in oxy-Hb and deoxy-Hb concentrations around their isobestic points under the condition where scattering is almost independent of wavelength. (To confirm the validity of this condition, we used a multiwavelength (nine wavelengths) instrument developed to evaluate the wavelength dependence of light scattering, water absorption and cytochrome oxidase absorption.) Each channel consists of a pair of semiconductor lasers with different wavelengths to enable dual-wavelength spectroscopy. A pair of dual-wavelength light signals at 780 and 840 nm, whose intensities are modulated at different frequencies between 1 and 10 kHz, are combined by a beam coupler, then led to the surface of the scalp by a flexible optical fiber with a diameter of 1 mm. Part of the incident light penetrates the scalp and skull and is reflected from brain tissues including the cerebral cortex. Any change in the light extinction is mainly due to changes in the oxy-Hb and/or the deoxy-Hb concentration during the activation of a functional area linked to a neuronal activity. The reflected light is detected on the surface of the scalp by an optical fiber 30 mm from the incident position, then is picked up by an avalanche photodiode. The dual-wavelength signals are decoded by a lock-in amplifier. We have used various numbers of channels up to 72 depending upon the measurement configuration. The temporal resolution of the signal is 50 ms and each functional image can be observed every 0.5 s quasicontinuously.

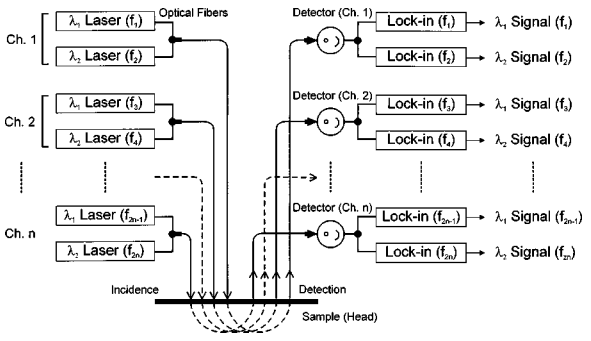

Fig. 5 Position encoding in optical topography.

A typical position arrangement for light injectors and detectors to obtain brain function topograms is shown in Figure 6. Strictly speaking, we should map this pattern in the same way the earth is drawn on a two-dimensional map because the round shape of the superficial part of the brain will be developed on a two-dimensional plane. The effect of the sulci is not taken into account here. The positions of the injectors and detectors form a mesh as shown in Figure 6. The cortical information can be obtained at a position underneath the central point between an injector and a detector. Therefore, the measurement positions within the brain also form a mesh, whose size is 1/2 of the mesh size of the injectors and detectors, and the two meshes form a 45° angle with each other. This configuration is the simplest of the 17 patterns of two-dimensional groups in space group theory. Spatial resolution assessed by point spread function was about 20–25 mm without applying any sophisticated reconstruction technique when the distances between injectors and detectors are 30 mm by the configuration in Figure 6. The spatial resolution may be improved by future developments.

A NIRS functional image cannot be reconstructed by simply positioning a number of commercially available optodes (each optode consisting of a light injector and a light detector) on the surface of the head because the direct cross talk of light between the optodes is a common problem. This would be the case even if the optical fibers were allocated using the configuration shown in Figure 6. In this configuration, a detector placed at the central position among the light injectors is surrounded by at least four injectors. Inevitably, the light detectors will receive light with the same intensity from all the surrounding light injectors if the reflection is homogeneous. This cross talk makes it impossible to obtain spatial brain information. Thus, a method to distin-

guish the light from each injector is essential in NIRS imaging. Frequency modulation allows the unique identification of each light source which encodes spatial information.

3.3 SPECTROSCOPIC MEASUREMENT

Homogeneous absorption is exponentially related to the integration along the light path. This is explicit mathematically, and in optics this relationship has been called the Lambert–Beer law since it was found empirically. If we assume a linear relationship for other light extinction sources, we can obtain the following relationship concerning an individual constituent:

$$A = \log(I_0 / I) = e \cdot C \cdot L + S,$$

where the absorbance A equals $\log(I_0 / I)$ (I_0 / I is the transmittance), e is a specific extinction coefficient, C is the concentration, L is the light path length, and S is the scattering coefficient. Different scattering samples mean a different L for the distance between the source and the detector. Therefore, unless the photon path length can be determined by time-resolved spectroscopy or some other method, we can only know the change in the concentration of the constituent. In the case of multiconstituent samples with different absorption spectra, the number of different wavelengths must equal the number of constituents to enable solution of the simultaneous equations. In human studies we have to apply a fitting method under several assumptions because we seldom have exact knowledge concerning all the constituents. We should be very careful in making these assumptions, though, because a poor assumption can lead to an incorrect result, even, for example, the wrong direction of signal change.

3.4 ELIMINATING INTERFERENCE FROM HAIR

We also faced a serious problem due to the severe effect hair had on the probing light intensity. Even one hair caused a serious artifact in an image. Although the conventional optodes did not work properly when they encountered hair, we found that we could place the ends of thin plastic optical fibers (1 mm diameter) in contact with the skin surface between the hairs at their roots. (This is similar to the tips of a comb's teeth touching the surface of our head.) The optical fibers were fixed in a helmet-like platform made of thermo-plastic material. The hair roots of black hair in the skin absorbed the scattered light resulting in a 20%–50% decrease in the probing light intensity. However, we compensated for this light loss by improving the optics. We also found that the decrease in light intensity was smaller when the subject had lighter colored hair.

3.5 LIGHT PENETRATION

The use of optical methods in the study of the brain relies on sufficient light penetration through the skin and skull to the cortical surface. This important issue has been addressed in a number of recent studies. Early on, we have performed experiments with rats,[34–36] cats and baby pigs[40] utilizing transmission-type NIRS imaging with time-resolved spectroscopy which confirm that light can penetrate across the animal head (optical CT). In the case of the pig brain, which is comparable in size to the human infant, it took considerable time for measurement (at least 30 min per image). Delpy's group has done extensive theoretical and experimental studies on the behavior of photons in brain models. This has led to the development of image reconstruction methods, which have been applied to NIRS imaging.[41–43] Computer simulation studies from this group have shown the effect of the CSF layer which suggested to us the problems of transmission type NIRS imaging because the penetration of light can be significantly disturbed by the layer of CSF.[44]

Recently, we developed a new probe for fMRI and optical topography to investigate the penetration of light. We have performed simultaneous observations and compared the results from these techniques. Although, of course, the spatial resolutions were different across modalities, the coincidence of the activation signals was observed. In the case of motor activation during finger tapping, the optical signal yielded a deoxy hemoglobin concentration change which was consistent with the fMRI signal. The depth of the activated area, which was observed by fMRI, was distributed around 13 mm from the surface of the cortex. Therefore, it was proven that sufficient light can penetrate through the region to at least an 8–18 mm depth in the brain. Further results on this comparative study with fMRI and optical topography will be reported soon elsewhere.[45]

3.6 SAFETY ISSUES

Since light absorption can lead to tissue heating, we have studied the safety of NIRS techniques. Slightly invasive experiments were performed on a human subject. From the ethical point of view, the subject was the director of this optical topography project (the first author of this paper). The spatial map as well as the temporal map of subcutaneous tissue heating were obtained around the point where near-infrared laser light was injected. We utilized laser power up to about 10 mW, although 1 mW is sufficient in practice. The study shows very small temperature effects which are well below risk levels. We concluded that the method used in the optical topography system is completely safe and can be applied on a wide range of subjects. Our paper on safety issues will soon appear elsewhere.[46]

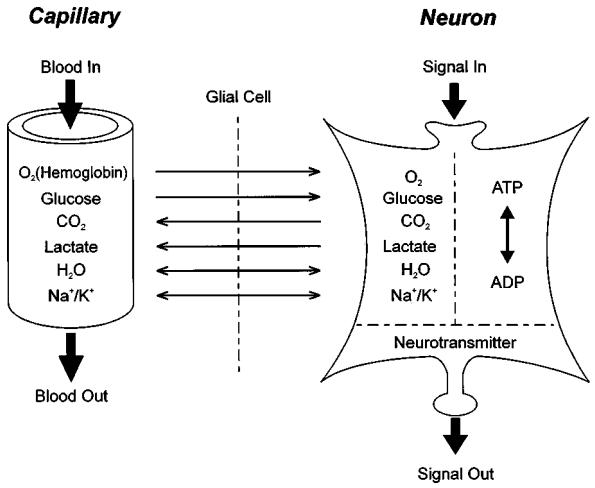

Fig. 7 The linkage between blood flow and neuronal activity through metabolites.

4 PHYSIOLOGY OF SIGNAL GENERATION

It is empirically well known that rCBF (regional cerebral blood flow) and rCBV (regional cerebral blood volume) significantly increase with neuronal activity. The linkage between the blood supply and neuronal activity is shown schematically in Figure 7. The metabolites are exchanged through glial cells. Oxygen transported by oxy-Hb in red blood cells is released through the lipid wall of capillaries, and then diffuses into mitochondria through glial- and neuron-cell membranes. Glucose also diffuses into mitochondria, and reacts with the oxygen to produce the high-energy phosphoric bonds of ATP. The breaking of one of these bonds as ATP changes into ammonium dihydrogen phosphate (ADP) generates the energy necessary for information transfer through the neurons. The information transfer at various points uses the action potential, neurotransmitters, or the postsynaptic potential as a medium. The energy demand during neuronal activity increases the blood flow in practice. However, the precise mechanisms of the linkage between neuronal activity and blood flow increase have not yet been clarified. There are some paradoxes, e.g., only a relatively small uptake of oxygen, while glucose uptake appears to increase about twice as much, in line with blood flow increases during activation.[47] The classic theory of capillary recruitment does not seem to be a dominant factor in the increase of the capillary flow during activation, and it is unknown whether the capillary flow is controlled by neuronal processes.[48] Therefore, we assessed the validity of the NIRS signal very carefully.

5 ASSESSMENT OF THE VALIDITY OF FUNCTIONAL MAPPING

Figure 8 shows optical topograms of the activation of a human motor cortex and somatosensory cortex obtained using the trans-cranial dynamic optical topography system developed in our laboratory. These topograms are very similar to those we obtained in 1994 where we used optical switching and could not obtain real-time images.[21,22] The neuro navigator, which was invented by our collaborator, Watanabe,[49] was used to determine the exact position of the central sulcus since the motor area on the frontal cortex and the somatosensory area on the parietal cortex are situated across the central sulcus.

Since we had studied higher-order human brain functions with echo-planar functional magnetic resonance imaging (EPI-fMRI), we carefully evaluated the validity of signals obtained through optical topography. Although we already knew the precise absorption spectra of deoxy-Hb and oxy-Hb, it was difficult to accurately determine the quantitative contributions to light extinction from various causes such as light scattering and the absorption of cytochrome oxidase since there was little reliable reference information available. Therefore, we assessed the effects of these factors by using a nine-wavelength (636–848 nm) instrument beforehand.

When we studied the motor and somatosensory activation by EPI-fMRI,[50,51] we observed independent activation of the somatosensory area when the subject's fingertips were brushed [Figure 9(a)], and activation of the motor and somato-sensory areas when the Roland's finger-opposition paradigm was used (a finger-tapping task) [Figure 9(b)].[52] We found that the finger-tapping task resulted in wider activation of the cerebral cortex as shown in Figure 9. (The position of the central sulcus is shown by an arrow in these sagittal MRI images.) We compared the results obtained by optical topography with those obtained by EPI-fMRI, and found that the laterality of the motor and somatosensory areas is the key to evaluating the validity of the signal. In both the contra-lateral and ipsi-lateral cases the EPI-fMRI signal showed a similar laterality. Also, we found that the peaks of optical topography signals appear at about 7 s after short stimulation. This delay was almost the same as that which we observed by EPI-fMRI.[53]

We also developed and applied a method of dual-optode analysis. The dual optodes each have one light injector and two light detectors. The distances between the injector and the detectors are 30 and 7 mm, the longer distance is for the deep signal from cortical areas and the shorter distance is for the shallow signal from the scalp. We found that while the deep signal correlated with stimulation tasks, the shallow signal did not unless the task caused a large emotional change.

From these results, we concluded that trans-cranial dynamic optical topography could be used for reliable measurement of the higher-order brain functions. We finished these studies at the early stage of the development, then started various applications with optical topography.

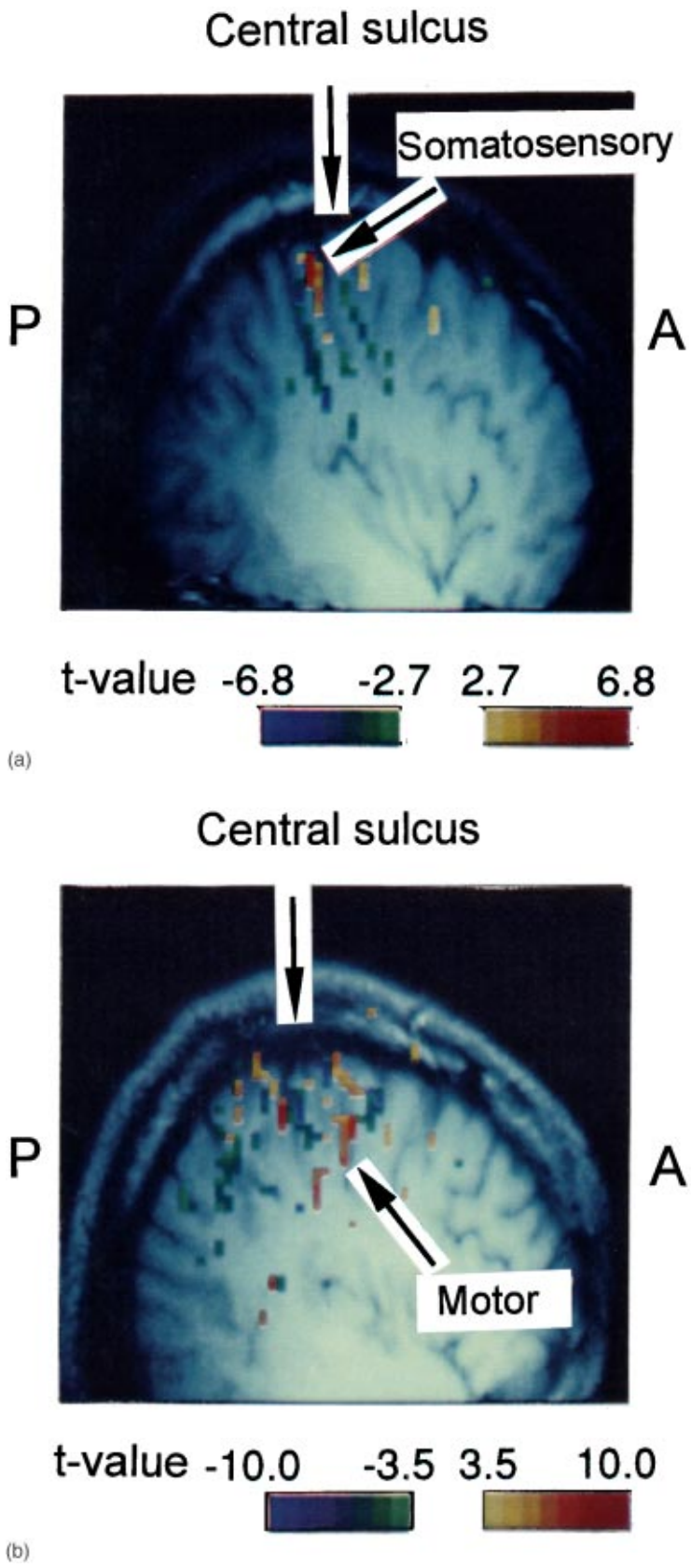

Fig. 9 Activation of the motor and somatosensory areas observed by fMRI. (a) Somatosensory activation during finger brushing. (b) Motor and somatosensory activations during a finger-tapping task.

Table 1 Applications of optical topography and collaborators.

Field	Collaborating group (domestic)
Neurosurgery	Tokyo Metropolitan Police Hospital (Dr. E. Watanabe, Dr. Y. Mayanagi)
Neurology	Tokai University (Dr. M. Haida, Dr. Y. Shinohara)
Sleep science	National Institute for Special Education (Dr. Y. Atsumi) Psychiatry, Tokyo Medical and Dental University (Dr. M. Toru)
Language	Neurology, Tokyo Women's Medical College (Dr. M. Iwata, Dr. H. Yoshizawa)
Development	Institute of Neuropathology (Dr. K. Kogure, Dr. M. Izumiyama)
Cognitive science	Neuro-psychology, The University of Tokyo (Dr. K. Sakai, Dr. J. Kawachi) Tokyo Metropolitan Institute for Neuroscience (Dr. M. Watanabe)
Stress monitoring	Environmental Medicine, Osaka University (Dr. K. Morimoto)

6 APPLICATIONS OF TRANS-CRANIAL DYNAMIC OPTICAL TOPOGRAPHY

Noninvasive dynamic optical topography has a wide variety of applications from basic science to clinical medicine.[54–65] Table 1 shows the fields where we have applied noninvasive dynamic optical topography by working with various collaborators. Several applications, such as the study of the Broca and Wernicke language areas, the assessment of the dominant hemisphere of the brain, epilepsy focus determination, and sleep studies are reported in this special issue of the Journal of Biomedical Optics.

7 FUTURE ASPECTS

We have started studying the development of the infant brain in cooperation with laboratories doing work on developmental cognitive neuroscience. For example, we recently completed an experiment concerning the visual perception of a 14-month-old baby with an extremely abnormal brain.[54,58] We believe that experiments on the cognitive development of neonates and infants, such as the ability to recognize specific sounds and language ability, will have very important implications for learning and education. Furthermore, the observation of early development on a monthly time scale will provide an enormous amount of information about the architecture of the neuronal processing system in the brain.

Trans-cranial optical topography is the only imaging methodology available that allows the study of higher-order brain functions in infants without sedation. In optical topography, the measurement coordinates can be fixed on the brain, unlike with conventional methods for brain-function imaging such as PET, fMRI, and MEG. This represents a breakthrough.

Furthermore, optical topography is promising in principle and in practice as a diagnostic modality because optical spectroscopy will provide high diagnostic specificity through a compact, low cost instrument. The major elements of an optical topography system such as the semiconductor near-infrared lasers, avalanche photodiodes, and frequency-domain filters, are fabricated as a computer chip and are thus very small and light. We even envision compact portable instruments that can be worn by a subject while walking or running. Optical topography would propel various kinds of trans-disciplinary studies in the future.[64–66]

Acknowledgments

We would like to express our sincere thanks to those who have been working with us in applying optical topography in various fields (listed in Table 1). Especially, we thank Dr. Eiju Watanabe (Tokyo Metropolitan Police Hospital) for his continuous collaboration through our optical topography and fMRI studies since 1993. Thanks are also due to Dr. Koichi Koike, Dr. Noriyoshi Ichikawa and Dr. Fumio Kawaguchi (Hitachi Medical Corp.) for their close collaborations. We also express our sincere gratitude to Professor Britton Chance (University of Pennsylvania), Professor David Delpy and Professor Robert Turner (University of London), Professor Arno Villringer (Humboldt University), Professor Amiram Grinvald (The Weizmann Institute of Science), Professor Marco Ferrari (University of L'Aquila), Professor Mamoru Tamura (Hokkaido University), Professor Seiji Ogawa (AT&T, Bell Labs), and Professor Toshinori Kato (University of Minnesota) for sharing their ideas and opinions concerning optical topography with us.

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