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Application of near-infrared spectroscopy in clinical neurology

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Near-infrared spectroscopy (NIRS) monitoring has been used mainly to detect reduced perfusion of the brain during orthostatic stress in order to assess orthostatic intolerance (OI). Many studies have investigated the use of NIRS to reveal the pathophysiology of patients with OI. Research using NIRS in other neurological diseases (e.g., stroke, epilepsy, and migraine) is continuing. NIRS may play an important role in monitoring the regional distribution of the hemodynamic flow in real time and thereby reveal the underlying pathophysiology and facilitate the management of not only patients with OI symptoms but also those with various neurological diseases.

Key words: Orthostatic intolerance; Near-infrared spectroscopy; Clinical neurology

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INTRODUCTION

Many studies have investigated the hemodynamics and functions of the brain in various fields.[1] Several noninvasive methods have been introduced in recent decades for measuring neuronal activity in the brain.[2] Neurophysiological techniques such as electroencephalography, magnetoencephalography, and event-related potentials offer the ability to measure overall changes in the electromagnetic field with an excellent time resolution, but these methods have poor spatial resolution. On the other hand, brain imaging techniques such as positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) have greatly increased our knowledge about neural circuitry. However, PET is highly sensitive to motion artifacts, confines the patient, and involves the injection of radioactive materials. Although fMRI is noninvasive and has excellent spatial resolution, it is expensive, highly sensitive to motion artifacts, and difficult to integrate with other imaging modalities.[3,4]

Near-infrared spectroscopy (NIRS) was introduced as a new neuroimaging modality for

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use in functional brain imaging studies. NIRS utilizes light at specific wavelengths to noninvasively measure changes in the relative levels of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) in the capillary beds during brain activity. HbO provides the strongest correlation between fMRI changes and optical measurements—including for the scalp, skull, and brain tissue—in the average blood-oxygen-level-dependent (BOLD) signal. HbO may provide a superior contrast-to-noise ratio for detecting the physiology associated with BOLD signals.[5] These qualities make NIRS suitable for studying changes in hemodynamics due to cognitive and emotional brain activities under many physical and psychological conditions, as well as in the field of brain–computer interfaces.

Principle of NIRS

NIRS is a noninvasive optical imaging tool for observing changes in the hemodynamics in the prefrontal area that is based on measuring the concentrations of HbO and HbR in the blood. Since Franz Jöbsis first studied the oxygenation of living tissues, NIRS has been extensively applied in imaging studies of brain activation.[6] The physiological activation of neurons leads to an imbalance between oxygen supply and utilization, increasing the concentration of HbO and decreasing the concentration of HbR. Most tissues are relatively transparent to light in the near-infrared range from 700 to 900 nm, and photons interact with tissues via absorption and scattering. This means that near-infrared light is less absorbed and scattered by tissue than is light at other wavelengths.[7] This range of wavelengths is often called an optical window since the light can easily pass through most tissues; however, it is reflected by HbO and HbR, and hence the absorption and scattering of light used for NIRS can provide information relevant to neural activity.[8] This light penetrates several centimeters through tissue and can still be detected (Fig. 1).

The NIRS system consists of a light source and a photodetector. The light source is a device such as a light-emitting diode that irradiates the tissue with near-infrared light, and the nearby photodetector receives photons returning to the surface of the tissue.[7,9] In general, the near-infrared light incident on the scalp reaches a depth of about 3 cm via absorption and scattering, and the unabsorbed near-infrared light reaches the scalp at 3-5 cm from the light source after following a banana-shaped path, as shown in Fig. 2.

The photodetector is therefore typically positioned 3–5 cm from the light source for measuring the unabsorbed near-infrared light. A greater separation between the light source and photodetector will allow the oxygen saturation to be measured in deeper regions. However, the amount of light reaching the photodetector will be reduced, which can make the signal noisy and unstable. It is therefore important to choose the optimal distance between the light source and photodetector for recording the optical signals.[10]

Measuring the change in the intensity of the unabsorbed near-infrared light will allow the change in the

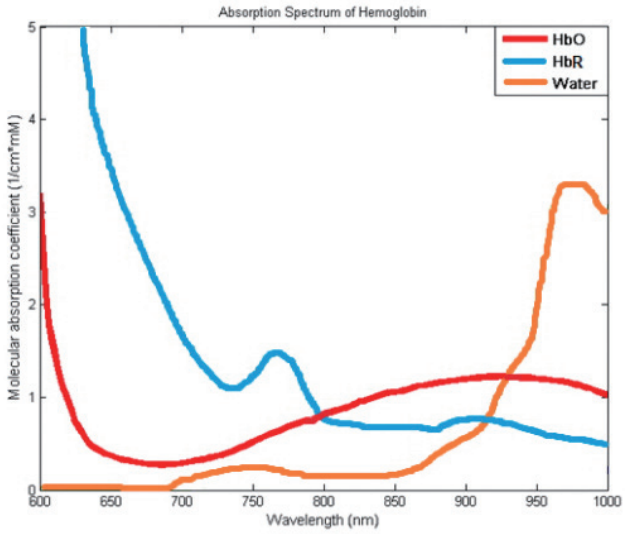

Fig. 1. Absorption spectra of oxygenated hemoglobin (HbO), deoxygenated hemoglobin (HbR), and water.

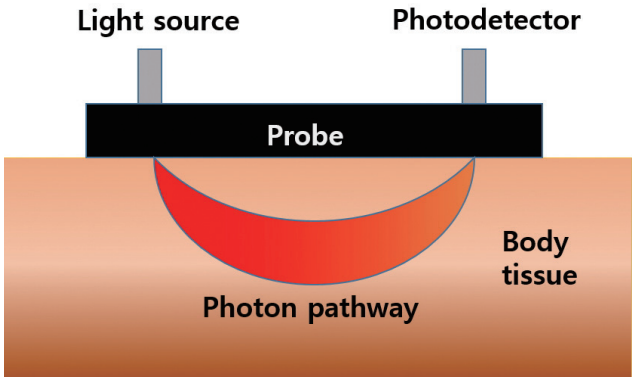

Fig. 2. Near-infrared light paths in the human brain from the light source to the photodetector.

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concentrations of HbO and HbR to be calculated. Because HbO and HbR are the main absorbers of near-infrared light with distinct absorption spectra, the relative changes in their concentrations within a target region can be assessed by measuring the absorption of light at two wavelengths.[11] The NIRS system displays these data in real time using basic mapping. Positioning light sources and photodetectors with various separations will allow complex meshes representing two-dimensional spatial information of the frontal lobe to be generated, and there are various ways to present the information obtained by this mapping method.

NIRS is very safe due to the use of near-infrared light, NIRS systems are smaller than other instruments used to measure physiological changes in the brain (making them more portable), and they provide high temporal and spatial resolutions. While these features make NIRS suitable for observing the human body, the poor penetration of light confines NIRS to evaluations of the cerebral cortex and only measuring the oxygen saturation. This limits the ability of NIRS to evaluate neurological diseases that mainly involve electrophysiological changes.

The distance between the light source and photodetector determines the penetration depth, and the sensitivity to gray-matter changes is greatest when the separation is at least 30 mm.[12] Before calculating the NIRS metrics, the data were low-passed filtered using a cutoff frequency of 0.2 Hz, smoothed with a five-point moving-average filter, and then the first calculated HbO, HbR, and total hemoglobin (HbT) signals were normalized as the zero baseline.

Resolving the changes in optical density or the log ratio of the baseline intensity (I_0) and transient changes in intensity I at two wavelengths (760 and 830 nm) enabled accurate measurements of the relative changes in HbO, HbR, and HbT,[13] where HbT was proportional to the blood volume.[14] The relative concentration changes in HbO and HbR can be resolved using the modified Beer-Lambert's Law[7,15]

$$(1)\quad \Delta HbO = \frac{\varepsilon_{HbR}^{\lambda_2} \log\left(\frac{I_0}{I}\right)^{\lambda_1} - \varepsilon_{HbR}^{\lambda_1} \log\left(\frac{I_0}{I}\right)^{\lambda_2}}{L\left(\varepsilon_{HbR}^{\lambda_2}\varepsilon_{HbO}^{\lambda_1} - \varepsilon_{HbR}^{\lambda_1}\varepsilon_{HbO}^{\lambda_2}\right)}$$

$$(2)\quad \Delta HbR = \frac{\varepsilon_{HbO}^{\lambda_1} \log\left(\frac{I_0}{I}\right)^{\lambda_2} - \varepsilon_{HbO}^{\lambda_1} \log\left(\frac{I_0}{I}\right)^{\lambda_1}}{L\left(\varepsilon_{HbR}^{\lambda_2}\varepsilon_{HbO}^{\lambda_1} - \varepsilon_{HbR}^{\lambda_1}\varepsilon_{HbO}^{\lambda_2}\right)}$$

Where ΔHbO and ΔHbR are the changes in HbO and HbR, respectively, from the baseline state L is the optical path vlength, and $\varepsilon_{HbO,\,HbR}^{\lambda_1}$ and $\varepsilon_{HbO,\,HbR}^{\lambda_2}$ are the extinction coefficients for HbO and HbR for the two wavelengths λ_1=760 nm, λ_2=830 nm.[16] A full review of NIRS methodology and the terms above can be found elsewhere.[17] This technique has been used to evaluate several types of brain function, such as motor and visual activation, auditory stimulation, and performing various cognitive tasks.[7]

NIRS interface

The NIRS probe was attached to the forehead area because hair can significantly degrade the signal quality. NIRS electrodes should be attached over a wide area for multichannel mapping, but the area is restricted when applying electrodes to a scalp with hair. In recent years it has become possible to apply multichannel NIRS to evaluate whole-brain cortical functioning in both clinical and research fields.

The use of NIRS electrodes on the forehead has been shown to be appropriate for monitoring changes in cerebral oxygenation in the prefrontal area.[18,19] The experimentalist visually ensured good contact for all light sources and photodetectors before the experiment started. In addition, the NIRS software included a module that identified channels

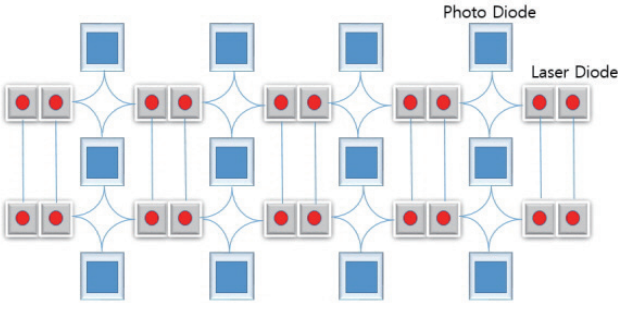

Fig. 3. Arrangement of the photo and laser diodes.

with saturated or low signals based on an empirically tested range of light intensities. This was confirmed by the experimentalist before the tests began. The subjects were instructed to avoid large head motions that could induce motion artifacts in the NIRS signals. The channel matrix is shown in Fig. 3.

Application of NIRS in autonomic nervous system disorders

Orthostatic intolerance (OI) is defined as the inability to tolerate upright posture that is relieved by recumbence, which is due to dysregulation of cardiovascular homeostasis during orthostasis. OI presents with symptoms such as lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue upon standing. The typical signs and symptoms are often related to reduced perfusion of the brain during orthostatic stress for common forms of OI,[20] orthostatic hypotension, neurally mediated syncope, and postural orthostatic tachycardia syndrome.

Fig. 4. A clinical application of NIRS. NIRS, near-infrared spectroscopy.

Autonomic function testing is an important diagnostic tool for assessing the autonomic nervous system in patients with symptoms of OI. Various autonomic function tests have been used to evaluate autonomic dysfunction, but only a few such tests have been validated as clinically quantitative methods for evaluating major autonomic domains including sudomotor, cardiovagal, and adrenergic. However, monitoring the blood pressure and heart rate alone is not enough to detect pathological dysfunction of the autonomic nervous system. In addition, the mechanisms that determine the symptoms induced by autonomic dysfunction are still unclear, and these techniques cannot measure dynamic changes in cerebral blood flow. Moreover, OI symptoms are atypical and difficult to diagnose due to their similarity with those caused by various diseases.[21] The autonomic nervous system may also be influenced by changes in the environment, psychological state, drugs, and other factors.[22]

NIRS has been shown to be a useful tool for evaluating cerebral hemodynamics during orthostatic stress for identifying the common forms of OI. In particular, NIRS has been successfully used to observe cerebral hemodynamics regulated by autonomic function tests (Fig. 4).[23-26]

Many studies have investigated the use of NIRS to reveal the pathophysiology of patients with OI.[27-31] NIRS offers an alternative solution for understanding the effects of a dysregulated autonomic nervous system on the delivery of blood to the brain. In addition, NIRS can potentially be used to monitor patients with inconclusive blood-pressure or heart-rate readings.

The common tests for OI due to autonomic dysfunction include the heart-rate response to deep breathing (HRDB), Valsalva maneuver (VM), and head-up tilt-table test (HUTT).[32] The HRDB is measured twice when evaluating parasympathetic system using the following procedure: 1 minute of baseline recording → first HRDB → 2 minutes of rest → 1 minute of baseline recording → second HRDB. The VM is performed two or three times with adrenergic sympathetic and parasympathetic evaluations using the following procedure: 1 minute of baseline recording → first VM → 3 minutes of rest → second VM → (when a flat-top reaction occurs, the VM can proceed to a position where the upper body is raised by 20° and 40°) → 2 minutes of testing. Finally, the HUTT evaluates adrenergic sympathetic function and pressure reflexes as follows: record the baseline

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value for 5 minutes in the supine condition → 10 minutes of testing in a tilted state or 30 minutes test in a tilted state (for syncope) → 3 minutes recording in a tilted-down state.[33]

Several recent studies have measured hemodynamics changes in the brain during autonomic function tests using NIRS.[34,35] Previous studies that analyzed the NIRS results of patients who had vasovagal syncope during the HUTT found clear changes in cerebral oxygenation as measured by NIRS at an average of 3.3 minutes before syncope.[36] These changes appeared before presyncope symptoms and reductions in blood pressure, heart rate, and arterial blood saturation. That study showed that vasovagal syncope is due to decreased cerebral perfusion and that NIRS is useful for assessing changes in cerebral blood flow.

NIRS was applied to the forehead and above the left paravertebral level at the T10-to-L1 space during the HUTT in order to confirm the difference in hemodynamic perfusion in the brain and kidney in normal and syncope patients. During syncope there was a marked increase in visceral perfusion suggestive of paradoxical visceral vasodilation with decreased cerebral perfusion.[37] One study found a sustained reduction of HbO during the HUTT in patients with severe carotid artery stenosis, which might be associated with orthostatic dizziness.[38] Those authors concluded that NIRS monitoring is suitable for evaluating cerebral autoregulation in patients with severe carotid artery stenosis. Performing a VM has dose-dependent effects on cerebral perfusion and can cause fainting. NIRS measurements on healthy participants during VM showed that changes in the mean arterial pressure induced by the VM resulted in changes in cerebral blood flow and cerebral oxygenation.[27] Another study compared HbO values measured at 30 mm below the scalp and HbO values measured at a depth of 15 mm with the mean arterial pressure during VM, and found that the overall changes in hemodynamics can affect NIRS signals.[28]

These studies are valuable in showing that changes in cerebral hemodynamics occurring during autonomic dysfunction can be measured using NIRS. However, there were limitations in clinical evaluations because of the small number of participating subjects and the focus on NIRS measurements. NIRS is becoming more applicable to clinical practice thanks to technological developments in the utilized equipment, including the provision of larger numbers of measurement channels. Further well-structured clinical studies that employ these advanced NIRS devices are needed.

NIRS could play an important role in monitoring the regional distribution of the hemodynamic flow in real time, which also highlights the potential of this technology in researching the pathophysiology and management of patients with OI symptoms.

Application of NIRS in other neurological disorders

Cerebrovascular disease

Changes in cerebral oxygen saturation associated with cerebrovascular disease have been the most common research field in which NIRS has been applied. NIRS is easy to use in a stroke unit, and real-time NIRS monitoring may be used to manage brain swelling and space-occupying stroke.[39] However, it is not appropriate for assessing disturbances of the cerebral hemodynamic deep below the scalp due to the poor penetration of the near-infrared light used in NIRS.[40] Moreover, there have also been some ethical limitations in applying NIRS because prompt diagnosis and therapeutic approaches are required in patients with suspected acute cerebrovascular disease.

In patients with subacute anterior cerebral artery infarction, NIRS showed that arterial oxygen saturation was more than twofold lower in the affected hemisphere than in the unaffected hemisphere.[41] That study suggested using NIRS as a long-term follow-up tool for assessing cerebral hemodynamics and autoregulation. An assessment of patients with subacute middle cerebral artery stroke and sleep-disordered breathing using nocturnal polysomnography and NIRS revealed that sleep-disordered breathing causes changes in hemodynamics that are larger in the unaffected hemisphere than in the affected hemisphere,[42] which could reflect diminished cerebral metabolism. The autoregulation of cerebral blood flow is presumed to result from changes induced by cerebrovascular disease.

NIRS has also been used in investigations into how to maximize the therapeutic effect during rehabilitation after cerebrovascular disease and how to improve lifestyle habits so as to prevent secondary stroke. The utilization of NIRS in the clinical diagnosis, treatment, and rehabilitation of stroke is expected to increase.[43]

Epilepsy

NIRS has been applied mainly in three areas of epilepsy. NIRS may be helpful for characterizing the seizure type, monitoring subclinical seizures, and recovering from status epilepticus during an induced therapeutic coma, and in localizing the seizure focus in patients undergoing evaluations for temporal lobectomy.

Whether cerebral oxygenation is increased or decreased by convulsive seizures remains controversial. However, a relatively consistent decrease in oxygen saturation was observed the cases of rapidly secondarily generalized seizure.[44] One explanation for this difference between focal and generalized seizures is that blood is more evenly distributed during the latter. A second explanation is that factors such as hypermetabolism associated with generalized seizures may reduce venous oxygen saturation. Thirdly, hypoxia may have caused the decrease in cerebral oxygenation during a generalized seizure. This is consistent with the finding that the oxygenation state as measured using NIRS decreases with increasing mean flow velocity in transcranial Doppler ultrasonography in patients undergoing electroconvulsive therapy for depression.[45]

While not involving a form of epilepsy, a study that used NIRS to monitor the hemodynamics responses in rat brains during transcranial direct current stimulation found that the HbO concentration increased almost linearly during this stimulation.[46] In a study of patients with periodic limb movements during sleep, the cerebral hemodynamics varied among the different sleep stages, and there were also changes in the phase differences between HbO and HbR during the different sleep stages in normal controls.[47] The present study has demonstrated the presence of cerebral hemodynamics disturbances in restless leg syndrome patients with periodic limb movements in sleep and suggests that NIRS can be used to determine the cerebral blood flow.

There have been many attempts to localize seizure foci. NIRS revealed significant hyperperfusion on the side of seizure foci compared with ictal single-photon-emission computed tomography in recordings of patients with nonlesional refractory frontal-lobe epilepsy.[48,49] NIRS and electroencephalography (EEG) were successfully applied simultaneously to the mouse brain to spatiotemporally track hemodynamics responses to epileptic episodes that had been induced pharmacologically.[50] Another study combining NIRS and EEG has also revealed complex local and distant oxygenation changes during temporal-lobe seizures,[51] and so this methodology can be expected to be actively used in clinical researches.

Epilepsy often occurs in the cerebral cortex, which makes it is easier to apply NIRS compared to other diseases that occur in deep brain areas. However, NIRS does not provide direct measurements of electrophysiological changes associated with brain damage. Instead, NIRS measures the secondary changes in brain oxygen saturation, and so further work is needed into the clinical interpretation of NIRS measurements.[40]

Migraine

The application of NIRS to migraine provided further information about the risk of migraine-related cerebrovascular disease.[52] A previous study involving women suffering from migraine with aura found that NIRS could discriminate between those with and without a patent foramen ovale.[53]

NIRS has been applied in migraine studies most widely to study cortical spreading depression, which is a brain electrical phenomenon that propagates through the cortex followed by prolonged depression of cortical neuronal activity. A study using NIRS identified the areas of cortical hypoperfusion corresponding to the topography of aura symptoms that were the result of a decreased metabolic demand rather than an ischemic mechanism.[54]

While the NIRS indices used in previous studies were not well established and were not widely used for determining or assessing treatments in clinical practice, they are expected to play a major role in future studies of the pathophysiology of migraine, especially aura symptoms.

CONCLUSION

NIRS is widely used to investigate the pathophysiology of various neurological diseases, but its application is currently limited by technical problems. Although the utilization of NIRS for diagnosis and for determining the pathophysiology of autonomic nervous disorder remain insufficient compared to other neurological studies, its use will increase rapidly in the future given that changes in cerebral perfusion are the cause of clinical symptoms of autonomic dysfunction. NIRS

represents an alternative methodology that can successfully measure changes in brain activity in both healthy human subjects and patients while they are performing a variety of behavioral tasks under ecologically relevant conditions.

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