

Progress of near-infrared spectroscopy in cerebral blood oxygenation detection: A mini review

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Highlights

- Near-infrared spectroscopy (NIRS) technology transmits a beam of near-infrared light through a transmitter to the brain.
- The changes in hemoglobin concentration and cerebral blood oxygen levels can be estimated using near-infrared light, by comparing the changes in light attenuation over time.
- This paper introduces the basic concept of measuring blood oxygen levels in brain tissue using NIRS technology, and presents the potential applications of the most recent developments in this field of study.

Abstract

In contrast to conventional oximeters, near-infrared spectroscopy-based brain tissue oximetry monitoring devices are capable of non-invasive, continuous, and real-time quantitative monitoring of cerebral oximetry parameters. Initially, these devices were utilized for intensive care or surgical monitoring of oxygen saturation. Due to the rapid advancement of optoelectronic sensing and measurement technologies over the past decade, the derived functional near-infrared brain imaging devices have been widely used in a variety of fields. This paper first introduces the basic principles of near-infrared spectroscopy-based cerebral oxygenation parameter detection, then focuses on the most recent developments in this field of study. Finally, a prospect on their future application in practical settings is also provided.

Keywords: Near-infrared spectroscopy, cerebral oximetry, non-invasive measurement

Introduction

Brain, a very energy-intensive organ, has a much higher oxygen demand and consumption than its oxygen reserves. Even at rest, the brain consumes 25% of the body's total oxygen, making it particularly susceptible to ischemic and hypoxic conditions. Prolonged hypoxia may cause irreversible neurological damage [1]. According to previous literature, the hypoxia-related mortality rate can reach 90% in cases of fatal brain injury [2]. Numerous studies have demonstrated that regional cerebral oxygen saturation (rSO_2) is a valid indicator of severe cerebral hypoxia [3].

These years, patients with brain injuries are clinically diagnosed using cutting-edge imaging

technologies like CT, MRI, and positron emission tomography-computed tomography (PET-CT). Yet, devices to accurately monitor blood oxygenation and hemodynamic changes in real time in brain tissue is urgently needed in clinical practice. Near-infrared spectroscopy (NIRS), a novel method for measuring oxygen saturation, enables non-invasive, continuous monitoring of rSO_2 in local brain tissue [4]. This technique can assess the balance of oxygen metabolism in brain tissues as well as early imbalances in blood flow and blood oxygen supply and demand. Through real-time monitoring of changes in the oxygen saturation of specific brain tissues, NIRS can quickly reveal pathological changes in patients with craniocerebral injuries [5]. For surgery, treatment, prognosis, and patient monitoring, this information is in-

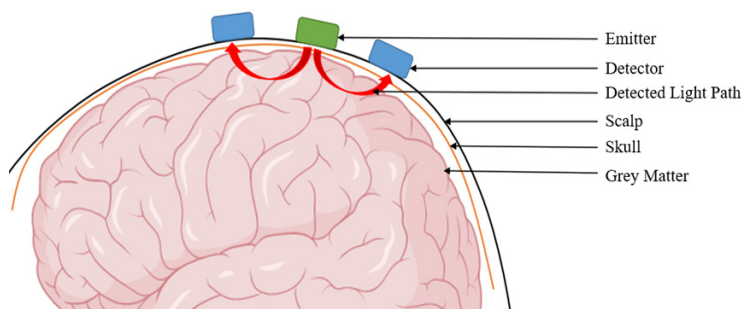


Figure 1. Diagrammatic representation of the light source and photodetectors mounted on the skull's median sagittal cross-section.

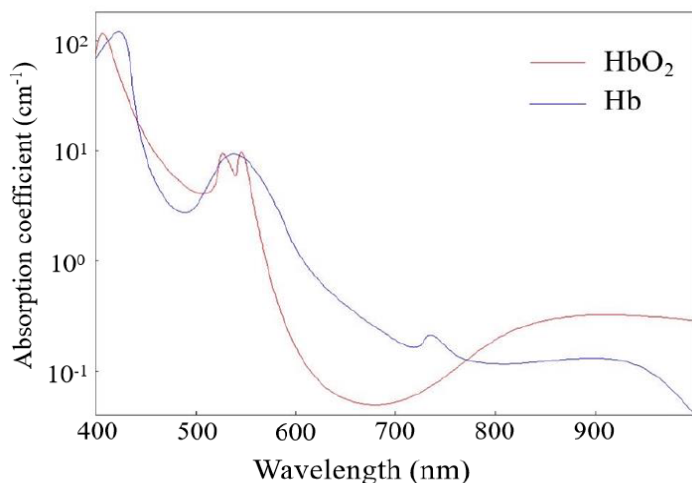


Figure 2. Spectrum of HbO₂ and Hb absorption.

structive. In recent years, NIRS has developed rapidly in fields of biomedical engineering like neonatology, cardiothoracic surgery, and neurosurgery. The goal of this study is to give a general overview of the monitoring principles, the current status of the research, and possible future directions for this technology.

Methods

Lambert-Beer Law

Lambert-Beer's law describes the relationship between incoming and outgoing light, the concentration of the light-absorbing material, and the distance a photon travels. The amount of absorption during photon propagation in a light-absorbing medium depends only on the photon's length and the concentration of the light-absorbing material; it is independent of the intensity of the incident light. During photon transmission, each layer of the light-absorbing medium absorbs photons at the same rate. The formula is $OD = \epsilon \cdot C \cdot L$, where ϵ is the coefficient of light extinction, C is the concentration of light-absorbing material, L is the linear separation between the light source and the detector, and OD , optical density, is the amount of light attenuation. It only works when the me-

dium's absorbing substance is constant, and the path taken by the light is straight.

However, due to the fact that the actual path of photons passing through the brain is more complex and there exists other substances absorbing minute amounts of photons, the original law is updated. The modified formula is $OD = \epsilon \cdot C \cdot DPF \cdot L + G$, which expresses the actual optical path in terms of the product of the distance L and the path-length correction factor DPF (i.e., the path length amplification factor), and G is the total attenuation of the light intensity caused by all other variables aside from oxyhemoglobin (HbO₂) and hemoglobin (Hb).

Principle of NIRS

In the NIRS measurement process, a brain scalp surface positioned light source emits near-infrared light, which is absorbed and scattered as it passes through brain tissue. Two photodetectors are then symmetrically positioned on the scalp near the light source emitter to collect the light scattered in all directions. The entire optical path distribution is shown in **Figure 1**. The human brain's outer tissues are made up of the scalp, skull, cerebrospinal fluid, cerebral gray matter, and cerebral white matter in the order from the outside to the inside, and the near-infrared light has to penetrate all these layers to detect brain tissue effectively [6].

The American Society for Testing and Materials designated the range of 780 nm to 2,526 nm as the near-infrared spectral region after it was found by British astronomer Herschel in 1800 during energy measurements in the infrared portion of the visible region of the solar spectrum. Since first being introduced by Frans Jöb-sis in 1977, NIRS has grown into a highly effective and popular technique for optical diagnosis [7]. The technique is based on the optical properties of biological tissues, specifically the ability of near-infrared light to extract biochemical data from the tissues by penetrating skulls and other biological tissues to a particular depth. By observing the series of near-infrared light absorption and scattering processes that take place in biological tissues, this method can be used to estimate the oxygen saturation in brain

Table 1. Absorption coefficient and scattering coefficient of near-infrared light of different wavelength in different tissues (Absorption coefficient/Scattering coefficient, Unit: cm^{-1})

| Tissue | 690 nm | 760 nm | 780 nm | 830 nm |
|---------------------|------------|------------|------------|------------|
| Scalp | 0.159/8.0 | 0.177/7.3 | 0.164/7.1 | 0.191/6.6 |
| Skull | 0.101/10.0 | 0.125/9.3 | 0.115/9.1 | 0.136/8.6 |
| Cerebrospinal fluid | 0.004/0.1 | 0.021/0.1 | 0.017/0.1 | 0.026/0.1 |
| Gray matter | 0.178/12.5 | 0.198/11.8 | 0.170/11.6 | 0.186/11.1 |

tissue.

The 'spectral window' in tissue optics, in the range of 650-1,000 nm, exhibits notable near-infrared light penetration ability into human tissue. HbO_2 and Hb, which can be distinguished optically due to their different near-infrared absorption coefficients, are the main light absorbers in this region, as shown in **Figure 2**. **Table 1** displays the near-infrared light absorption and scattering characteristics of various tissues. It is possible to choose proper light sources and related detectors referring this table to implement spectral analysis, and the oxygen saturation of brain tissue can be calculated by applying the modified Lambert-Beer law to the measurements of incident and reflected light intensity [8].

NIRS has become a potential method for detecting intracranial injuries as a result of improvements in optical fiber and sensor technology, as well as their integration with computer network technology. This method has important clinical applications because it can be used for noninvasive and real-time monitoring of blood oxygenation parameters in specific localized brain tissues [9].

Functional near-infrared spectroscopy (fNIRS)

The capacity of near-infrared light to reach deeply into biological tissues and the neurovascular coupling mechanism are prerequisites for fNIRS. Functional brain imaging works on the same principle as functional magnetic resonance imaging (fMRI): local hemodynamic changes are caused by neural activity in the brain. It primarily uses the variation in the rates at which Hb and HbO_2 in brain tissue absorb various near-infrared light wavelengths to directly measure the hemodynamic activity of the cerebral cortex in real-time. Such hemodynamic alterations allow for the inverse inference of brain activity.

The primary distinction between NIRS and fNIRS lies in their fields of application and goals. The similarity is that they both use NIRS to measure light absorption, but the difference is the application or focus.

NIRS was first applied to measure physiological parameters like tissue blood flow and oxygen saturation. The medical and biological sciences make extensive use of it, particularly when it comes to blood oxygen level monitoring in the brain and muscle tissues. A specific type of NIRS called fNIRS measures the concentrations of Hb and HbO_2 in the brain to investigate cerebral blood flow, neural activity, and cognitive function. The physiological parameters that NIRS focuses on include blood oxygen saturation, blood flow, and the total Hb concentration in tissues. Understanding changes in tissue oxygen metabolism and hemodynamics can be aided by this. fNIRS is primarily used to measure variations in brain blood oxygen levels brought on by neural activity. It can offer functional details about particular brain areas for research on neurological and cognitive functions.

The benefits of fNIRS include its non-invasiveness, relative portability, and increased tolerance for small head movements. These attributes make fNIRS applicable for young children and infants, as well as individuals with difficulty in remaining motionless when using traditional fMRI equipment. In contrast to fMRI, fNIRS has lower spatial resolution and penetration depth and measures activity primarily at the cortical surface.

fNIRS, which focuses more on the study of brain function, can be considered as a specific application of NIRS overall. Despite the fact that they both employ NIRS techniques, in actuality, they differ slightly due to their areas of focus and application.

Research progress in NIRS

Current Research Status of NIRS

The ability of near infrared to penetrate biological tissues, particularly animal skulls, was first made known by Jöbsis in 1977 [7]. This ground-breaking discovery offered a strong foundation for further research into the dynamics of Hb concentration in the cortex of the human brain. This study pioneered a novel non-invasive measurement of changes in tissue blood oxygenation in addition to confirming the via-

bility of NIRS in monitoring brain activity. Since then, the majority of healthcare professionals have expressed great concern about the interaction of NIRS technology with cerebral blood oxygen monitoring and brain function imaging.

A research team from Hokkaido University in Japan discovered the underlying mechanism of neurovascular coupling in 1994 [10]. They found that neural activity in the brain increases oxygen consumption, which in turn results in increased blood flow in the cerebral white matter. This finding led to the development of useful near-infrared brain imaging tools and the recent emergence of a research hotspot of using NIRS to study neural activity in the brain [11].

From their distinct vantage points, various research groups have offered insights into the use of near-infrared in tissue testing. Their perspectives range from measuring muscle blood oxygenation parameters to monitoring brain activity. Farrel and Binzoni used it to measure the parameters of muscle oxygenation [12]. Esnault compared the cerebral blood oxygenation parameters measured by NIRS with measurements of brain tissue oxygen pressure and came to the conclusion that the two measurements cannot be used interchangeably as a test for people who have suffered craniocerebral trauma [13]. In patients with craniocerebral trauma, Leal-Noval also investigated the relationship between cerebral oxygen parameters and brain tissue oxygen pressure and discovered a weak correlation between these two measurements [14]. Additionally, Esnault's observations were supported by the low accuracy of cerebral oxygen parameter values in detecting moderate cerebral hypoxia.

The high sensitivity of NIRS for monitoring brain oxygenation has been demonstrated in the treatment of cerebrovascular disease. Zweifel's observation using arterial imaging suggested that NIRS could synchronize the detection of decreased cerebral oxygen secondary to vasospasm with high sensitivity [15]. Arterial spasm was significantly correlated with ipsilateral decreases in rSO_2 , and as the degree of spasm increased, ipsilateral rSO_2 decreased dramatically. Taussky found a strong correlation between cerebral oxygen saturation and local cerebral blood flow in 1,287 patients using both NIRS and CT perfusion imaging techniques [16]. These suggest the potential of NIRS as a real-time, reliable, non-invasive cerebral oxygen monitoring tool that could be used at the bedside in intensive care units.

Internationally, non-invasive cerebral oximetry

monitoring technology has made some early strides, and several companies and academic organizations have already launched their own monitoring programs. China, on the other hand, began its investigation into this topic somewhat later. But in recent years, a number of Chinese institutions, including academic institutions and research facilities, have begun to carry out in-depth investigations on cerebral oximetry monitoring devices using this technology.

In 2005, Prof. Haisu Ding of Tsinghua University successfully developed the TASH-100 non-invasive cerebral oximetry monitoring device, a brain tissue oximetry detector with independent intellectual property rights, and China became the third country after the United States and Japan to do so [17]. Additional Chinese academics and researchers have been inspired by this innovation and stepped up their research on near-infrared cerebral oximetry monitoring. According to trial data from more than 900 clinical cases, the device provides relative and absolute values of brain tissue oxygen saturation and its trend. However, there are still limitations in data sampling frequency and data storage capacity of this device.

Universities like Huazhong University of Science and Technology and Nanjing University of Aeronautics and Astronautics have since conducted studies on cerebral oximetry monitoring devices based on NIRS. While researching near-infrared brain functional imaging, Luo's team at Huazhong University of Science and Technology concentrated on applications like cerebral blood flow momentum detection and brain-computer interface [18]. Using NIRS, they were able to identify the relative alterations in HbO_2 and Hb concentrations separately. The changes in HbO_2 and Hb concentrations responded to stimulation in very different ways, with more increased HbO_2 concentration than Hb concentration. In contrast, as the brain tissue continued to use oxygen, the concentration of Hb increased, while the concentration of HbO_2 decreased. This finding not only adds to previous physiology findings, but also opens up the possibility of further research into the functional processes that lead to the oxygen depletion in brain tissues.

A non-invasive near-infrared cerebral oximetry monitoring system was successfully developed by Qian's research team at Nanjing University of Aeronautics and Astronautics, and its effectiveness was first demonstrated through prospective blocking experiments and oximeter comparison experiments [19]. They discovered that when pressure was applied to the upper

Table 2. Comparison of three near-infrared imaging methods

| | CWS | FDS | TRS |
|---|----------------------|----------------------|------------------|
| Distinction between scattering and absorption | Minimum | Moderate | Maximum |
| Reference measurement | Relative changes | Absolute changes | Absolute changes |
| Sampling rate (Hz) | <100 | <50 | Around 1 |
| Signal-to-noise ratio | Maximum | Moderate | Minimum |
| Depth resolution | Minimum | Moderate | Maximum |
| Equipment cost | Both high and low | Relatively high | Relatively high |
| Equipment volume | Varying sizes | Moderate | Relatively large |
| Application scenario | Oximetry and Imaging | Oximetry and Imaging | Oximetry |

Note: CWS, continuous wave spectroscopy; FDS, frequency domain spectroscopy; TRS, time resolved spectroscopy.

arm, the blood oxygen concentration changed over time. After the value of the blood oxygen concentration was collected and stabilized, it decreased gradually with an instantaneous pressurization to 130 mmHg in 75 seconds. Then, after an instantaneous decompression to 0 after pressurization for 180 seconds, it significantly increased due to the inflow of oxygenated blood and then slowly recovered to its initial value over time. Under a pressurized situation, they found that this device reacted well to changes in the forearm blood oxygen concentration in the upper arm.

NIRS technology has been extensively applied in numerous clinical scenarios, including functional brain imaging, brain tumor imaging, cerebral blood flow detection, and cerebral hematoma detection [20-23]. Currently, the three imaging techniques that are most commonly used by mainstream NIRS cerebral oximetry monitoring devices are continuous wave spectroscopy (CWS), frequency domain spectroscopy, and time resolved spectroscopy detection techniques [24]. **Table 2** provides a detailed comparison of the performance characteristics of these three near-infrared detection systems.

CWS employs a direct method that compares the difference in light intensity before and after the projection of near-infrared light into the brain tissues in order to calculate and assess the degree of oxygen saturation in the brain [24]. It also incorporates a modified version of the Lambert-Beer law.

Frequency domain spectroscopy is more complex as it involves superimposing high-frequency sinusoids from 50 MHz to 1 GHz on the incident light first [25]. Then, it uses phase-modulation spectroscopy to measure the phase shift and intensity of the light, which allows it to calculate precise blood oxygen parameters.

On the other hand, time resolved spectroscopy uses picosecond ultrashort pulse excitation and sends these pulses into the brain [26]. Then,

by measuring the light intensity at various time intervals to compute the time dilation function and obtain the optical parameters of the tissue, the absolute amount of blood oxygen within the brain tissue can be precisely determined.

Compared to the latter two, CWS provides clearer and more accurate information about changes in the relative concentrations of HbO₂ and Hb. This feature makes it an excellent choice for continuous monitoring scenarios, particularly when equipment cost is an issue. Therefore, both in commercial product design and in research settings, continuous wave measurements are currently the most popular technique for measuring cerebral oximetry [24].

NIRS has a wide range of intricate applications in biomedical engineering and medical testing, particularly in the non-invasive monitoring and evaluation of blood oxygen levels in the brain and other biological tissues. In addition to providing new insights into fundamental biological processes, this technology encourages innovation in medical diagnostics and therapeutics.

Factors affecting NIRS

The importance of NIRS in clinical diagnosis and treatment is gradually increasing as its application in a variety of fields deepens. However, due to a dearth of prospective studies and high-caliber scientific evidence, the technology still needs to be improved, given its status as a relatively new method of monitoring.

NIRS is affected by a variety of factors in real-world applications, such as extracerebral blood flow, cerebrospinal fluid, skull thickness, and myelin sheaths. The fact that individual differences in rSO₂ measurements might result from the light-absorbing qualities of skin pigments was further supported by a retrospective study by Sun using a large number of samples [27]. Individual variations in rSO₂ measurements might be caused by light-absorbing properties, as shown by lower rSO₂ values for deeper pigmentation and higher rSO₂ values for

Table 3. Type and number of light sources and detectors

| References | Light source type | Wavelength number | Wavelength /nm | Number of light sources /pcs | Detector type | Number of detectors /pcs | Number of channels /pcs | Light source - Detector distance /mm |
|--------------|-------------------|-------------------|----------------|------------------------------|---------------|--------------------------|-------------------------|--------------------------------------|
| Cheng [29] | LED | Dual- Wavelength | 735/850 | 4 | PD | 12 | 30 | 26 |
| Francis [30] | LED | Dual- Wavelength | 740/850 | 1 | SiPD | 4 | 4 | 5/10/23/28 |
| Maira [31] | LED | Dual- Wavelength | 700/830 | 12 | SiPM | 13 | 156 | 20 |
| Yaqub [28] | LED | Dual- Wavelength | 735/850 | 128 | SiPD | 1 | 128 | 5/20/25/30/35 |
| Tsukasa [32] | LED | Dual- Wavelength | 730/855 | 2 | SiAPD | 2 | 4 | 30 |
| Danial [33] | LED | Octa- Wavelength | 750-900 | 1 | PD | 4 | 4 | 36/42 |
| Wathen [34] | LD | Dual- Wavelength | 690/852 | 32 | SiPM | 32 | 32 | 13 |

Note: LED, light emitting diode; LD, laser diode; PD, photo diode; SiPD, silicon photo diode; SiPM, silicon photo multiplier; SiAPD, silicon avalanche diode.

Table 4. Technical comparison of NIRS and fMRI, EEG, MEG, PET

| | NIRS | fMRI | EEG | MEG | PET |
|---------------------|----------------------|----------------------|-----------------|----------------------|---------------------|
| Measurement method | Indirect | Indirect | Direct | Direct | Indirect |
| Measured signal | Hemodynamic response | Hemodynamic response | Scalp potential | Brain magnetic field | Cerebral metabolism |
| Spatial resolution | ~1 cm | ≥0.5 mm voxel | 5~9 cm | ~1 cm | 3~4 mm |
| Penetration depth | Cerebral cortex | Whole head | Cerebral cortex | Deep structure | Whole head |
| Sampling rate | ≤25 Hz | ≤3 Hz | > 1,000 Hz | > 1,000 Hz | < 0.1 Hz |
| Subject population | No limit | Have limits | No limit | Have limits | Have limits |
| Outdoor condition | Suitable | Unsuitable | Suitable | Unsuitable | Unsuitable |
| Wearability | Suitable | Unsuitable | Suitable | Unsuitable | Unsuitable |
| Long-term detection | Suitable | Unsuitable | Suitable | Unsuitable | Unsuitable |
| Cost | Low | High | Low | High | High |

Note: NIRS, near-infrared spectroscopy; fMRI, functional magnetic resonance imaging; EEG, electrical encephalogram; MEG, magnetoencephalography; PET, positron emission tomography.

lighter pigmentation. Although rSO_2 has made significant progress in the neonatal population, its use in adults has been somewhat constrained by adults' relatively thicker skulls and more pronounced attenuation of near-infrared light.

In addition to the aforementioned variables, different NIRS devices have different detector modules with varying degrees of sensitivity. **Table 3** lists different light sources and detectors that have been used in various NIRS systems over the last few years. Among them, Yaqub created a cutting-edge system with a 12-bit successive-approximation analog-to-digital converter and used a silicon photodiode set up in the photoconductive mode to achieve a high sampling rate when processing significant amounts of NIRS data [28]. Additionally, a filter circuit was specifically included in this design to efficiently reduce high-frequency noise brought on by the high-voltage power supply. In conclusion, choosing the right photodetectors not only significantly improves the detection sensitivity of NIRS system, but also improves the overall performance of the system. This establishes a strong foundation for the use and advancement of NIRS technology.

Future outlook for NIRS

Even after over 20 years of research, NIRS still has some problems in diagnosing and treating patients with craniocerebral injuries. The relationship between rSO_2 and other crucial markers of brain function, such as intracranial pressure, cerebral perfusion pressure, internal jugular venous oxygen saturation ($SjvO_2$), and partial pressure of oxygen in brain tissue ($PbtO_2$), should be further explored in future studies. Through the combined use of transcranial Doppler ultrasound, evoked potentials, and other multimodal monitoring techniques, a comprehensive assessment of the cerebral blood oxygen metabolism and other conditions can be realized, providing more thorough and accurate diagnosis and treatment plan for critically ill patients. These comprehensive analyses will help to accurately define the rSO_2 threshold at the onset of craniocerebral injury.

Clinical staff can more intuitively evaluate the balance of cerebral blood flow and cerebral oxygen supply and demand thanks to real-time rSO_2 monitoring by NIRS. Although this technology has been widely used in Europe and the United States in some clinical areas (such as cerebral oximetry monitoring in cardiothoracic surgery), its potential in clinical settings remains significant. Despite having numerous applications, it is important to note that there is limited data to support the use of NIRS for

clinical decision-making and intervention. More clinical trials are therefore required in the future, particularly to assess the application of NIRS in hemorrhage screening in patients with craniocerebral injuries. Verifying whether the advantages of NIRS technology actually translate into better clinical outcomes and facilitating further optimization of medical decision-making and therapeutic approaches should be part of the main research objectives.

Conclusion

Even though modern NIRS is not yet a stand-alone diagnostic tool, it has clear benefits when used in conjunction with noninvasive, portable, and reasonably priced imaging methods like CT. Especially in the field of cranial brain injury detection, the importance of NIRS is unquestionable.

In functional brain imaging, NIRS has different advantages and limitations compared with other techniques, such as fMRI, electrical encephalogram, magnetoencephalography, and PET, and their technological comparisons are shown in **Table 4**. For example, NIRS outperforms fMRI in temporal resolution, outperforms electrical encephalogram in spatial resolution, and, more importantly, is portable and less disturbed by artifacts.

More patients are anticipated to benefit from NIRS as it improves. The technique is not only being utilized more frequently in the rehabilitation of patients with traumatic brain injuries, but also allows for continuous and noninvasive tracking of changes in the parameters governing cerebral blood oxygenation. NIRS data can be a potent addition to existing monitoring measures, providing more thorough information on cerebral pathology, even though there are still certain technical restrictions. The comprehensive performance of NIRS is anticipated to be considerably enhanced with the further development in detection methods and systems, which implies that it is anticipated to be employed for quick screening of casualties in combat or field settings, freeing up crucial time for treatment.

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