



# A Review of Cerebral Hemodynamics During Sleep Using Near-Infrared Spectroscopy

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Investigating cerebral hemodynamic changes during regular sleep cycles and sleep disorders is fundamental to understanding the nature of physiological and pathological mechanisms in the regulation of cerebral oxygenation during sleep. Although sleep neuroimaging methods have been studied and have been well-reviewed, they have limitations in terms of technique and experimental design. Neurologists are convinced that Near-infrared spectroscopy (NIRS) provides essential information and can be used to assist the assessment of cerebral hemodynamics, and numerous studies regarding sleep have been carried out based on NIRS. Thus, a brief historical overview of the sleep studies using NIRS will be helpful for the biomedical students, academicians, and engineers to better understand NIRS from various perspectives. In this study, the existing literature on sleep studies is reviewed, and an overview of the NIRS applications is synthesized and provided. The paper first reviews the application scenarios, as well as the patterns of fluctuation of NIRS, which includes the investigation in regular sleep and sleep-disordered breathing. Various factors such as different sleep stages, populations, and degrees of severity were considered. Furthermore, the experimental design and signal processing, as well as the regulation mechanisms involved in regular and pathological sleep, are investigated and discussed. The strengths and weaknesses of the existing NIRS applications are addressed and presented, which can direct further NIRS analysis and utilization.

**Keywords:** cerebral hemodynamics, near-infrared spectroscopy, sleep stages, sleep disorders, cerebrovascular autonomic regulation

## INTRODUCTION

The brain has a complex cerebral autoregulation mechanism which guarantees the normal function during daily activity and nocturnal sleep. The mutual regulation of the neurons, glial cells, and the vasculature of the brain constantly regulate the homeostasis to maintain health. Sleep, as an essential part of physiological activity, facilitates the recovery of humans' physical function in daily life. Humans spend roughly one-third of their lives asleep (1). However, an increasing number of people are undergoing sleep disorders resulting from the accelerated pace of life and the pressure of work. Sleep disorders are associated with several morbidities as well as increased mortality (2), affecting the functional output of the brain in terms of alertness, cognition, and mood (3), as well as increasing the risk of cerebrovascular disease (4).

Polysomnography (PSG), as a gold standard diagnostic test for sleep disorders, provides multiple physiological signals containing brain activity (electroencephalography: EEG), eye movement (electro-oculogram: EOG), chin muscle tone (electromyography: EMG), and oxygen saturation (peripheral capillary oxygen saturation: SpO<sub>2</sub>). The amplitudes and/or frequencies of these physiological signals would change with sleep events. For instance, a specific of EEG signal rhythmicity would be present in specific sleep stages, and the decline of SpO<sub>2</sub> would result from the termination of respiration during apnea. Even though EEG signals during sleep provided significant information for clinical diagnosis and basic researches, the cerebral low frequency oscillations in terms of cerebral hemodynamics could provide supplementary information for a better understanding of sleep neurophysiology which cannot be detected by the EEG (5–8). Moreover, the high energy requirements of the brain renders it more susceptible to hypoxic conditions (9). The detection of arterial oxygen saturation may not provide sufficient information for instantaneous detection of apneic episodes and its effects on brain tissues. Accordingly, investigating cerebral hemodynamic changes during sleep contributes to the understanding of cerebrovascular regulation mechanisms in pathological conditions associated with sleep disorders, such as sleep apnea, and insomnia. Moreover, understanding the similarities and differences between physiological and pathological mechanisms can enhance the efficiency of the treatment and reduce the complications of these common sleep disorders.

Near-infrared spectroscopy (NIRS) as an emerging non-invasive functional imaging technique has the capability to detect the changes of oxygen hemoglobin (HbO<sub>2</sub>), de-oxygen hemoglobin (HHb), and total oxygen hemoglobin (tHb) concentrations. The low-frequency changes in HbO<sub>2</sub>, HHb, and tHb could reflect the brain functional activity involving the cerebral blood supply and cerebral oxygen consumption, as well as sufficient or impaired cerebrovascular autonomic regulation. The synchronous acquisition of EEG and NIRS provides an opportunity to comprehensively understand brain activities in terms of neurovascular regulation.

Based on the advantages of NIRS in detecting cerebral oxygenation, this review focuses on the patterns of cerebral

hemodynamic changes during regular sleep cycles and the pathological conditions in patients with sleep-disordered breathing. Even though the experimental studies in patients with sleep-disordered are significant in further understanding of the role of persistent or intermittent apnea in cardiovascular and cerebrovascular injury, as well as cognitive disorders, the related experimental design studies such as cognitive performance and exercise tolerance for patients with sleep-disordered breathing are beyond the scope of this article.

This review is structured as follows: the first section presents the background of the related studies, including the physical principles of NIRS and the potential application of NIRS in sleep studies. The second section is dedicated to discuss the hemodynamic signal changes during sleep state transitions and episodic apnea/hypopnea. Then, the interpretation of physiological and pathological mechanisms mediating sleep transitions and apnea syndromes are introduced. Finally, the last section is devoted to reporting the differences in the experimental design and the signal processing methods. A future perspectives section ends the review.

## BACKGROUND

### Basic Principles of NIRS

NIRS is an emerging non-invasive functional imaging technique. It progressively gains attention owing to its relatively high temporal resolution (ms), portability, non-invasiveness, low cost, and relative insensitivity to subject movements. It has been widely used in areas involving brain-computer interface (BCI), language, motor task behaviors, psychology, cognition, etc. Details regarding the application of NIRS have been well-reviewed previously (10–12). The technique of NIRS is based on the principles that human tissues are relatively transparent in the near-infrared wavelength range (650–1,000 nm), since the main transmission path is scattering (13). Furthermore, human tissues have particular absorption properties that the domain absorbers, HbO<sub>2</sub> and HHb located in small vessels (<1 mm diameter), have varying absorption spectra (13, 14). The scattering property in human tissues is typically 100 times larger than absorption (15). NIRS relies on the procedure that the near-infrared light penetrates human tissues and then the detectors obtain the attenuated light emerging from the head. Due to the complex scattering caused by the multi-tissue layers, the optical path-length passing through the tissue is longer than the distance between the source and the detector located on the surface of the scalp. The spatial distribution of the optical path-length exhibits banana-shaped. According to the different illuminating types, there are three different NIRS techniques: continuous wave (CW), frequency-domain (FD), and time-domain (TD) based system. CW-based NIRS system is widely used due to the low cost and portable properties. More details about the differences of the three types of instruments were discussed in the related articles (10, 11). The following NIRS description is mainly focused on the CW-based system.

The attenuated light collected by detectors was converted into the changes in HbO<sub>2</sub> and HHb by the modified Beer-Lambert law (MBLL). The typical changes in the cerebral hemodynamic

**Abbreviations:** NIRS, Near-infrared spectroscopy; PSG, polysomnography; EEG, electroencephalography; EMG, electromyography; EOG, electrooculogram; BCI, brain-computer interface; CW, continuous-wave; FD, frequency-domain; TD, time-domain; MBLL, modified Beer-Lambert law; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; TCD, transcranial Doppler; HbO<sub>2</sub>, oxygen hemoglobin concentration; HHb, deoxy-hemoglobin concentration; tHb, total hemoglobin concentration; HbD, hemoglobin difference; StO<sub>2</sub>, brain tissue oxygen saturation; TOI, tissue oxygenation index; FTOE, fractional tissue oxygen extraction; SaO<sub>2</sub>, arterial blood oxygen saturation; SpO<sub>2</sub>, peripheral capillary oxygen saturation; LFO, low frequency oscillations; VLFO, very low frequency; R&K, Rechtschaffen and Kales; AASM, American Academy of Sleep Medicine; CBF, cerebral blood flow; CBV, cerebral blood volume; CBFV, cerebral blood flow velocity; CMRO<sub>2</sub>, cerebral metabolic rate of oxygen; MAP, mean arterial pressure; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea; W, wakefulness; LS, light sleep; SWS, slow wave sleep; REM, rapid eye movement; NREM, non-rapid eye movement; CAP, cyclic alternating pattern; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; AHI, apnea-hypopnea index; PSD, power spectral density.

response to the external stimulus or cognitive tasks underlying neurovascular coupling mechanism is an increased HbO<sub>2</sub> accompanied by a decreased HHb (10). The canonical pattern of the hemodynamic response to stimulation is shown in **Figure 1**. The changes in HbO<sub>2</sub> and HHb reflect brain activity during different physiological/pathological states or under specific brain tasks (16). A simultaneous increase in HbO<sub>2</sub> and a stable level or decrease in HHb indicate that the rise of cerebral blood flow (CBF) is larger than cerebral oxygen metabolism (17, 18). The total hemoglobin concentration (tHb), that is, the sum of HbO<sub>2</sub> and HHb, reflects cerebral blood volume (CBV). The hemoglobin difference (HbD)—the difference between HbO<sub>2</sub> and HHb—could reflect the intravascular oxygenation and cerebral blood flow (19).

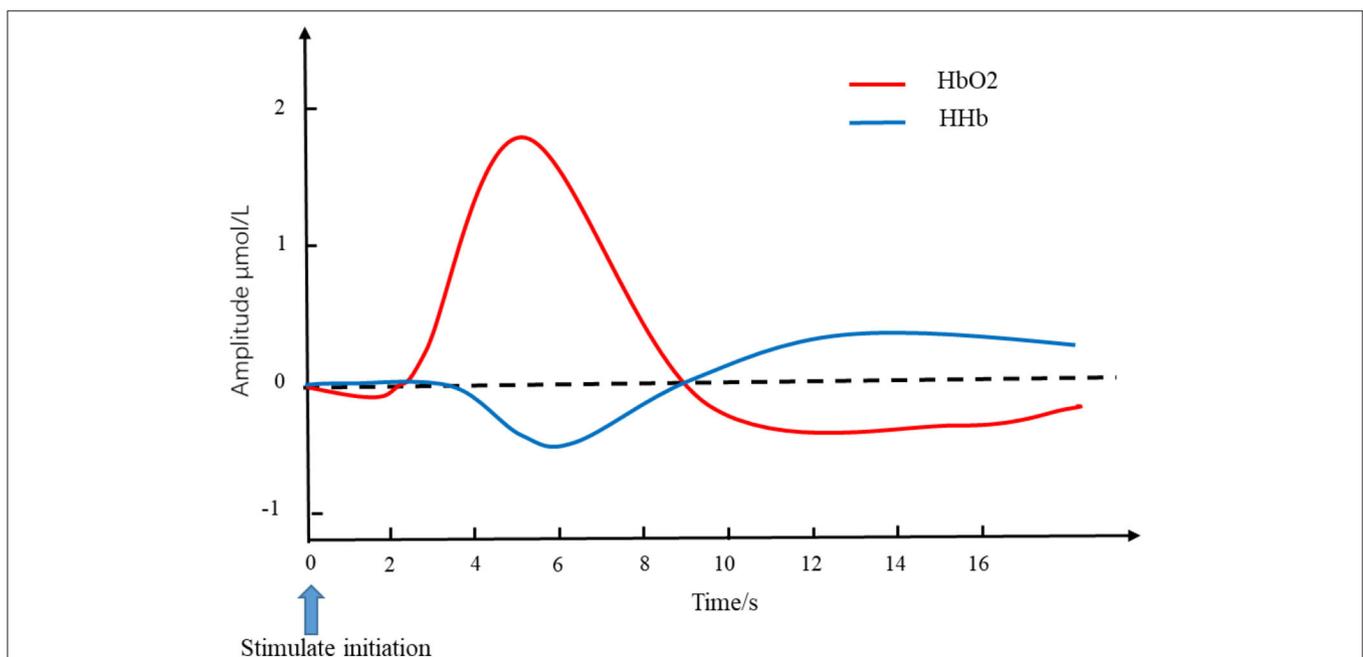
Excluding the straight forward assessment of cerebral hemoglobin concentrations and derivatives, two indices of cerebral oximetry, which are cerebral tissue oxygenation index (TOI) and regional cerebral oxygen saturation (StO<sub>2</sub>), could provide absolute values of the regional cerebral oxygen saturation. The two parameters were obtained from spatially resolved spectroscopy with multi-distance optodes (20). TOI showed an absolute value of tissue oxygenation in percentage, which was measured at three close distances using the diffusion equation, reflecting cerebral oxygenation, and cerebral venous saturation (21). StO<sub>2</sub> can be obtained from two interoptode distances with a short distance and a larger distance, reflecting the amount of regional oxyhemoglobin in the unit volume of tissue. Although the two parameters are obtained from two distinct devices and algorithms, the values between the two parameters are comparable and highly correlated (22, 23). The

two indices of cerebral oximetry are more concerned in the clinical use.

Changes in cerebral hemodynamics are associated with the autoregulatory system, spontaneous brain action, and systemic physiological components (24). In general, the dynamic changes in HbO<sub>2</sub> and HHb in human cerebral tissues are contaminated by natural oscillations of cardiac activity at frequencies of 0.6–2 Hz and respiration at frequencies of 0.15–0.6 Hz (25–28). The low frequency oscillations (LFOs) ranging between 0.06 and 0.10 Hz and very low frequency (VLFOs) ranging between 0.01 and 0.05 Hz are important features of cerebral hemodynamics and play an important role in the resting-state and activation-state connective networks of human brain (29, 30). Additionally, spontaneous low and very low hemodynamic oscillations (3–150 mHz) measured with NIRS reflect the endothelial (5–20 mHz), neurogenic (20–50 mHz), and myogenic (50–150 mHz) components of vasomotion (31).

## Potential Application of NIRS in Sleep Researches

Over the last couple of decades, functional neuroimaging has been used to investigate neural mechanisms associated with the generation of sleep stages and pathophysiological mechanisms of sleep disorder (8, 32). The functional neural imaging, such as positron emission tomography (PET), transcranial Doppler (TCD), and functional magnetic resonance imaging (fMRI) have provided insight into cerebral metabolism, neuronal functioning, and vasomotor activity in terms of cerebral hemodynamics (3). These modalities provided global and regional brain activities during regular sleep cycles and sleep-disordered. However, they



**FIGURE 1** | Simulated hemodynamics in response to stimulation. The red line and blue line represent the changes of HbO<sub>2</sub> and HHb, respectively. The blue arrow pointing at time 0 is the initiation of stimulation. The typical changes of cerebral hemodynamic in response to the external stimulus is an increased HbO<sub>2</sub> accompanied by a decreased HHb. HbO<sub>2</sub>, oxygen hemoglobin concentration; HHb, de-oxygen hemoglobin concentration.

**TABLE 1** | Comparison between neuroimaging modalities (10, 32, 34).

Technique	Origin	Strengths and limitations
TCD	Blood circulation	Strengths: <ul style="list-style-type: none"> <li>• Non-invasive;</li> <li>• Low cost;</li> <li>• Provide relative changes of cerebral blood flow velocity</li> </ul> Limitations: <ul style="list-style-type: none"> <li>• Only measure basal arteries;</li> <li>• Low spatial resolution;</li> </ul>
PET	Biochemistry activity	Strengths: <ul style="list-style-type: none"> <li>• Provide whole brain scan at high spatial resolution;</li> </ul> Limitations: <ul style="list-style-type: none"> <li>• Invasive (request inject radioactive tracer);</li> <li>• Low temporal resolution;</li> </ul>
EEG	Electrophysiological activity;	Strengths: <ul style="list-style-type: none"> <li>• Non-invasive;</li> <li>• High temporal resolution;</li> </ul> Limitations: <ul style="list-style-type: none"> <li>• Low spatial resolution;</li> </ul>
fMRI	Blood oxygenation	Strengths: <ul style="list-style-type: none"> <li>• Non-invasive;</li> <li>• High spatial resolution;</li> <li>• Provide whole brain scan at high spatial resolution;</li> <li>• Highly reproducible and reliable;</li> </ul> Limitations: <ul style="list-style-type: none"> <li>• Discomfort of scanning environment;</li> <li>• Susceptible to motion artifacts;</li> <li>• Moderately expensive;</li> <li>• Merely reflect changes of de-oxyhemoglobin concentrations;</li> </ul>
(f)NIRS	Blood oxygenation	Strengths: <ul style="list-style-type: none"> <li>• Non-invasive;</li> <li>• Compatible with other modalities;</li> <li>• Safe and easy to set up;</li> <li>• Provide changes in oxy- and deoxy-hemoglobin concentrations;</li> </ul> Limitations: <ul style="list-style-type: none"> <li>• Merely cerebral cortex instead of deep structure;</li> <li>• Contaminated by the extracerebral hemodynamics;</li> </ul>

have limitations in terms of spatial and temporal resolution, safety and cost (33). A comparison of neuronal imaging techniques was shown in **Table 1**. PET has a limited temporal resolution, which fails to assess the transient changes of brain activities such as spindles or slow waves, and it has radiation stemming from the injection of radioactive isotopes. The high noise and restricted requirements of the fMRI environment limit the utilization of bedside monitoring, and the high cost is not suitable for routine monitoring. Regarding the indices detected by kinds of neuroimaging modalities, the cerebral hemodynamics underlying the regional tissues and blood components are different due to the different detection

principles. fMRI is based on the principle of blood oxygen level-dependent (BOLD), which derives a change in local deoxy-hemoglobin resulting from the paramagnetic properties of deoxy-hemoglobin. It provides the mapping of neuroimaging of the entire brain. However, the change in HHb detected by fMRI can only reflect the change in the relative concentration of HHb before and after the event of interest. TCD provides a way to measure cerebral blood flow velocity in the basal brain arteries, which lacks the evaluation of the other parts of the brain. PET can measure the blood flow and glucose metabolism in the brain according to the injected radioactive tracer isotope. Moreover, the decay time of tracers was short, which could not realize the bedside sleep monitoring all night. NIRS is simple to set up and compatible with other techniques, such as EEG, and fMRI. It is not constrained by the environmental restrictions, such as fMRI or PET suffered from. NIRS has been validated against other neuroimaging modalities confirming that cerebral hemodynamics derived from NIRS correlated and were in sufficient agreement with the results derived from TCD, fMRI, PET, etc. (35–37). Although the deep tissue illumination depth is limited by NIRS (~2 cm) and is contaminated by the interferences of the extracerebral hemodynamics, these limitations do not affect the development and utilization of NIRS in academic studies and clinical scenarios. Considering the advantages of the NIRS including flexible application scenarios, suitable for specific populations (infants), and detection signals reflecting cerebral cortex cerebral oxygenation, cerebral blood volume, and cerebral perfusion, NIRS is important and has potential application in monitoring sleep activities at the bedside.

The first area for the NIRS in the sleep filed is the application for sleep staging. Manuals of Rechtschaffen and Kales (R&K) were used as the guideline for visually scoring sleep since 1968. It divided sleep into seven distinct stages as follows: wake, stage 1, stage 2, stage 3, stage 4, stage REM, and movement time (38). Based on the R&K manual, the American Academy of Sleep Medicine (AASM) manual was proposed in 2007, as the standard guidelines for terminology, technical specifications, and scoring rules for sleep-related phenomena. According to the manual of AASM which was suitable for both adults and children, five sleep stages are defined (i.e., wakefulness (W), non-rapid eye movement (NREM) stage 1, stage 2, stage 3, and rapid eye movement (REM) (39). NREM stage 3 represents slow wave sleep (SWS) or deep sleep and is equivalent to the stage 3 and stage 4 of R&K. The scoring of each stage is based on the scoring rules for sleep-related phenomena, which correlate with changes in physiological signals, such as EEG, EOG, and EMG (40). One of the most apparent features of these phenomena is the variation in EEG waves. Previous functional neuroimaging studies have proved that the EEG rhythms underlying phasic events within specific sleep stages are associated with the activation or deactivation of corresponding cerebral regions (32). Because the increase and decrease of neural activity during sleep are accompanied by changes in cerebral oxygen demand and cerebral oxygen supply, this change can be reflected by the fluctuation of the NIRS signal. Continuous NIRS measurement contributes to a better understanding the interaction in cerebral

blood volume (CBV), cerebral blood flow velocity (CBFV), and cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) (41).

The second important research area of NIRS is related to sleep disorders. Sleep apnea syndromes have been associated with medical complications such as pulmonary and arterial hypertension, cardiovascular disease, excessive daytime sleeping, fatigue, morning headaches, and increased risk of cerebral infarction (42, 43). Three categories, obstructive, mixed, and central sleep apnea, are classified based on the criteria of respiratory events (44). Recognized as a major health concern, obstructive sleep apnea (OSA) syndrome is a chronic disease characterized by repeated partial or complete upper airway obstruction that leads to chronic intermittent hypoxia and sleep fragmentation during the night (45). OSA is associated with neurocognitive impairment, as the report that cognitive functions are altered in patients with OSA (46). OSA is also an independent risk factor for stroke (47). Hence, OSA-induced brain consequences have been of growing interest in the past few years (48). Moreover, continuous positive airway pressure (CPAP) therapy is used as a proper method to reduce the occurrence of OSA, however, it is necessary to determine its quantitative effectiveness. Therefore, it is important to understand the changes in the cerebral autoregulation mechanism under pathological conditions and the improvement in cerebral autoregulation during CPAP therapy.

## HEMODYNAMIC SIGNAL VARIATION IN HUMAN SLEEP

Studies investigating the dynamic features of cerebrovascular perfusion and neurovascular coupling with synchronized detection of PSG and NIRS initiated in the 1990s. Hoshi and Livera first used NIRS to assess cerebral blood flow (CBF) and the cerebral oxygen metabolic rate (CMRO<sub>2</sub>) during nocturnal sleep and investigate the effect of hypoxemia and bradycardia on cerebral hemodynamics in preterm infants (49, 50). Regarding the investigation of cerebral hemodynamics during sleep, specific sleep events, that is, sleep stages and apneic events, annotated by the gold standard PSG or experienced clinicians, can serve as an instructor. Relevant cerebral hemodynamic features can then be extracted from the synchronous NIRS signals. The cerebral hemodynamic and oxygenation changes among different sleep events expressed as the changes of HbO<sub>2</sub>, HHb, tHb, HbD, and several derivatives (i.e., TOI, StO<sub>2</sub>, and FTOE), yield important brain activation information during sleep. The diagram of the application of NIRS is shown in **Figure 2**. A significant number of studies are dedicated to investigating the characteristic changes in cerebral hemoglobin concentration associated with sleep stages and sleep disorders. For regular sleep, researchers compared the cerebral hemodynamics among different sleep stages using grand averaged values of the specific sleep stages and investigated the transient hemodynamic patterns during stage transitions. The investigation of the short-term performance of NIRS signals may yield inconsistent results compared to the grand averaged method. Additionally, NIRS acted as an auxiliary tool to monitor the occurrence of sleep disordered

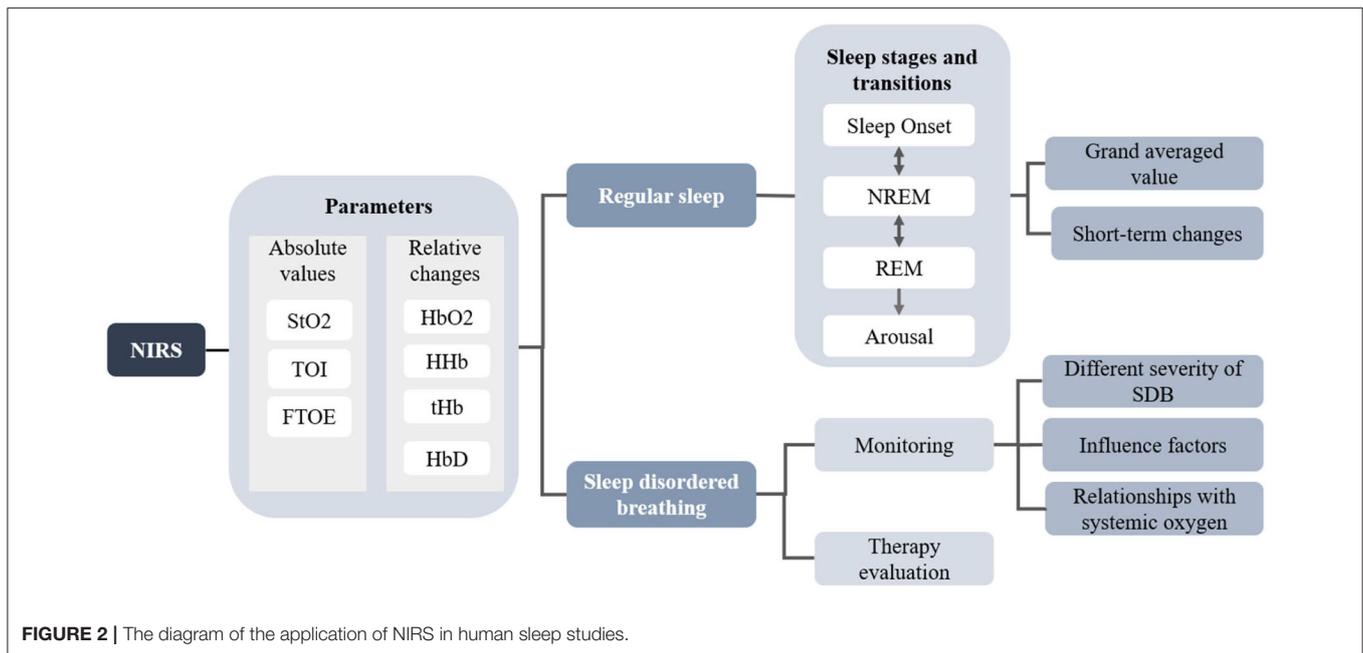
breathing and as an auxiliary method to evaluate the treatment efficiency. According to the two main applications of NIRS in the sleep field, the studies investigating the fluctuation of cerebral hemodynamics are divided into the following two sections.

## Cerebral Hemodynamics in Regular Sleep Staging

In earlier studies, the limited sampling rate of NIRS provided the opportunity to investigate the overall trend of sleep changes. The temporal trend of hemoglobin concentration changes provided us with basic information regarding hemodynamic changes during a sleep procedure. With the advancement of NIRS technology, the sampling rate has gradually increased, and multi-channel devices can simultaneously analyze changes in different brain regions. The increased sampling rate provided more detailed information about the phasic event within specific sleep stage [e.g., the transitions between light sleep (LS) and slow wave sleep (SWS) during NREM]. An example (34) showing the changes of cerebral hemodynamics during the transition between different sleep stages was shown in **Figure 3**. During the signal pre-processing procedure, the awake state before sleep was used as a baseline in the NIRS study, and the changes in HbO<sub>2</sub> and HHb detected by the CW-based system during sleep indicated the fluctuation of cerebral hemodynamics relative to the baseline. The specific changes in the NIRS signal in response to the distinct sleep stages were introduced as follows.

The sleep stage transition from wakefulness to sleep is usually accompanied by a subjective experience of self-awareness reduction. According to the temporal trend of NIRS signals, a decreasing trend in HbO<sub>2</sub> and tHb, and an increasing trend in HHb was visually detected upon transitioning from wakefulness to sleep (50, 51). The results using grand averaged values of wakefulness and sleep were consistent with the visual inspection of the temporal trend during the initiation of sleep, showing larger values in HbO<sub>2</sub> and tHb, and smaller values in HHb after entering sleep (34, 52–54). In the perspective of short-term changes in cerebral hemodynamics, NIRS has the capability to acquire transient changes in HbO<sub>2</sub> and HHb during sleep stage transitions. Synchronized and parallel decreases in both HbO<sub>2</sub> and HHb at a resolution of 5 s constructed the Switch Points after the points of Scored Sleep Onset (55).

With the progress of sleep stage, the sleep stages entered into NREM from wakefulness. The transitions between LS and SWS were exhibited during NREM. The grand averaged temporal values and power in the frequency domain presented suppression in SWS compared with other sleep stages (i.e., W, LS, and REM) (34, 56). An asymmetric change in terms of the short-term performance between LS and SWS exhibited a larger increase in HbO<sub>2</sub>, a decrease in HHb during the transitions from SWS to LS, and relatively constant state during the transitions from LS to SWS (34). In contrast, one study reported by Zhang using the grand averaged method presented increases in HbO<sub>2</sub> and tHb during the SWS period compared to LS (54). Excluding the comparison of the NIRS parameters between LS and SWS during NREM sleep, significant details regarding neuronal activity were found during the NREM period. Cyclic alternating pattern (CAP)



**FIGURE 2 |** The diagram of the application of NIRS in human sleep studies.

is a typical neuronal activity during the NREM state (57), which exhibits a fluctuation between phase A and phase B within one min (58). Phase A comprised the following three subtypes: A1, A2, and A3. The oscillations of hemodynamic signals corresponding roughly to the repetition rate of the CAP cycles were produced by alternating phases A and B, which exhibited a significant increase in HbO<sub>2</sub>, HHb, and tHb during phase A, especially in subtype A3, and thereafter decreased during the same cycle in B (58).

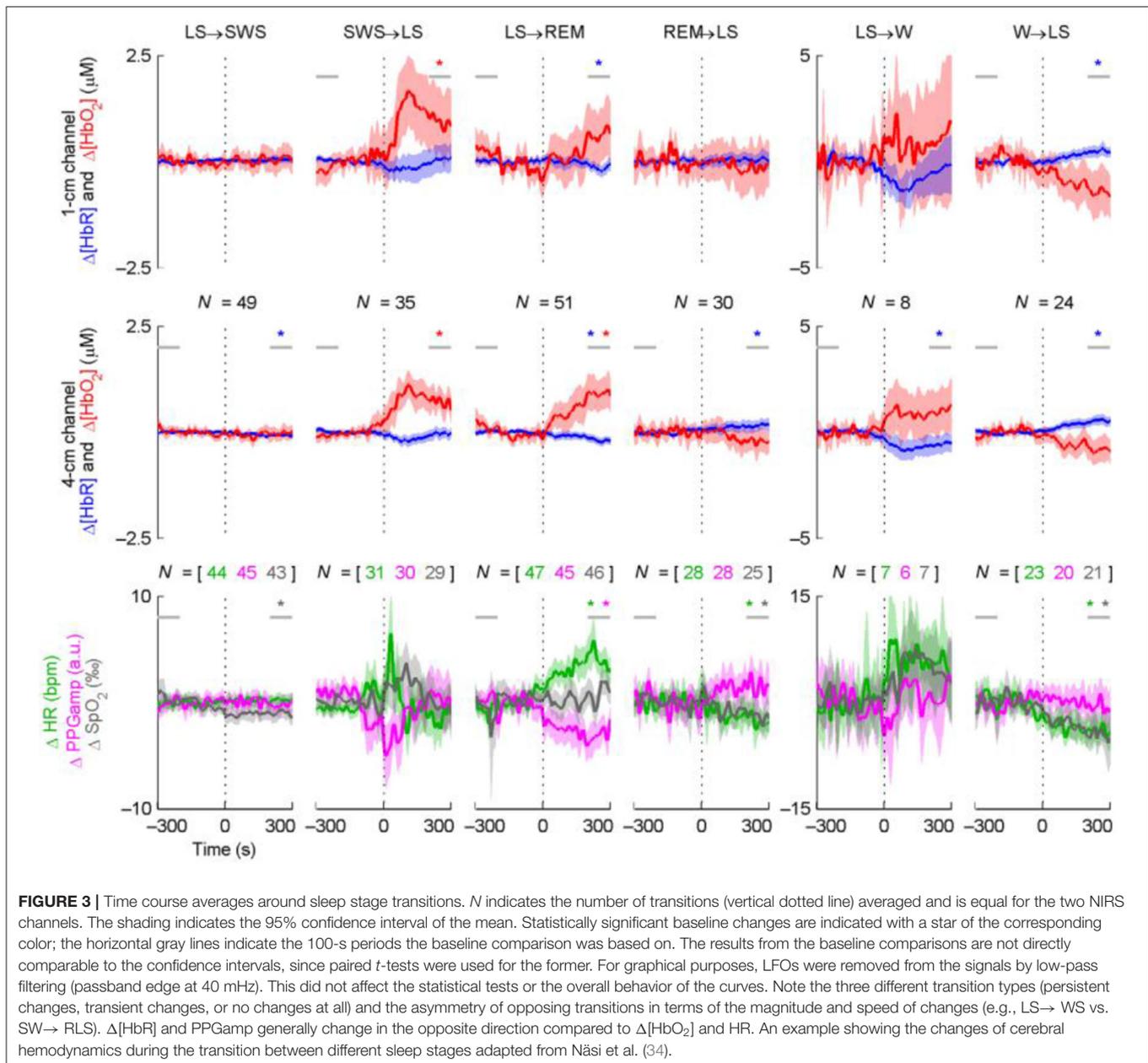
When entered into REM, transitions between REM and NREM recurrently appear. During the transition from NREM to REM, increases in HbO<sub>2</sub> and tHb concomitant with a gradual decrease in HHb were observed in both studies evaluated by grand averaged values and transient changes (34, 50, 52, 53). Opposite and smaller changes with increased HHb and a slight decrease in HbO<sub>2</sub> and tHb were observed during the transition from REM to NREM (34, 53). Significant differences in phase differences between HbO<sub>2</sub> and HHb existed across sleep stages (24). The phase differences were found to progressively increase as the sleep stages progressed from wakefulness to the deeper sleep stages, and returned to the baseline when entered into REM.

Arousal from sleep is an important protective response to life-threatening events. A distinct change in NIRS parameters compared to sleep onset, namely an increase in HbO<sub>2</sub> and tHb was observed for the sleep offset (55, 59). People also have the capability to wake up spontaneously at a desired time without receiving external stimuli. The increase in HbO<sub>2</sub> accompanied the decrease in delta power in the right prefrontal cortex ~30 min prior to self-wakening was shown, suggesting that the prefrontal cortex has the ability to estimate time (60).

TOI and StO<sub>2</sub>, the indicators for cerebral oxygenated saturation, were detected by spatially resolved spectroscopy (20). They provided absolute values instead of relative changes as

HbO<sub>2</sub> and HHb were detected by the CW-based NIRS system. Gradual decreases in TOI were exhibited as the sleep stages progressed from wakefulness to sleep, and from stage 1 to stage 2, as well as a reversed increase in TOI when entering REM from stage 2 (52). The temporal trend of StO<sub>2</sub> presented a positive slope during the entire night using linear regression (59). In the short-time perspective of sleep transitions, the direction of changes in StO<sub>2</sub> was the same as HbO<sub>2</sub> which presented decreases upon sleep onset and during transitions from REM to NREM and an increase during transitions from NREM to REM (59). A comparison of the changes in StO<sub>2</sub> between young adults and elderly subjects indicated that the StO<sub>2</sub> level was the same before sleep in both groups (53). However, it presented an opposite trend between the two groups after falling asleep. StO<sub>2</sub> decreased upon the sleep onset in the elderly group but increased in young adults. When the subjects went into a deeper sleep, a further decrease in StO<sub>2</sub> was observed in older subjects, whereas reversed changes were observed in the young adults.

Although studies regarding sleep in adolescents and adults have been conducted, no systematic comparison of the hemodynamic changes during sleep across different age groups has been made. Andreas et al. demonstrated that there was no significant difference in StO<sub>2</sub> between adolescents and adults (53). Additionally, preterm and term infants are special populations, because of the immature autonomic regulation of cerebral blood flow and rapid development of cranial nerves in premature and term infants, the sleep structure and sleep events are different from those of adolescents and adults, such as the discontinuous EEG activities during quiet sleep (61). NIRS is particularly suitable for the study of infants because other methods cannot routinely be used without sedation (25). In preterm infants, an initial decrease in HbO<sub>2</sub> with an opposite change in HHb and subsequent



increased HbO<sub>2</sub> were coupled with the burst of EEG activities during quiet sleep (62). Additionally, based on the studies as measured by PSG, failure to arouse may be one of the reasons for sudden infant death syndrome (63). The NIRS study in preterm infants found that tHb, HbD, and TOI, as well as heart rate and respiratory frequency remained constant during arousals (64). An investigation of the effects of sleep stage on cerebral hemodynamics in healthy term newborns found that cerebral FTOE, HbO<sub>2</sub>, and tHb increased significantly from active sleep to quiet sleep accompanied by a moderate decrease in HHb and reversed changes in tHb and HbO<sub>2</sub> during the transitions from quiet to active sleep (65).

## Cerebral Hemodynamics in Sleep-Disordered Breathing

The investigation of cerebral hemodynamics in patients with sleep-disordered breathing syndromes provided significant clinical information regarding the effects of respiratory events on cerebral oxygenation. Typically, a pulse oximeter is used as the clinical method to evaluate sleep apnea in terms of the oxygenation by considering the changes in arterial oxygen saturation. Considering that changes in oxygenation may differ between tissues due to the difference in sensitivity to hypoxia, various studies have been conducted to assess the cerebral hemodynamic changes during nocturnal and daytime napping apneic episodes in age groups ranging from infancy to the elderly.

Most studies have focused on infants and adults, and few have focused on children and the elderly. We summarized the studies into the four categories below.

### Cerebral Hemodynamics Under Different Sleep-Disordered Breathing Events

The impact of cerebral hemodynamics on different sleep disordered breathing events has been investigated and compared in this review. The sleep-disordered breathing events include periodic breathing, apnea (central apnea, mixed apnea, and obstructive apnea), restless leg movement, differing severity of respiratory events, and breath hold test.

Due to the immature mechanism of autonomic regulation and the rapid development in the brain, newborns have a high risk of hypoxic cerebral injury and subsequently poor long-term neurodevelopmental outcomes, especially in ex-preterm infants (66). Period breathing is a unique and prevalent syndrome in pre-term and term infants compared to children or adults. Although the periodic breathing was benign and would disappear accompanying the maturation of the central nervous system with age (67), researchers concentrated on whether the periodic breathing would trigger fluctuations in cerebral hemodynamics and the patterns of cerebral oxygenation in response to periodic breathing. The results indicated that cyclical oscillations in cerebral hemodynamics were related to the occurrence of periodic breathing (67, 68). An increase in HHb and decreases in HbO<sub>2</sub>, HbD, StO<sub>2</sub>, or TOI were found in term and preterm infants (68–70); however, the changes in tHb were heterogeneous increasing in preterm infants and decreasing in term infants during periodic breathing (67, 68). Furthermore, Jenni et al. analyzed the causal relationship between periodic breathing and the fluctuation of CBV (67). They speculated that both periodic breathing and cyclical variations in CBV were mediated by the central nervous system, disproving the driving relationships between the two phenomena.

Previous studies have investigated changes in NIRS parameters associated with different types of apnea. Significant oscillations of cerebral hemodynamics with declined HbO<sub>2</sub>, tHb, and TOI/StO<sub>2</sub> accompanied by a synchronized increase in HHb were observed during the initiation of apneic episodes, and reverse changes of hemoglobin indices accompanied by inconsistent changes in tHb were obtained after the termination of apnea (71–79). An example of the changes of NIRS indices in response to apnea is shown in **Figure 4**. The fluctuation in NIRS was associated with the occurrence of apnea (77). However, NIRS in patients with OSA shows minor hemodynamic changes during apneic episodes and a subsequent significant decrease in tHb and HbO<sub>2</sub> at the termination of the respiratory event (80). When comparing the effects of central, obstructive and mixed apnea on tHb in term and pre-term infants, all three types of apnea induced the following four distinct patterns of tHb: no change, isolated increase, isolated decrease, and both (81). It revealed that the OSA had the strongest impact on tHb compared to the other two types in the case of decreased tHb. Consistent results were found in adults and elderly subjects showing that subjects with OSA or severe SDB have more significant changes in NIRS (82, 83). Restless legs syndrome

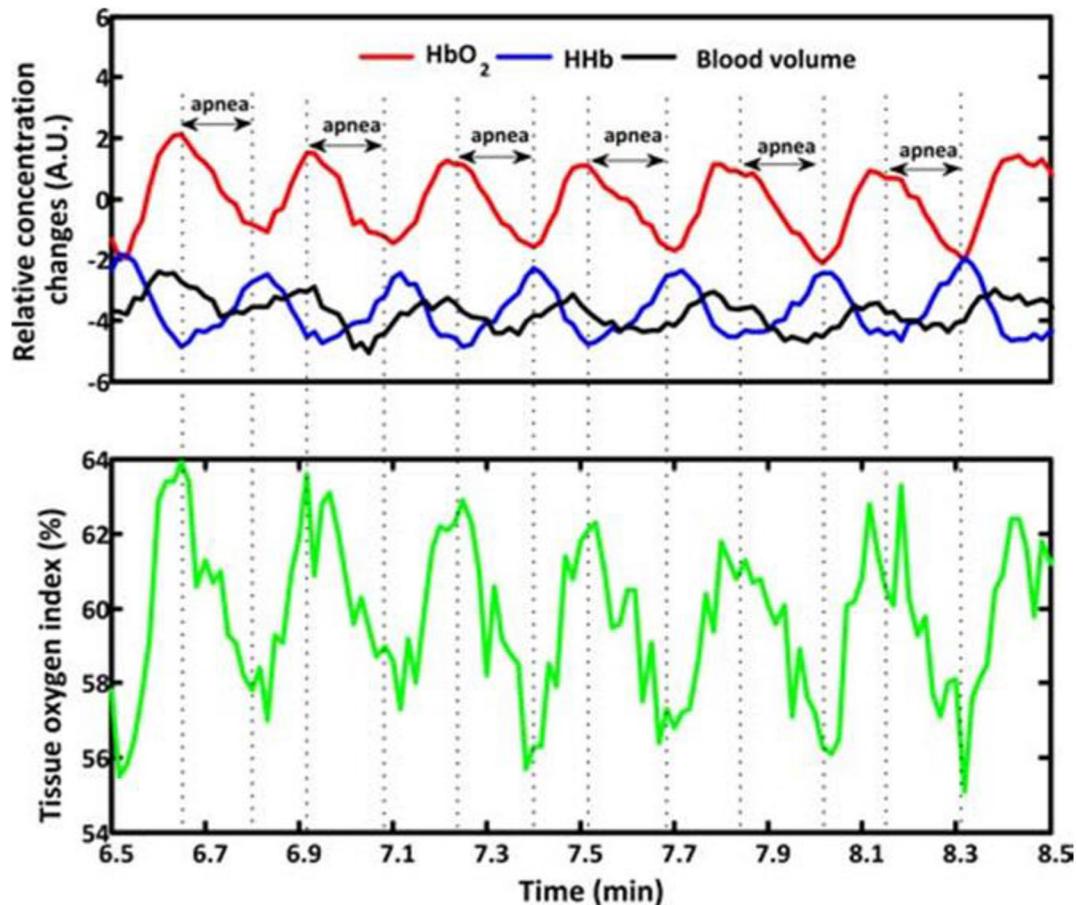
(RLS) with periodic limb movement during sleep is one of the common sleep disorders. An increased HbO<sub>2</sub>, tHb, and heart rate accompanied by heterogeneous changes in HHb were observed during RLS (79, 84). Owing to the distinct patterns in heart rate and CBV induced by OSA and RLS, the authors speculated that the occurrence of OSA and RLS were regulated by a different nervous system.

The change in NIRS is not only related to the type of apnea but also the severity and duration of apnea and desaturation degree of the pulse/arterial oxygen saturation. The severity of apnea was assessed using apnea-hypopnea index (AHI), which would affect the changes in NIRS (82). The threshold of AHI causing significant changes in cerebral hemodynamics was 30/h (82). A negative correlation was observed between StO<sub>2</sub> and AHI (85), and the changes in the NIRS parameters significantly correlated with the duration of apnea in adults with OSA (75). Studies of different populations have found that various degrees of respiratory disorders have no apparent effect on TOI, FTOE and tHb (74, 86). However, a short duration of apnea accompanied by significantly reduced SpO<sub>2</sub> results in significant changes in NIRS parameters (87), which validated that the severity of apnea cannot be evaluated by the isolated duration of apnea (88).

In previous studies, breath-holding in healthy subjects has been used to simulate the process of apnea and investigate the difference in the NIRS indices between breath-holding and apnea. Compared with the breath-holding group, the fluctuation magnitude of NIRS parameters during sleep was larger and the averaged absolute values in HbO<sub>2</sub>, tHb, and StO<sub>2</sub> were significantly smaller in patients with OSA (77, 85). The canonical pattern with an increased HbO<sub>2</sub> and decreased HHb was shown in healthy subjects during the breath-holding experiment (89). Although two distinct patterns of cerebral hemodynamics were observed in OSA patients, one presented a similar pattern to healthy subjects (80, 90) and the other was a reversed pattern when compared to healthy subjects during breath holding (89).

### Physiological Factors Affecting Cerebral Hemodynamics During Sleep-Disordered Breathing

The consequence of changes in cerebral oxygenation during sleep-disordered breathing may be caused by complex physiological interactions. A few of studies discussed the factors which would affect cerebral oxygenation, including bradycardia, age, and sleep stages. Bradycardia, which is the main physiological parameter, is related to cardiac output and affects the oxygen delivery (91). Researchers have found that bradycardia with hypoxemia induces significant decreases in tHb and StO<sub>2</sub> (49, 92). The changes in NIRS correlated with age. Premature and term infants with periodic breathing and apnea presented a decrease in TOI with increased age, and the reduction of TOI was greater in premature infants compared to full-term infants (69, 70, 93). Furthermore, the active sleep and spine position increases the incidence of periodic breathing and apnea in infants (69, 93). A positive correlation was found in StO<sub>2</sub> with mean arterial pressure (MAP), arterial blood oxygen saturation (SaO<sub>2</sub>),



**FIGURE 4** | Typical fragments of cerebral hemodynamics during baseline measurements measured from Subject 1. The apnea events are marked by dash lines and double arrows. BV, HbO<sub>2</sub> and HHb changes are expressed in arbitrary units (A.U.), as the mean value of first 60-s measurements was set at 0. During apnea events, the BV, HbO<sub>2</sub> and tissue oxygen index signals show parallel decrease that are opposite to the HHb which increases after the initiation of apnea. Then an increase of BV, HbO<sub>2</sub> and tissue oxygen index, while a decrease of HHb appears after the termination of apnea. An example of the changes of NIRS indices in response to apnea adapted from Zhang et al. (78).

age, and REM sleep stage in children with sleep-disordered breathing (71). Especially, NREM would augment the decline of TOI caused by SDB in children (73, 74), whereas the decline in NIRS was more pronounced during REM in adults (75, 76).

### Comparison and Relations Between Cerebral Oxygenation and Systemic Oxygenation

As an indicator of peripheral capillary oxygen saturation detected by pulse oximeter and an indicator of cerebral oxygenation assessed by NIRS, the relationships between SpO<sub>2</sub> and NIRS during apneic episodes attracted the attention of the researchers. Both techniques are sensitive to hypoxia induced by the pause of respiration, and the changes in SpO<sub>2</sub> and cerebral oxygenation were found to be weakly correlated with small changes but strongly correlated in the case of for larger changes and severity SDB (77, 82, 94). The changes in SpO<sub>2</sub> were several seconds later than NIRS (76, 77). A SpO<sub>2</sub> threshold was found in preterm infants during apneic episodes, where

SpO<sub>2</sub> lowered to <85% would trigger a decrease in cerebral blood volume (95). Researchers have also quantified the changes in SpO<sub>2</sub> and StO<sub>2</sub>, which reported that the desaturation of SpO<sub>2</sub> was twice the reduction in StO<sub>2</sub> (92, 94). There was no significant difference in CBV change for apnea with the same degree of desaturation at different durations of apnea. CBV decreased significantly when the apnea lasted for an extended period of time and was accompanied by a significant decrease in SpO<sub>2</sub> (87). Notably, the values of StO<sub>2</sub> remained above 60% for most infant subjects, despite having suffered severe SpO<sub>2</sub> hypoxemia (92). The synchronized change in arterial oxygen saturation and cessation of airflow, as assessed by the apnea/hypopnea index (AHI) was the basic information for diagnosing apnea. The finding that AHI calculated by the StO<sub>2</sub> was larger than that calculated by SpO<sub>2</sub> (91), as well as the distinct patterns in the brain and muscles responding to intermittent hypoxia (96) verified that brain tissues were more sensitive to reduction in oxygen delivery induced by apnea.

## The Evaluation of Treatment Efficacy of Positive Airway Pressure Therapy

Continuous positive airway pressure (CPAP) is the standard treatment for OSA. In addition to investigating the hemodynamic changes during sleep disorders, NIRS has the capability of evaluating the treatment effects of CPAP on obstructive sleep apnea. The occurrence of apneic episodes was accompanied by fluctuations in cerebral hemodynamics. The majority of studies have investigated the changes in cerebral tissue hemoglobin indices (HbO<sub>2</sub>, HHb, tHb) with and without CPAP or non-invasive ventilation (NIV) treatment in patients with OSA to evaluate the effect of treatment (72, 77, 78, 89, 97). Consistent reductions in the fluctuations of HbO<sub>2</sub>, HHb, and TOI were found in children and adults during CPAP. A sufficient treatment outcome and correcting cerebral oxygenation, further indicates that effective treatment may improve neurodevelopment. There was a significant improvement in behavioral problems and academic attention in patients with NIV treatment (72). Although efficient CPAP would suppress the fluctuation of NIRS and the occurrence of SDB, CPAP withdrawal after 2 weeks of therapy would result in the recurrence of OSA (97).

## DISCUSSION OF THE PHYSIOLOGICAL AND PATHOLOGICAL MECHANISMS IN SLEEP ASSOCIATED WITH NIRS

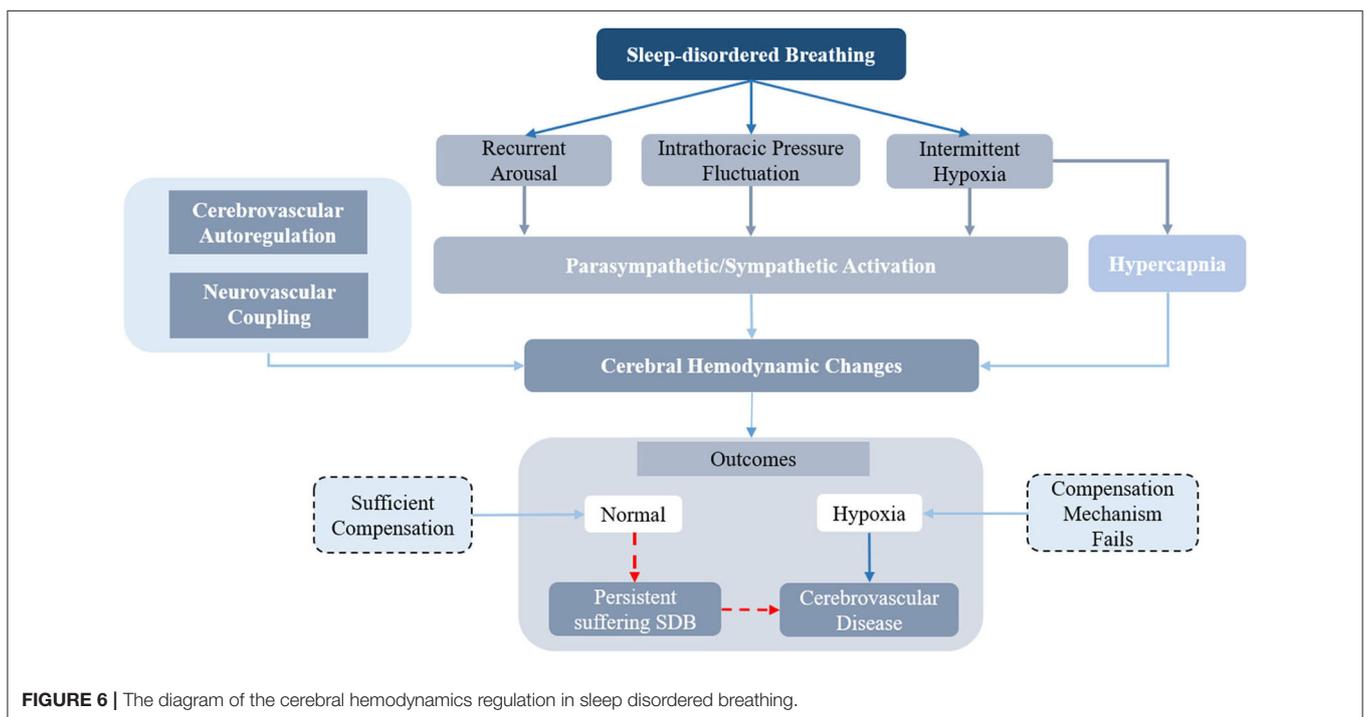
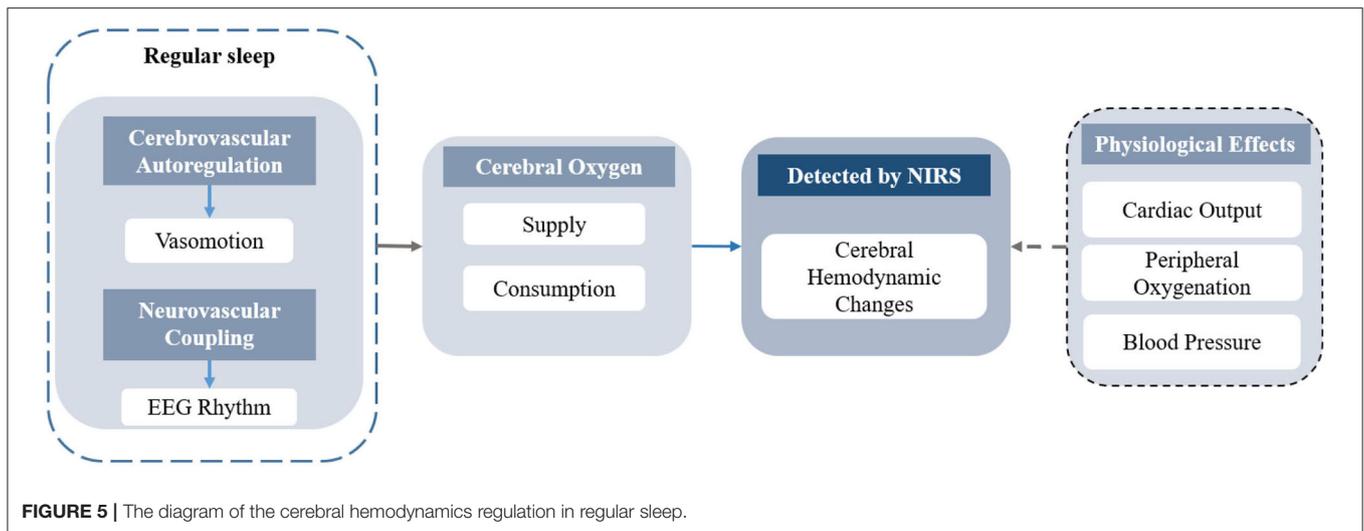
The fluctuation of hemoglobin concentrations, induced by changes in sleep states or sleep disorders, reflects the different functional cerebral activities related to neuronal activities and physiological changes. A diagram of the cerebral hemodynamic regulations during regular sleep is presented in **Figure 5**. During regular sleep, the fluctuations in NIRS were coupled with the EEG rhythm and influenced by the interaction of the complex cerebrovascular regulatory mechanisms (98, 99). Although fluctuations in heart rate, blood pressure, and pulse oxygen saturation were reported during the sleep transitions (100, 101), the effect of these physiological parameters on the changes in cerebral hemodynamics needs further investigation (99). Based on neurovascular coupling, the changes in cerebral hemodynamics detected by NIRS reflect the interaction between cerebral oxygen consumption and cerebral oxygen supply. For instance, the occurrence of REM and arousal accompanied by the generation of dreams and the awakening of consciousness, respectively, indicate enhancement in neural activity, corresponding to the increases in HbO<sub>2</sub> and tHb. With the reduction of self-awareness, the consistent decrease in HbO<sub>2</sub>, tHb, and TOI/StO<sub>2</sub> during sleep onset reflect the reduction of CBF and CBV.

In pathological conditions involving sleep-disordered breathing, the physiological changes induced by respiratory events will affect the cerebral hemodynamic changes and increase the risk of cerebrovascular disease. The flowchart of the cerebral hemodynamic regulation system in sleep disordered breathing is shown as **Figure 6**. The recurrent arousal, fluctuation of intrathoracic pressure, and intermittent

hypoxia induced by the occurrence of apneic episodes would further influence parasympathetic/sympathetic activation. The complex physiological and pathological mechanisms, such as neuro-vascular coupling (80), sympathetic activity (90), and cerebral autoregulation (82, 92, 96) are responsible for the hemodynamic changes during the occurrence of sleep-disordered breathing. A sufficient compensating oxygen supply to the brain could protect the brain from hypoxia caused by apnea or periodic breathing. However, the persistence of SDB or severe apnea would disturb the regulation of cerebral hemodynamics and eventually lead to cerebrovascular disease. The cerebrovascular autonomic regulation mechanism and the regulation mechanism between peripheral oxygenation and cerebral oxygenation are presented below.

## Discussion of Cerebrovascular Autonomic Regulation Mechanism

The cerebrovascular autonomic regulation mechanism includes a wide range of cerebral blood flow regulation mechanisms, such as the neurovascular coupling. Neurovascular coupling is fundamental in NIRS studies; it is considered as the increase in cerebral blood flow induced by localized brain activity, and the increased blood supply is larger than the concomitant increase in oxygen consumption, resulting in a local increase in hemoglobin oxygenation (102). Therefore, the typical pattern of the NIRS signal responding to the neuronal activity presents an increased HbO<sub>2</sub> with a decreased HHb, as shown in **Figure 1**, and the hemodynamic changes lag behind the neuronal activities (103). The neurovascular coupling mechanism provides sufficient explanation for the changes in blood flow and oxygenation stemming from neuronal activity during sleep periods. The increased HbO<sub>2</sub> (i.e., REM and sleep offset) may be due to an increase in oxygen supply, determined by the increased cerebral blood flow, bringing hyper-oxygenated hemoglobin into the brain (62). In contrast, the decreased HbO<sub>2</sub> (i.e., sleep onset and NREM) may be the consequence caused by the reduction of cerebral blood supply or maybe the reason for the decline in cerebral metabolism (54, 55). However, an inconsistent study indicated that the decrease in HbO<sub>2</sub> during sleep onset reflected an unbalanced increase in cerebral metabolism and cerebral blood flow rather than a decline in cerebral metabolism (50). Both oxygen consumption and oxygen supply have an influence on the HHb concentration (104, 105), resulting in inconsistent variations with low amplitude. On the other hand, the time lags of cerebral hemoglobin concentrations behind the EEG rhythm fluctuations (52, 98) were consistent with the causal relations underlying neurovascular coupling. However, the EEG-NIRS time lag differs between sleep studies. Several studies have determined that hemodynamic changes are present prior to visible EEG activity (53, 54, 62). This may be due to the fact that PSG measurements with limited spatial information of EEG reflect global low-frequency synchronization of neural activity (106), and that NIRS has the capability of obtaining the local hemodynamics (11, 107), thus, the local hemodynamics occurring before global neural activity may be a hemodynamic marker of the measured cortex (54). Spontaneous oscillations



of HbO<sub>2</sub> and HHb are associated with regulated vasomotion (25, 26, 56, 108), and the fluctuations of HbO<sub>2</sub> and HHb induced by SDB are partially related to cerebral vasomotor activity. Under normal circumstances, cerebral vessels regulate regional blood flow to accommodate changes in cerebral perfusion and arterial oxygenation, thereby maintaining the cerebral oxygen reserve at a fairly stable level (109). Vasomotion was identified by rhythmic oscillation in the tone of the blood vessels. Hemodynamic oscillations could reflect the vasomotion indirectly by the associated hemodynamic parameters such as blood flow, HbO<sub>2</sub>, and HHb (31, 110, 111). Cerebral vasomotion-induced hemodynamic oscillations are related to

sleep stages, reflecting the variations in endothelial, neurogenic, and myogenic components of vasomotion detected by NIRS (56). In pathological conditions, the sustained elevation of cerebral blood flow is unique to the brain, thereby compensating for hypoxia and protecting the brain from anoxic injury (112). The cerebral vasodilatation induced by an increase in arterial carbon dioxide and subsequent decrease in cerebral resistance vessels may raise the cerebral blood volume, which reflects the increase in tHb (77, 110). The increased cerebral blood flow induced by hypopnea efficiently prevents the brain from severe hypoxia, and the pattern of cerebral hemodynamic changes is analogous to the canonical hemodynamic response to functional brain

activities; namely, an increased HbO<sub>2</sub> and tHb accompanied by a decreased HHb. However, the increased blood flow may not always be sufficient to compensate for oxygen desaturation, especially in patients with severe obstructive apnea (75, 77, 82). In patients with severe OSA, the failure of cerebral compensatory mechanisms cannot prevent the brain from hypoxia. The loss of cerebrovascular autoregulation is likely responsible for the inability of the brain to increase HbO<sub>2</sub> in response to apnea events in patients with moderate to severe OSA. Additionally, similar patterns of cognitive performance between patients with OSA and patients with multi-infarct dementia verified that OSA is responsible for neuropsychological dysfunction (113). Therefore, the fluctuation of cerebral hemodynamics caused by apnea could affect normal sleep and disrupt cerebral autoregulation functions during sleep (78).

Sympathetic activity plays an important role in regulating cerebral hemodynamics in pathological conditions. Intrathoracic pressure swings and recurrent arousals induced by OSA would lead to increased sympathetic activation, and subsequently affect cortical cerebral vessels (114). The regulation between the cerebral blood volume and the whole-body blood volume was mediated by the sympathetic/parasympathetic system. Considering the composite of all information from the changes in cortical vascular LFO amplitude in animal and human models (115, 116), the increased cortical LFO amplitude was associated with increased sympathetic activation induced by hypoxia. However, there was no significant difference in the LFO amplitude between OSA patients and healthy controls during the resting state, suggesting that the influence of sympathetic activity induced by obstructive apneic episodes may be more pronounced during nocturnal sleep than during wakefulness. Contrary to the increase in tHb after the initiation of apnea events, several studies have indicated a decline in tHb during apneic episodes, especially in severe OSA (78). The decrement would be terminated by arousal, which was mediated by sympathetic activity and, subsequently, restored the airflow, resulting in an increase in cerebral CBV and HbO<sub>2</sub> and a concomitant decrease in HHb (90).

## Discussion of the Regulation Mechanism Between Peripheral Oxygenation and Cerebral Oxygenation

The changes in peripheral oxygenation induced by sleep events reflect changes in arterial blood oxygen saturation (SaO<sub>2</sub>) and SpO<sub>2</sub>. The relationship between peripheral oxygenation and cerebral oxygenation was well-represented during regular and disordered sleep the regulation was associated with diverse factors, such as different populations. Accordingly, considering all these factors contributes to an all-around discussion on the topic of regulation.

Normal cerebral circulation relies on an intact cerebral autoregulation system to maintain adequate cerebral blood flow. In general, the values of SaO<sub>2</sub> changed with sleep stages, specifically, it presented a decline when falling asleep (117–119). Once the SaO<sub>2</sub> values fell below the normal level, regional vasodilatation would be evoked to compensate for desaturation. However, if cerebral blood flow increases, increased

cerebral blood flow showing increased cerebral oxygenation can compensate for desaturation in SaO<sub>2</sub> (73). The interaction between peripheral oxygenation and cerebral oxygenation is more prominent in pathological conditions. A majority of studies have found that the amount of decreased TOI is less than the reduction in SpO<sub>2</sub> during apnea or hypopnea (72, 96, 97), which could be sufficiently explained by the complex mechanisms for modulating cerebral circulation. On the other hand, changes in the NIRS signal are a mixture of arterial (~10%), capillary (~20%), and venous (70%) contributions. The changes, predominantly depending on the veins, may result in a different response to the changes in oxygen supply/consumption compared to pulse oximetry. In addition to the incommensurate fluctuations in magnitude between SpO<sub>2</sub> and cerebral hemodynamics, there is also a significant correlation between the changes in SpO<sub>2</sub> and hemodynamics. A significant correlation between the changes in peripheral SpO<sub>2</sub> and cerebral hemoglobin indices during sleep in OSA patients indicated that cerebral oxygenation was dependent on systemic oxygen delivery.

Moreover, the balance between peripheral and cerebral oxygenation was disrupted in several populations, for example preterm infants and the elderly (120, 121). The lower baseline SaO<sub>2</sub> levels in the elderly would more likely suffer from mild-to-moderate hypoxemia and further influence the levels of cerebral oxygenation. It can also lead to more serious conditions such as cognitive impairment in the elderly (122). In preterm infants, the degree of cerebral oxygen desaturation was associated with a reduction in SpO<sub>2</sub> induced by apneic episodes. The decline in cerebral oxygenation would affect the immature brain, which may cause irreversible brain damage. Apart from considering the significant reduction in SpO<sub>2</sub> during apnea or hypopnea, researchers have suggested that a larger decline in TOI in response to central and obstructive events and periodic breath holding in children and infants compared to SpO<sub>2</sub> indicated a better sensitivity of NIRS in evaluating cerebral hypoxia compared to peripheral oxygenation (74). Therefore, the use of NIRS as an adjunct to PSG would improve the ability to diagnose sleep apnea and better detect the effects of sleep apnea (72, 96, 97).

## DISCUSSION OF THE EXPERIMENTAL DESIGN AND SIGNAL PROCESSING

The studies in section Hemodynamic Signal Variation in Human Sleep summarized the cerebral hemodynamic changes during sleep under different sleep events. There have been inconsistent results that would obfuscate the real cerebral oxygen supply in the course of sleep, resulting from the differences in experimental design, individual variation, and signal processing methods. The techniques that were used in the investigation of cerebral hemodynamics during sleep and the potential reasons for the discrepancy of the results are presented below.

### Discussion of Experimental Design

Commercial NIRS devices are mainly based on the following three techniques: continuous wave (CW), time domain (TD), and frequency domain (FD) system. Among the three techniques,

the FD and TD methods require assessment of the path-length, thus obtaining the absolute changes in hemoglobin concentrations (123). The CW-based method cannot fully determine the optical properties of tissue, and therefore only relative changes of hemoglobin concentrations can be detected (11). Furthermore, the spatially resolved spectroscopy could obtain the absolute values, i.e., TOI and StO<sub>2</sub>. The structure of instruments differs between studies, resulting in cerebral hemodynamic activation variance.

Most sleep studies used NIRS to detect cerebral hemodynamic changes over the forehead. Neuroimaging and electrophysiological studies have indicated that the mediation of sleep and dreaming requires the participation of various cerebral regions, including the brainstem, thalamus, basal forebrain, and so on (124). The prefrontal cortex is implicated in executive control, personal expression, and planning complex cognitive behavior (125). In particular, the function of the prefrontal cortex is sensitive during sleep, which indicates early changes in the transition from wakefulness to sleep and exhibits a deactivation during NREM compared with waking (32, 126, 127). Additionally, the prefrontal cortex contributes to controlling the timer rate, attention allocation, and temporal memory processing (128). Therefore, the investigation of the prefrontal hemodynamics may provide more information regarding slow specific temporal activation patterns during sleep. Furthermore, the hair on the scalp significantly attenuates light and reduces the signal-to-noise ratio. In neonates, the temporal areas are rather flat and most sensitive to hypoxia during growth. Premature infants, particularly, are susceptible to brain impairment on the left side of the temporal areas. Although it is convenient for the long-term monitoring of cerebral hemodynamic changes in the prefrontal region during sleep, the different patterns and activation in different cerebral regions (51, 52, 98) indicate that it is necessary to monitor different cerebral regions using multiple channels.

Studies investigating cerebral hemodynamics during normal sleep were conducted in both nocturnal sleep and daytime napping. To shorten sleep latency, subjects were restricted to sleep deprivation for several hours from their regular sleep time, especially in daytime experiments (55). Subjects experienced 1–2 sleep cycles due to the limited duration of experiment. Additionally, the guidelines for sleep stage scoring are different, and the rules of R&K and the manual of AASM were commonly used. Comparing the two guidelines for sleep stage scoring, the major differences involve the definition of sleep–wake transition, sleep state terms, and the recording method (40). The different sleep structures for the sleep stages may lead to discrepant results. Furthermore, the syndrome or severity of sleep disorders including snoring, periodic breathing, sleep apnea (obstructive sleep apnea, central apnea, and mixed sleep apnea), and the inclusion criteria of subjects (i.e., AHI value and the reduction of SpO<sub>2</sub>), differ between studies. Heterogeneous patients with sleep disorders accompanied by abnormal cardiac function or blood pressure may further influence cerebral hemodynamics (71, 96).

NIRS, as a potential bedside monitoring tool, shows an advantage in assessing the hemodynamic changes of the cerebral cortex. However, one major disadvantage of NIRS is that the

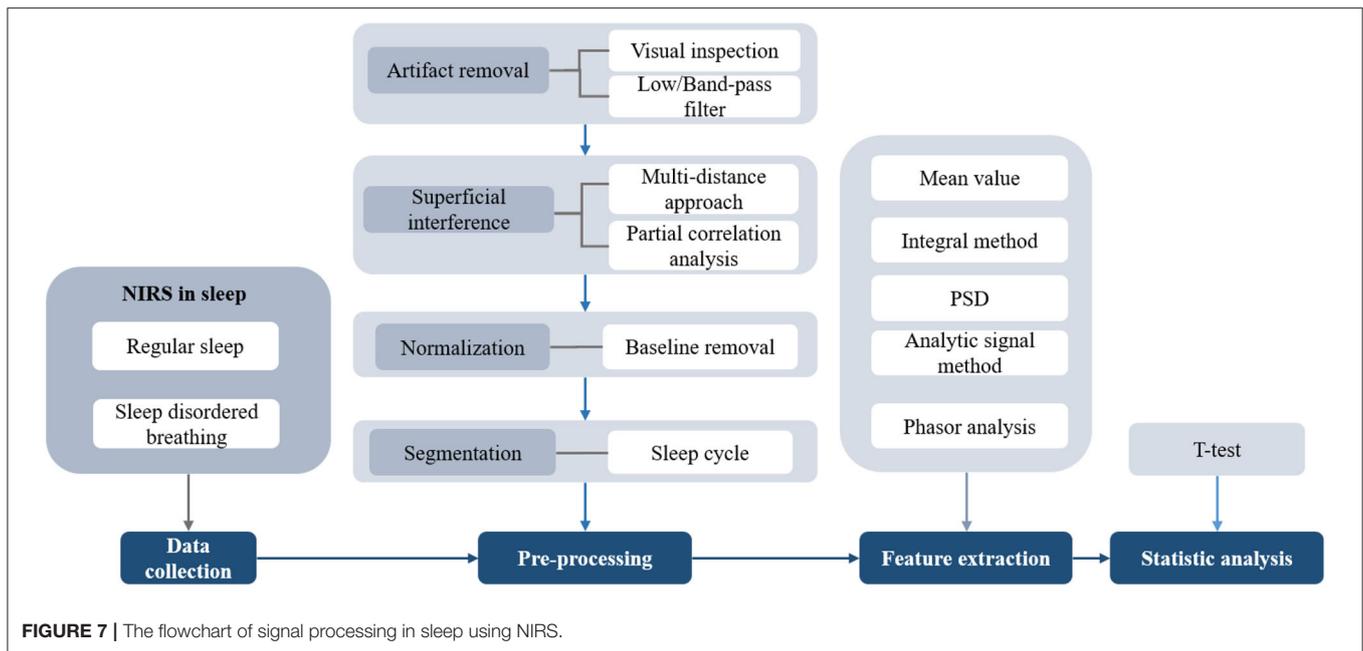
changes in cerebral hemodynamics are significantly affected by the extracerebral tissue contaminants (such as the scalp). The prevalent method used to reduce scalp hemodynamics is performed using a multi-detector at varying distances from the source. The short distance primarily scalp hemodynamics, and the other distance measures both the scalp and cerebral hemodynamics. NIRS signals obtained from a short distance subtracted from the larger one receive a corrected NIRS (129). Although the predominant changes in the NIRS signal are the result of changes in cerebral hemodynamics, the extracerebral hemodynamic changes affect the outcome to some extent (130).

## Discussion of Signal Processing Method

The standard procedure for signal processing during sleep is shown in **Figure 7**. Motion artifacts are often a significant component of the measured NIRS signals. The magnitude of the motion artifacts is typically significantly larger than that of the NIRS signals. To properly interpret the changes in cerebral hemodynamics, motion artifacts should be detected and removed (131). In general, the following two distinct methods are used to eliminate or reduce motion artifacts: a method with an additional input (e.g., inertial measurement unit) and a method that does not require additional sensors (e.g., Wiener filter and wavelet-based filtering). Details regarding the motion artifact correction techniques can be found in previous studies (132). In sleep studies using NIRS, motion artifacts are usually removed directly with visual inspection, and subsequently, low-pass or band-pass filters are used to extract the signals of interest.

One of the disadvantages of NIRS is that, the detected NIRS signals mixed with the scalp blood flow signals could interfere with cortical hemodynamic signals of interest. A common method eliminates the interference of superficial tissue by using the multi-distance approach (56). Different patterns in HHb were found between the two distances of NIRS signals (58). Moreover, the non-correlation between NIRS changes and MAP changes represent the intact cerebrovascular autoregulation (133). One proposed method is partial correlation analysis (98). The relationships between EEG and NIRS could be better reflected after eliminating the interference of MAP on cerebral hemodynamics. Most studies have focused on the changes in HbO<sub>2</sub> mainly due to the apparent variation in response to brain activities. Additionally, the investigation of the changes in tHb, StO<sub>2</sub>, and TOI was prevalent in clinical situations, as the robust property for motion artifacts and visualized the absolute values (23). The parameters commonly used and the proportion of the NIRS parameters in the sleep studies are summarized in **Table 2**.

In data preprocessing, the standard of data segmentation is different. Sleep time included sleep procedures during the entire night, daytime napping, or only included the first sleep cycle (52, 54). In the time series analysis techniques, the NIRS signal was first normalized to obtain the relative changes according to the principle of CW-based NIRS. Then, the baseline corrected data were divided into multiple segments of interest with the time windows. The window length ranged from several seconds to several minutes. The data were analyzed by averaging segmentations of NIRS or the transient activation time-locked to the shift of EEG burst. To compare the significant changes in the



**TABLE 2 |** List of the most reported parameters in sleep studies using NIRS (12) and the proportion of their utilization.

Abb.	Parameter	Interpretation for physiology	Proportion
HbO <sub>2</sub>	Oxygen hemoglobin concentration	Changes in cerebral hemodynamics and blood oxygenation	++
HHb	De-oxygen hemoglobin concentration	Changes in cerebral hemodynamics and blood oxygenation	++
tHb	Total hemoglobin concentration	Marker for cerebral blood volume	++
HbD	Hemoglobin oxygenation index (HbO <sub>2</sub> -HHb)	Changes of cerebral oxygenation	-
TOI	Cerebral tissue oxygenation index	Absolute value to assess oxygenation	+
StO <sub>2</sub>	Regional cerebral oxyhemoglobin saturation	Absolute value to assess oxygenation	+
FTOE	Fractional tissue oxygen extraction	Ratio of cerebral oxygen consumption to delivery	-

++: prevalent used. +: commonly used. -: less used.

difference of cerebral hemodynamics in response to sleep events, *t*-tests and analysis of variance were used. Thus, the selection criteria of the time windows cause inconsistent results, such as the synchronized and reciprocal changes of HbO<sub>2</sub> and HHb at sleep onset using short-term analysis and the mean values of sleep stages, respectively (54, 55). The insufficient signal-to-noise ratio (SNR) stemming from the limited sleep segmentations or subjects may not be able to extract a representative pattern for specific sleep events. Furthermore, the sleep stages are labeled based on the PSG results, which require an analysis using an epoch of 30 s. The inconsistent result may be due to the limited time resolution caused by the annotation (55).

There was no standardized method for extracting the cerebral hemodynamic parameters. The integral method which calculates the integrals of changing curve in NIRS, proposed by Pizza (82), is a useful tool for analyzing the NIRS signals, which considers the duration of the event and suppresses any artifact

interferences (79). In addition to the temporal trends in cerebral hemodynamics, studies using the power spectral density (PSD), analytic signal method and phasor analysis provide a better way to interpret the intrinsic hemodynamic oscillations during sleep (24, 56). The phasor representation, which decomposed the changes in hemoglobin concentrations into CBV and CBFV, provided a new way to investigate the physiological origin of the oscillations in HbO<sub>2</sub> and HHb (24).

## FUTURE PERSPECTIVES

The benefit of combining EEG with fNIRS during sleep in neuroscientific research and clinical applications provided a comprehensive understanding of the interaction between the nervous system and cerebral vasculature. The investigation of spontaneous cerebral hemodynamic oscillations with NIRS provides novel information regarding the neurophysiological

features of sleep. In this paper, we reviewed previous sleep studies that utilized NIRS in both regular sleep cycles and pathological conditions with sleep disorders. However, the relationship between oxygen supply, oxygen consumption, and oxygen perfusion in a specific sleep state is still unknown. Regarding the complex interactions between CBF, CBV, CBFV, and cerebral perfusion pressure, conflicting conclusions on the causality between oxygen metabolic rate, oxygen consumption, neuronal activity, and hemodynamic changes should be further investigated.

During regular sleep cycles, the fluctuation of cerebral hemodynamics was correlated with the transitions of sleep stages (fluctuation in specific EEG-wave). NIRS utilization in sleep studies provides insight into functional neuroanatomy by comparing the changes between different sleep stages and transient fluctuations during sleep transitions benefiting from the relatively higher temporal resolution compared with other neuroimaging techniques. The significant fluctuation of cerebral hemodynamics during the awakening period increased the risk of cerebrovascular disease due to the immature brain autoregulation ability in premature infants and the decline of autonomic regulation ability in the elderly. Therefore, bedside monitoring is particularly important for these illumination depth of populations. The disruption of normal nocturnal sleep induced by apnea leads to fluctuations of cerebral hemodynamics, which jeopardizes the cerebral autoregulation mechanisms and ultimately increases the risk of cerebrovascular disease. Fortunately, CPAP treatment can reduce or eliminate airway obstruction, thereby suppressing cerebral hemodynamic fluctuations. Therefore, NIRS has potential application prospects in the monitoring and treatment evaluation of sleep disorders. Additionally, studies investigating impaired cerebral blood flow and cerebrovascular reactivity associated with sleep disorders should be noted and used for developing a personalized effective CPAP treatment utilizing NIRS.

Although NIRS is a promising tool for investigating cerebral hemodynamics during sleep, there are also limitations that need to be further explored. The experimental design is essential for acquiring robust signals, but it differs among existing studies. Neuroscientific research and clinical trials were conducted

during daytime napping or nocturnal sleep, and the population studied ranged from premature to elderly, and the sleep disorders ranged from mild to severe. In future experiments, the unification of the age of the populations and the severity of the disease, as well as the inclusion of an adequate number of subjects, should be considered.

Furthermore, the development of the brain during childhood is sequential (134) and the discrepancy results across cerebral regions, suggesting the significance of monitoring in multi-channels. The standardized method for signal processing is not well-established. Notably, the interference of the extracerebral hemodynamics on the NIRS signal needs to be considered when extracting cerebral hemodynamic responses. The traditional signal processing method for NIRS sleep is the study of the trend in NIRS signal changes. It is necessary to find effective methods for signal analysis and to extract efficient features. Additionally, the insufficient sampling rate of the existing instruments limits the potential role of low frequency oscillations of NIRS in investigating cerebral vasomotions, which play an essential role in regulating cerebral blood perfusion. Inspired by the multimodal neuroimaging utilized in studying and diagnosing pathologies (135) and the simultaneous EEG-NIRS measurements used in the context of BCI (136), the fusion of NIRS-EEG bimodal signals has potential applications in automatic sleep staging, automatic diagnosis of sleep disorders, and evaluation of therapeutic effects.

## AUTHOR CONTRIBUTIONS

HR, XJ, and KX reviewed the literatures and drafted the manuscript. CC, YY, CD, and WC revised and proofread the manuscript. All authors read and approved the final manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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