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Chapter

Vector-Based Approach for the Detection of Initial Dips Using Functional Near-Infrared Spectroscopy

Toshinori Kato

Abstract

Functional near-infrared spectroscopy (fNIRS) is a non-invasive method for the detection of local brain activity using changes in the local levels of oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb). Simultaneous measurement of the levels of oxyHb and deoxyHb is an advantage of fNIRS over other modalities. This review provides a historical description of the physiological problems involved in the accurate identification of local brain activity using fNIRS. The need for improved spatial and temporal identification of local brain activity is described in terms of the physiological challenges of task selection and placement of probes. In addition, this review discusses challenges with data analysis based on a single index, advantages of the simultaneous analysis of multiple indicators, and recently established composite indicators. The vector-based approach provides quantitative imaging of the phase and intensity contrast for oxygen exchange responses in a time series and may detect initial dips related to neuronal activity in the skull. The vector plane model consists of orthogonal vectors of oxyHb and deoxyHb. Initial dips are hemodynamic reactions of oxyHb and deoxyHb induced by increased oxygen consumption in the early tasks of approximately 2–3 seconds. The new analytical concept of fNIRS, able to effectively detect initial dips, may extend further the clinical and social applications of fNIRS.

Keywords: functional near-infrared spectroscopy, fNIRS, initial dip, phase, vector-based analysis, cerebral oxygen exchange, COE, oxyhemoglobin, deoxyhemoglobin

1. Introduction

Functional near-infrared spectroscopy (fNIRS) is a non-invasive method for the detection of brain activity using changes in the local levels of oxyhemoglobin (oxyHb), deoxyhemoglobin (deoxyHb), and total hemoglobin (total Hb) [1]. fNIRS imposes fewer physical restrictions on patients compared with positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), allowing investigators to measure and analyze cerebral circulation and metabolism while the patient walks or moves his/her upper body. Recently, studies showed that brain activity during rehabilitation [2] and car driving [3–6] may also be measured using fNIRS. In 1991, the first study of fNIRS utilizing localized changes in the levels

of oxyHb and deoxyHb was conducted by Kato and his colleagues at the National Center of Neurology and Psychiatry, Tokyo, Japan [1].

This study was the first to demonstrate that the activation of Hb in the human brain during photic stimuli was associated with increased levels of oxyHb, deoxyHb, and total Hb in the visual cortex. Of note, the measurements in the prefrontal cortex did not show clinically meaningful changes in the levels of these three indices. The original fNIRS technique was able to detect local activation of the brain during a task that is stronger than the signals during rest, by placing pairs of probes 2.5 cm apart on the scalp over the targeted cortex [7–9].

Thus, fNIRS solved the problem of oxygenation monitoring in NIRS [10, 11]. The measurement of targeted temporal changes in task-related activation markedly reduced data noise from the blood flow in the scalp at rest and from artifact-related bodily movement. Nowadays, more than 25 years later, statistical processing and mapping of changes in the levels of hemoglobin measured by fNIRS are used for the evaluation of brain activity.

The advantage of fNIRS over fMRI and other modalities is the ability to simultaneously and independently measure the levels of oxyHb and deoxyHb. Combined, these data may be used as indices reflecting changes in both blood volume and oxygenation.

However, the temporal resolution of fNIRS is fairly low on a 40–100 ms scale, compared with the underlying neural activity which is spanning from 1 to 3 ms of action potential firing and can be recorded extracranially using magnetoencephalography (MEG). MEG can be sensitive on subcortical activity in a case of large extent of activated neuronal assembly and spatial extent of activated cortical assembly [12, 13].

In slow voluntary movements of the self-paced index finger, the activity of the sensorimotor area was detected before 4.5 seconds of the pre-movement using electroencephalography (EEG) [14]. Consistent with the findings of EEG, early deoxygenation of 3–4 seconds prior to the movement of the finger was observed in the sensorimotor area using fNIRS [15]. Presently, research on simultaneous measurements using fNIRS and EEG is becoming an effective means of brain-computer interface [16].

In addition, a disadvantage of fNIRS is the low spatial resolution (5–10 mm) of the activation mapping of the cortical surface compared with those obtained from fMRI and PET. Research combining the use of fNIRS, fMRI, and MEG for source localization is currently ongoing [17]. These combination studies have advantages in temporal and spatial mapping of brain function.

A response involving increased and decreased levels of oxyHb and deoxyHb, respectively, has been considered the model of canonical activation in numerous studies utilizing fNIRS. However, the actual frequency of the occurrence of canonical activation, the most suitable index or indices for the differentiation between the center of activation and the surrounding area, and the associated degree of probability remain to be investigated. Following canonical activation, the rates of change in the levels of oxyHb and deoxyHb are not constant and may differ according to the task. Wylie et al. [18] performed a qualitative differentiation between two types of canonical activation according to the increase/decrease in the levels of total Hb. The investigators of that study identified four additional patterns of increase and decrease in the levels of oxyHb, deoxyHb, and total Hb that do not correspond to canonical activation.

Presently, the detection of the spatiotemporal characteristics of brain activity using fNIRS remains suboptimal. This fundamental limitation in evaluating brain activity may lead to misdiagnosis. fNIRS research is particularly challenging in the prefrontal cortex, responsible for complex higher functions. In areas of the brain

with clear localization of cerebral function (i.e., primary motor or visual cortices), it is possible to verify the accuracy of fNIRS data. However, in the human prefrontal cortex, there is currently no clear understanding of the localization of the more complex functions, and thus, the verification of the reliability of fNIRS data in this area remains a challenge.

Studies have attempted to bolster the reliability of fNIRS in the prefrontal cortex by comparing data obtained from fNIRS and fMRI [19, 20]. However, because the mechanisms differ between the two modalities [21–24], even if conformity is found between fMRI and fNIRS data, the reliability of the results is not necessarily increased. Several problems have been pointed out. Considerable attention is required when analyzing with the index of oxyHb alone. In the prefrontal region, task-dependent data noise in the oxyHb response (increased levels) resulting from skin blood flow has been reported [25, 26]. In 2011, an article criticized the use of NIRS in the clinical diagnosis of psychiatric disorders as being insufficiently supported by scientific evidence [27]. In mental illness studies, the actual localization of increases in the levels of oxyHb is not clear [28], and therefore, measurements of oxyHb levels cannot be linked to a specific brain activity.

Furthermore, analytical challenges in the field of fNIRS have been reported. This review introduces new composite functional indices incorporating ratios of changes in the levels of oxyHb and deoxyHb, along with a novel vector-based fNIRS method [29, 30]. This vector-based approach can be used to visually and quantitatively evaluate combinations of changes in the levels of oxyHb and deoxyHb as new indices. It was useful to classify variations in the levels of hemoglobin in response to neural activity, using combinations of changes in the levels of hemoglobin. It was effective especially when the signal change is small such as initial dips. Initial dips are the hemodynamic reactions of oxyHb and deoxyHb induced by increased oxygen consumption in the early tasks of approximately 2–3 seconds [31, 32]. The vector-based approach could improve the sensitivity of fNIRS in the detection of brain activity both temporally and spatially through recognition of the initial dips from the skull to hemodynamic responses [33–36].

In addition, this review discusses challenges with data analysis based on a single index, advantages of the simultaneous analysis of multiple indicators, and recently established composite indicators.

2. NIRS until 1990

Prior to the development of fNIRS, NIRS was used mainly for monitoring cerebral oxygenation. Changes in tissue oxygen saturation are accompanied by simultaneous changes in cerebral blood volume. Using NIRS, Jöbsis [37] reported hypocapnia and a reduction in cerebral blood volume during human hyperventilation. In addition, NIRS was used to prevent hypoxia through monitoring newborn and premature infants [10, 11]. Of note, NIRS had also been used to investigate the brains of animals [38–40].

In 1990, Takashima et al. [41] used NIRS to examine patients with probes placed 5 cm apart from each other. This study was based on the original concept of the research conducted by Jöbsis [29]. The results of this study showed reductions in the levels of oxyHb, deoxyHb, and total Hb in the prefrontal area during hyperventilation. Until 1990, research on NIRS did not target the specific localized brain function of the cerebral cortex. The technique was merely used to observe changes in the levels of hemoglobin (task-related and at rest), without specific spatial identification.

Hypocapnia is known to cause global changes in the scalp and the entire brain. Hence, the changes reported during hyperventilation did not constitute proof of
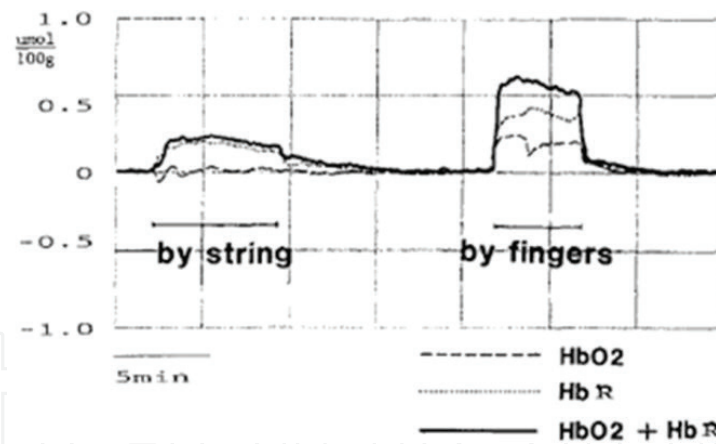
Figure 1.
Changes in the levels of HbO2 (oxyhemoglobin, oxyHb), HbR (deoxyhemoglobin, deoxyHb), and HbO2 + HbR (total hemoglobin, total Hb) with neck compression [40]. Comparisons between tasks had been reported at that time, unlike responses derived from specific cortical activity.

functional local brain activity. These early studies of hyperventilation suggested that blood volume was reduced in the region supplied by the external carotid artery, which distributes blood mainly to the scalp and muscles outside the skull. In brain death, in spite of the absence of blood flow through the internal carotid artery, the blood flow distribution through the external carotid artery remains unimpaired—an observation known as "the finding of the hollow skull" [42]. Early data obtained using NIRS data were affected by this blood flow from areas of the scalp supplied by the external carotid artery and the veins.

In addition, probes placed in the prefrontal area of seven healthy patients in a task of pressure for 1 minute on the jugular vein reported increases in the levels of oxyHb, deoxyHb, and total Hb [41]. These results were consistent with those obtained from an animal study (**Figure 1** [40]), indicating task-related hemodynamic changes prior to 1990. Importantly, the presence of a task does not differentiate fNIRS from NIRS.

Until 1990, NIRS had not been considered a tool for the identification of specific cortical activity. In the usage of NIRS at the time, there was no technique that data could be obtained selectively from a site on the cortex located directly under a site sandwiched between irradiation and detection probes, let alone evidence of brain activity. The near-infrared light paths and the range and depth of irradiation were unknown. Moreover, the influence of factors such as the external carotid artery was undeniable. Early NIRS did not associate changes in the levels of Hb with localized brain activity and was unable to clearly distinguish between signals derived from the external carotid artery or the veins and those derived from the cortex.

3. Conception and first experiment of fNIRS in 1991

fNIRS was developed in 1991 [1, 7–9, 31] as a functional imaging method using NIRS to detect local brain activity accurately. This was achieved by identifying changes in the levels of Hb in different areas of the brain at rest and during a task. It was necessary to initially demonstrate that NIRS was able to detect localized brain activity to establish fNIRS. The selection of an experimental task and the settings of the probe were the key factors in this process. In the search for a task, lesion studies and PET studies were reviewed to identify a small part of the brain that could be clearly stimulated and measured from the frontal lobe. A multifocal increase in regional cerebral blood flow (CBF) had been reported in a mental arithmetic task in the frontal lobe [43]. Furthermore, mental arithmetic tasks to induce an autonomic

nerve stimulus had been used to show the possibility of blood volume changes in the region supplied by the external carotid artery [44, 45]. Dyscalculia was not sufficiently localized, because it occurs in multiple sites of the frontal and temporal lobes from injury, etc. [46].

The cerebral metabolic rate of oxygen (CMRO2) was shown to increase by approximately 10% in a study using thinking tasks [47]. However, when compared with that observed at rest, this change in regional cerebral blood volume (CBV) was not significant. Exercise tasks produced side effects from movement of the probes and systemic circulation. In addition, a PET study had shown that blood flow increased in both the primary motor area of the frontal lobe and the nearby supplemental motor areas [48]. Overall, the confirmation of localization in the frontal lobe was challenging. The primary auditory cortex is located inside the Sylvian fissure, and there was no certainty that near-infrared light would be able to reach the site and reflect back to produce meaningful data.

In summary, an experiment designed to confirm that localization was possible using fNIRS required a task meeting the following conditions:

1. It should not stimulate the autonomous nervous system.

2. It should not induce global activation of the brain.

3. It should avoid the region supplied by the external carotid artery (possibility of changes in the volume of blood).

4. It should not involve pressure on the carotid artery.

5. It should not require bodily motion.

6. It should not target brain activity from the frontal or temporal lobes (possibility of movement of the scalp or muscles).

7. It should induce brain activity within a well-defined site.

According to these conditions, a suitable task would be one that stimulates the primary visual cortex, located in the occipital lobe and supplied with blood mostly from the posterior cerebral artery. An earlier study had reported an increase in CBF in the visual cortex with a task of 7.8 Hz photic stimulation [49]. A major question at that point was the following: "What kind of response in terms of local Hb levels would be obtained in a photic stimulation experiment using NIRS?" Other, more practical problems included the use of external light with the NIRS equipment and the irradiation of the stimulus light to the patient wearing the probes. However, these problems were resolved during the experiment. As shown by PC darkness in **Figure 2**, the influence of extraneous light could be eliminated in actual experiments.

In 1991, the time course of responses arising from changes in the local levels of oxyHb, deoxyHb, and total Hb remained unknown. Therefore, it was necessary to perform measurements on different sites that would demonstrate brain activity and a null response. It was thought that the detection of varied responses from different sites in response to a given stimulus could demonstrate the localization of function.

In the actual experiment, photic stimulation (8 Hz) was delivered using a photosonic stimulator (Nihon Kohden Co., Japan) from the front and at the height of the patient's line of sight for 5 minutes. As **Figure 2** shows, the activation observed in the visual cortex during the photic stimulus was associated with increased levels of oxyHb, deoxyHb (slightly), and total Hb. No changes were observed in the
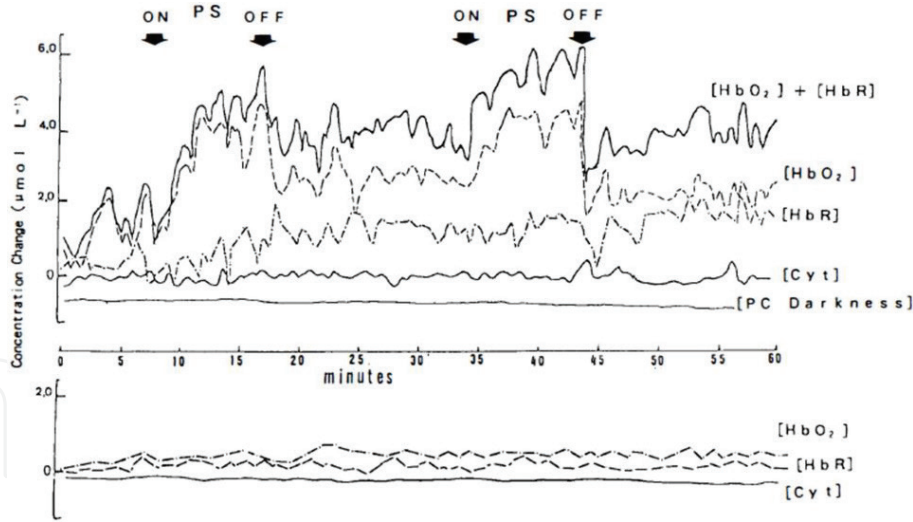
Figure 2.
Changes in the levels of oxyhemoglobin (oxyHb), deoxyhemoglobin (deoxyHb), total hemoglobin (total Hb), Cyt (Cytochromea$_3$), and PC darkness (photon counting darkness) measured over the occipital surface (above) and the frontal surface (below) prior to, during, and after photic stimulation in a healthy adult. Background noise from extraneous light was monitored as PC darkness. The data show spatial (site-dependent) and temporal (task on/off) differences in response [7, 8].

prefrontal cortex following photic stimulation. These findings demonstrated that fNIRS is able to detect spatial and temporal information (i.e., different hemody-namic responses), depending on the site and the presence or absence of stimulation.

Today, fNIRS is widely used for tasks or in environments difficult for other modalities. Although the above list of requirements for task selection may seem outdated, the first four conditions are still required to distinguish between local activity and global change. The difference between local activity and global changes is still determined by the presence or absence of a response, limitation to a specific site, and dependence on the duration of the task.

4. Probe placement on the skull

A fundamental part for fNIRS is probe placement. As **Figure 3A** shows, Jöbsis [37] used infrared transillumination and optical computed tomography (CT) to create images of blood flow distribution at rest corresponding to brain structures. He estimated the optical path length of the human head to be 13.3 cm [37]. In addi-tion, he stated that an interprobe distance of ≥4.25 cm would allow the detection of data from the brain tissue rather than the scalp (**Figure 3B** [50]). Although the diffused and reflected light used today had already replaced infrared transillumina-tion, subsequent research on cerebral oxygenation monitoring [41] continued to use this setting (distance between probes ≥4.25 cm).

During the design of the first investigation using fNIRS, MRI showed that the distance between the scalp and the primary visual cortex was <1 cm in neonates and <2 cm in adults and demonstrated the gentle curvature of the skull [51]. The shape of the skull permitted further reduction in the distance between the probes (**Figure 3C**) and improved the detection of activity in the cerebral cortex.

In the study, placement of the probes 5 cm apart revealed only a slight increase in the levels of oxyHb. When the distance between the probes was shortened to 4 cm, the increase in the levels of oxyHb became more pronounced. At an interprobe distance of 2.5 cm, a transient dip in the levels of oxyHb was observed. This effect occurred simultaneously with the initiation of the stimulus, followed promptly by an
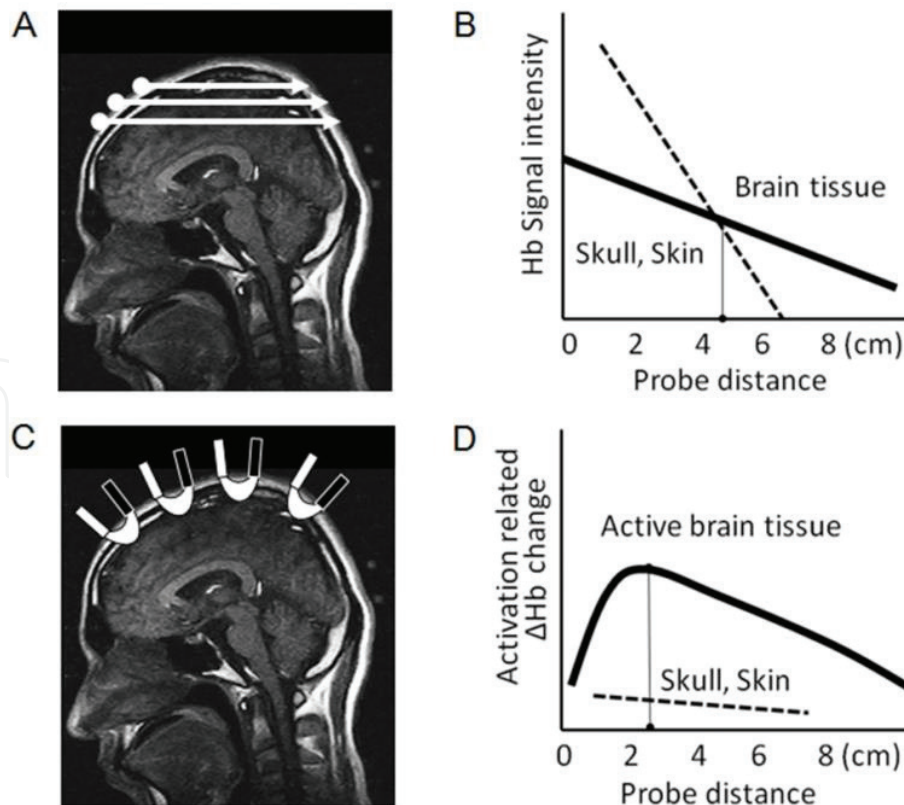
Figure 3.
(A) Conceptual schema of optical computed tomography performed by Jöbsis illustrated on a magnetic resonance imaging (MRI) image (revision from [37]). (B) Relationship between the signal intensity of hemoglobin and the distance between the light entry and exit locations, using the reflectance technique according to the origin of the reflected light (revision from [50]). (C) Conceptual schema of functional near-infrared spectroscopy illustrated on the same MRI image. (D) Relationship between the activation-related change in the levels of hemoglobin and the distance between the light source and detector [31].

increase in the levels of oxyHb, faster peak latency, and a post-stimulus undershoot in oxyHb. At an interprobe distance of 1.0–1.5 cm, there was either no response at all or the total amounts of Hb remained unchanged while small mirror-image changes were observed, namely an increase and decrease in the levels of oxyHb and deoxyHb, respectively. These mirror-image changes may have been derived from either the scalp (where metabolism does not increase) or from vascular changes in the veins on the surface of the brain. From these findings, it was established that an interprobe distance of 2.5 cm provided the most robust results (**Figure 3D**).

Based on this empirical hypothesis, the area on the scalp corresponding to the visual cortex that can be covered with two probes was considered to be 1.0 × 2.5 cm, as identified through sagittal MRI. Each pair of emitter and receptor probes was placed 2.5 cm apart vertically to prevent data noise from activity in the secondary visual cortex and the large vein running vertically through the sagittal sinus.

The movement of the probes outward by 1.0 cm impaired the detection of response in the pilot study. Thus, pairs of probes (channels) were placed within 1.0 cm of the target in the horizontal direction to ensure accuracy. This adjustment permitted the investigators to develop the concept of functional resolution (in this case 1.0 × 2.5 cm) for the identification of the precise area of response. The original NIRS apparatus used (NIRO 1000, Hamamatsu Photonics K.K., Japan), shown in **Figure 4**, had only two channels and 5-mm diameter optical fibers for the emission and reception of light with 8 × 8 mm contact surfaces.

The concept that the spatial resolution of fNIRS should be determined by the anatomy of the cerebral cortex and the range in which a response occurs was developed from this early research. To establish the desired resolution, the distance

between the probes and the distance between the channels should be controlled independently. The more recently available multichannel fNIRS devices have become essential for the localization of brain activity. Unless the interchannel distance is changed depending on whether the measurement target is deep or wide from the scalp, the likelihood of detecting a localized response is reduced. In newborns, the distance between the brain and the surface of the cortex is <1 cm [51, 52]. Thus, in infants, the distance between probes should be shortened to 1–2 cm [53], rather than being set at 2.5 cm apart [7–9, 54]. The 3-cm apart matrix array of probes commonly used in recent years [55, 56] cannot necessarily provide results corresponding to the actual distribution of brain function in usage not considering age and head size. Spatial identification may not be performed effectively when a probe "hat" with probes arranged without reference to the anatomy of the brain/scalp is used. Registration markers and MRI should be used to determine the localization of probe placement for each individual.

In late 1992, Hoshi and Tamura [57] reported findings from research using task-related NIRS. The investigators reported a calculation task which stimulated the autonomic nervous system with an interprobe distance of 4 cm. This protocol did not meet the requirements for either task selection or probe settings described earlier in this review, and thus, the method is not considered fNIRS. Villringer et al. [58] selected probe positions on the scalp with interprobe distances ranging from 4 to 7 cm. In 1993, Chance et al. [59] also performed the task-related NIRS experiments from the frontal skull. However, they were unable to demonstrate localization. Advances in techniques for the improvement of spatial resolution continued. The spatial resolution of the 3 cm^2 probe arrangement failed to provide detailed information regarding responses in the cortex [60]. Highly selective probe arrangements for establishing high-density measurement points have been reported (e.g., one with 10-mm channel interval and 25-mm probe interval [31, 32], and one with a center probe and surrounding probes [61]). Structural MRI has been used to evaluate the distance between the brain and the scalp [62]. Moreover, a method using diffuse optical tomography for removing signals on the scalp has been reported [63–65].

Of note, fNIRS has also been used in animal studies. The results have shown that measurement of fNIRS indices from the scalp with an interprobe distance of 4 and 8 mm was possible in the brain of rats [66] and cats, respectively. As **Figure 5** shows, using fNIRS (ETG-100, Hitachi Medical Co., Tokyo, Japan), an initial dip was able to

Figure 4.
The NIRO 1000 (Hamamatsu Photonics K.K., Japan) used in the first functional near-infrared spectroscopy experiment [7–9].
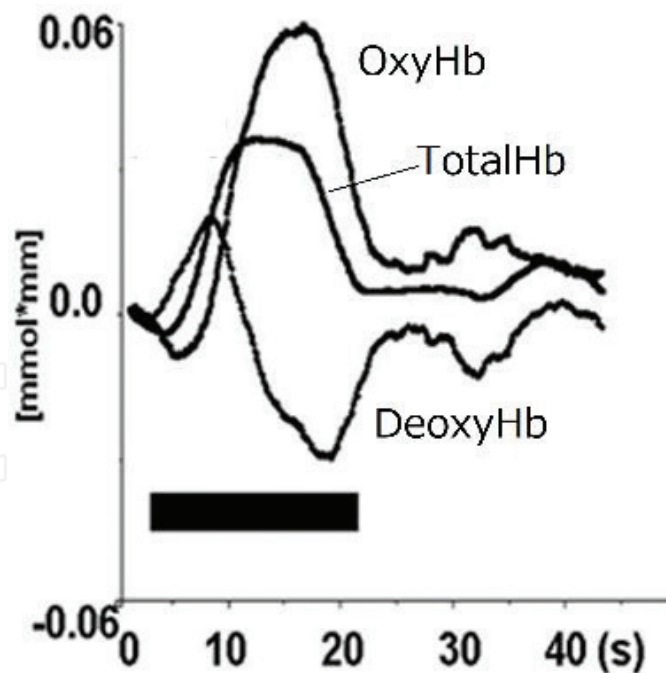
Figure 5.
Time series data of hemodynamic response showing an initial dip in the levels of total hemoglobin decreased through stimulation using light in the cat brain. A thick black line indicates stimulation using light.

measure hemoglobin indices in the visual cortex during photic stimulation from outside the skull of a cat. In particular, the fNIRS response pattern to photic stimulation was identical between the cat and the human brains [67, 68]. These animal studies suggested that it was possible to use fNIRS for the detection of activity in a 1–2 mm region of the targeting cortex from the scalp.

5. Brain function indices and oxygen responses in capillaries

Numerous current fNIRS devices measure the levels of oxyHb, deoxyHb, and total Hb independently. A new challenge is that spatiotemporal characteristics may vary in functional brain imaging depending on the index used, and this problem has not been widely recognized or studied. In 1991, Kato et al. reported increases in the levels of oxyHb, deoxyHb (slight), and total Hb in the primary visual cortex during photic stimulation. Subsequent studies using fMRI and fNIRS reported increases and decreases in the levels of oxyHb and deoxyHb, respectively, in motor and visual tasks [69–71]. These results were accepted as typical fNIRS responses and have been corroborated by numerous fNIRS studies [1].

Nowadays, atypical responses are mostly ignored and left unexplained. There is a widespread tendency, hypothesized patterns of hemoglobin reaction in advance and those that are not hypothesized reaction types tend to be statistically excluded from the analysis data without being insufficiently examined [72]. In response to this trend, recent studies also have processed statistically and mapped independently the observed increase and decrease in the levels of oxyHb [73, 74] and deoxyHb [75, 76], respectively. Even in studies using rats, their analysis may be performed using only oxyHb [77].

However, evaluation of brain activity using a single hemoglobin index is contrary to the physiological mechanisms involved, ignoring the fact that hemodynamic responses include both blood volume and oxygenation. The distinction between blood volume and oxygenation, applying to fNIRS and fMRI [23, 24], has

been a subject of controversy. This remains an unresolved problem common to all brain functional imaging research based on hemodynamic responses. The beginning of this argument can be traced back to Roy and Sherrington, who in 1890 proposed neurovascular coupling. Changes in oxygenation and blood volume in the capillaries reflect neuronal activity. However, as Roy and Sherrington noted, these data were not derived from the capillaries [78].

The first to report the quantification of CBF using Fick's law (i.e., subtracting the value of the veins from that of arteries, in units of per 100 g per minute) were Kety et al. [79]. Increases in CBF, calculated without taking the capillaries into account, show a positive correlation with increasing $CMRO_2$ [80]. Based on slight increases in $CMRO_2$ observed following an increase in CBF [81], a coupling model of a positive correlation between CBF and $CMRO_2$ [82, 83] was used widely to evaluate vascular response. Changes in CBF were used as a substitute for changes in oxygen metabolism. It is likely that this trend also affected fNIRS and led to the independent analysis of the levels of oxyHb, as performed today. Recent waveforms of increases in the levels of oxyHb closely resemble the waveforms of increases in blood flow reported by Roy and Sherrington in 1890. After more than 120 years, the interpretation of neurovascular coupling has not advanced considerably. Roy and Sherrington had foresight in their interpretation related to blood flow, but they did not observe cerebral oxygen metabolism.

Although the capillary transit time in humans is reported to be <10 seconds [84], PET sampling times are markedly longer. For this reason, PET data include changes in CBF in the capillaries related to oxygen exchange, coupled with the additional component of the delayed increase in CBF in the veins not accompanied by oxygen exchange. Using PET, a dissociation between $CMRO_2$ and CBF has been reported [85, 86]. Using fMRI, signals have been shown to remain unaltered during
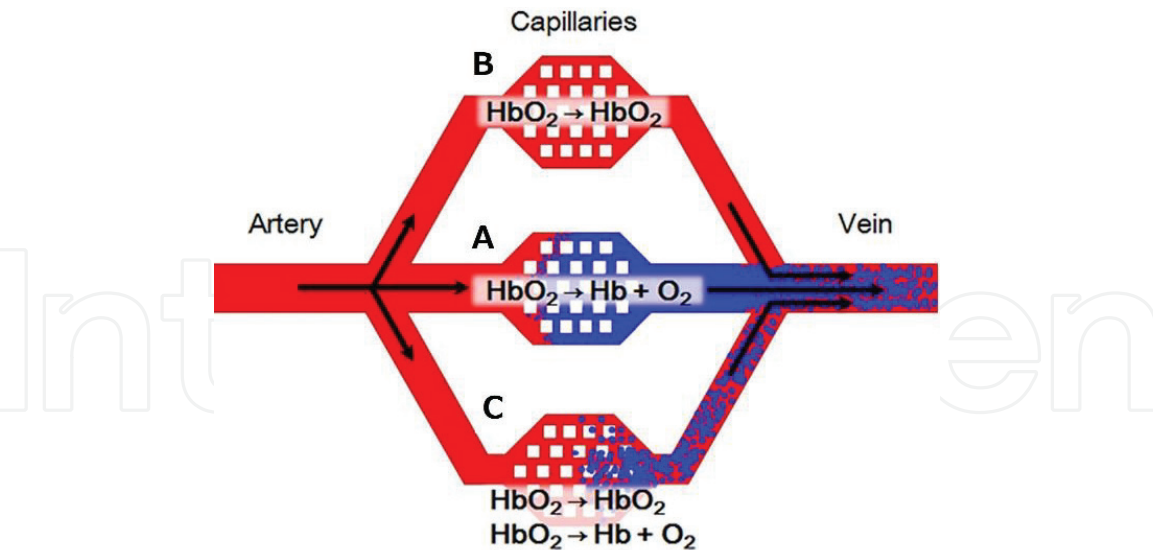

Figure 6.
Schematic diagram of the possible hemodynamic responses occurring simultaneously with neural activity (revision from [31]). In (A), oxygen demand is increased by neural activity, and consequently, transient deoxygenation increases in the capillaries (oxyhemoglobin [HbO2] → hemoglobin [Hb] + oxygen [O2]). In a site with little neural activity (B), minimal amounts of oxygen enter the cells and even during a task, increased levels of oxyHb from the artery pass through the capillaries, bypassing the cells (HbO2 → HbO2). This response—increased and decreased levels of oxyHb and deoxyHb, respectively—has been recognized as typical activation. In actuality, according to the variation in the amount of oxygen exchange due to neural activity (C), a mixed response combining these two responses must also be present. These responses, differing according to the strength of oxygen exchange, are likely to be distributed among different sites, depending on the strength of neural activity at each site. Because the blood flows from (A), (B), and (C) are further mixed in the large veins, the data may not provide specific spatial information if responses are measured at longer sampling times than the capillary transit time.

the capillary transit time [87]. In other words, there is a need to move beyond the simplistic interpretation of neurovascular coupling, which predicts an increase in the levels of oxyHb and blood flow in response to neural activity. **Figure 6** shows the relationship between neural activity and hemodynamic response schematically.

fNIRS is able to measure the levels of oxyHb and deoxyHb at the same time. Therefore, it is a useful tool to solve this serious problem of simultaneously measuring cerebral blood flow and cerebral oxygen metabolism which are faced by brain researchers for over 120 years. Future fNIRS research should distinguish between changes in blood volume and oxygenation occurring simultaneously with brain activity in the analysis of hemodynamic responses. In addition, it is necessary to re-evaluate activity-based hemodynamic responses using modalities such as EEG and MEG.

Research involving event-related optical signals [87] and invasive optical measurements [88, 89] has been unable to distinguish between oxygenation and blood volume. OxyHb and deoxyHb are involved in both oxygenation and blood volume. Thus, it may not be possible to evaluate brain activity based exclusively on the measurement of the levels of oxyHb.

6. Detection of initial dips

Currently, an experimental protocol termed block task design, employing tasks that continue for ≥10 seconds (longer than the capillary transit time), is being used in many fNIRS studies. The reason for this is that the peak latency of oxyHb is generally 10 seconds (occasionally longer) from the initiation of a task. The use of this method in fNIRS studies has followed from its use in fMRI and PET research, where the low temporal resolution of the modality justifies the use of a block design. When a task requires a longer period of time corresponding to a block design or the task requires a certain amount of time to elapse for observation, the selection of a block design protocol in research using fNIRS, providing higher temporal resolution, is appropriate. With fNIRS, there is no need to repeat cognitive tasks involving factors such as perception, recognition, or judgment for prolonged time to obtain a sufficiently strong peak response in oxyHb levels. A block design including many task components does not clarify the correspondence between each task component and spatiotemporal local brain activity. Studies have also analyzed post-task time periods [90, 91]. However, the data from these studies lacked simultaneity with local brain activity and were unable to temporally and spatially identify local brain activity. Although EEG shows high simultaneity between data and brain activity, it is characterized by poor spatial resolution. In this respect, if the spatial resolution of fNIRS can be set from the standpoint of functional resolution as described earlier, its high temporal resolution may be valuable for event-related measurements.

The initial dip, which is early deoxygenation in event-related experiments, is a highly accurate spatial indicator of neural activity [92]. In studies using optical intrinsic signals (OIS), increase in the levels of deoxyHb occurring prior to slow increases in the levels of oxyHb or total Hb has also been considered to be an index of increased oxygen metabolism [88, 93–97]. The absence of a correspondence (spatial or temporal) between increases in early deoxygenation and blood volume was also shown in a human study using invasive optical imaging [98]. Kato et al. [67, 68, 99, 100] conducted the first fNIRS study measuring initial dips appearing in fNIRS signals from the motor, visual, and language areas. Subsequently, the initial dip was observed in several fNIRS studies [18, 32–36, 101].

It has been suggested that this early increase in the levels of deoxyHb may arise from a transient increase in the consumption of oxygen in tissues [102, 103]. It has been obvious that this deoxyHb increase is useful as a precise indicator of brain

activity, but against the background that this increase in deoxyHb has been difficult to detect. For example, there is the case of less likely early deoxyHb increase depend on factors such as the type of task or the use of anesthesia [92]. A minimal and very localized increase may be attributed to imprecise fNIRS probe settings (i.e., missing the center of activity) or masking due to a strong increase in blood flow in the veins compromising detection.

With fMRI, what was reported previously as an early increase in the levels of deoxyHb was observed as an "initial dip" [21, 104, 105]. However, fMRI does not differentiate between oxyHb and deoxyHb. In addition, the relationship between increases or decreases in the levels of oxyHb and the increase in the levels of deoxyHb has not been investigated.

The more recently developed vector-based NIRS method [29, 30] is able to measure initial dips characterized by the canonical dip pattern showing increased deoxyhemoglobin, as well as several different hemoglobin patterns corresponding to differences in the degree of oxygen metabolism [32]. This method has permitted the reproducible measurement of hypoxic–ischemic initial dips (i.e., decreased levels of oxyHb) [34–36]. The initial dip at which the level of deoxyHb increases and the reaction where oxyHb increases after 2–3 seconds do not necessarily occur at the same site. Moreover, research on the intersection of these responses is limited, leading investigators to select one of the two responses (i.e., the typical oxyHb response or the initial dip) for the evaluation of brain activity. This serious problem may arise from the lack of quantification of brain activity. Indeed, the results of the evaluation of laterality in the language area [106, 107] may differ depending on the index used [108]. In addition, investigation of the relationship between event-related oxyHb and deoxyHb responses, especially those within seconds from neural activity, in previous fNIRS studies has been limited.

7. Composite indices derived from vector analysis

An advantage of fNIRS over other modalities is the simultaneous measurement of the levels of oxyHb and deoxyHb. However, this advantage leads to the following question: What do the various possible combinations of oxyHb, deoxyHb, and total Hb mean? Early fNIRS lacked a quantitative integrated theory for the interpretation of combinations of hemoglobin indices from multiple channels. Kato [29, 30] developed a quantitative method of analysis of the ratios between changes in the levels of oxyHb (ΔO) and deoxyHb (ΔD) to differentiate between oxygenation and blood volume.

This technique uses a two-dimensional vector plane on which vector tracks generated by task-related changes in cerebral blood volume (ΔCBV) and change in cerebral oxygen exchange (ΔCOE) are quantitatively classified into eight "phases." This provides a visible graphical display of information concerning hemodynamic responses (**Figure 7**). This vector-based approach is able to calculate the angle k, determining the phase of the response, and the intensity of response L. Subsequently, these may be used as indices of vector-based brain activity.

Figure 7 shows an orthogonal vector coordinate plane defined by the ΔO and ΔD axes. Rotating this vector plane 45° counterclockwise results in an orthogonal vector coordinate plane defined by the ΔCBV and ΔCOE axes. For ΔCOE, a positive value indicates hypoxic change from $\Delta COE = 0$, whereas a negative value indicates hyperoxic change. The relationships among these four axes are described by the following square matrix:

$$\begin{pmatrix} \Delta O + \Delta D \\ -\Delta O + \Delta D \end{pmatrix} = \begin{pmatrix} 1 & 1 \\ -1 & 1 \end{pmatrix} \begin{pmatrix} \Delta O \\ \Delta D \end{pmatrix} = \begin{pmatrix} \Delta CBV \\ \Delta COE \end{pmatrix} \tag{1}$$

$$\begin{pmatrix} \Delta O \\ \Delta D \end{pmatrix} = \frac{1}{2} \begin{pmatrix} 1 & -1 \\ 1 & 1 \end{pmatrix} \begin{pmatrix} \Delta CBV \\ \Delta COE \end{pmatrix} \tag{2}$$

Expansion of these shows ΔCBV and ΔCOE representing blood volume and oxygenation, respectively:

$$\Delta CBV = \frac{1}{\sqrt{2}} (\Delta D + \Delta O) \tag{3}$$

$$\Delta COE = \frac{1}{\sqrt{2}} (\Delta D - \Delta O) \tag{4}$$

The scalar L, drawn from the origin to the coordinates of an arbitrary point on the vector plane, indicates the amplitude of a vector, reflecting the amount of change in Hb. L can be described by the following equation:

$$L = \sqrt{(\Delta O)^2 + (\Delta D)^2} = \frac{1}{\sqrt{2}} \sqrt{(\Delta D - \Delta O)^2 + (\Delta D + \Delta O)^2}$$

$$= \frac{1}{\sqrt{2}} \sqrt{(\Delta COE)^2 + (\Delta CBV)^2} \tag{5}$$

The angle k, indicating the phase, is defined by the following equation:

$$k = Arc \tan \left(\frac{\Delta D}{\Delta O} \right) = Arc \tan \left(\frac{\Delta COE}{\Delta CBV} \right) + 45° \quad (-135° \leqq k \leqq 225°) \tag{6}$$

A vector on the polar coordinate plane contains the four Hb indices (i.e., ΔO, ΔD, ΔCBV, and ΔCOE). The relationships between the four Hb vectors (**Figure 7**) are defined by the equations shown earlier in this section: Eqs. (1) and (2) define hemoglobin changes; Eq. (5) defines the scalar L; and Eq. (6) defines the angle k, which determines the phase of a vector. Earlier evaluations of brain activity were
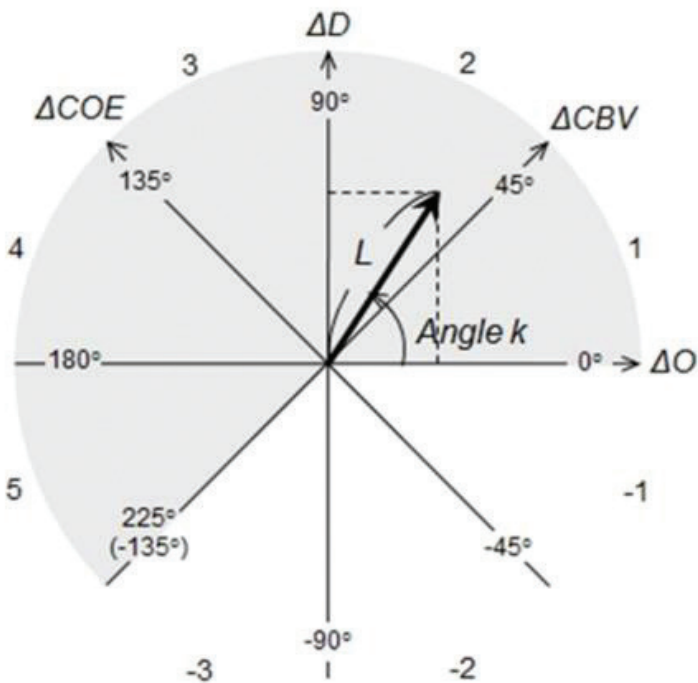

Figure 7.
Functional near-infrared spectroscopy vector plane. Revised from [29, 30].

based on signal intensity, without the concept of a phase. However, this method describes all the possible combinations of responses through eight phases on the vector plane. In addition, particular patterns of physiological responses are presented in a highly visual manner. This method provides a quantitative measure of oxygen metabolism, offering the advantage of measurements expressed in units of degrees. Moreover, measurements are determined from ratios of change rather than the actual extent of change in the levels of Hb.

8. Interpretation of initial dips using the vector-based approach

The angle k shows a positive value in the phases of initial dip occurrence. Previously, the initial dip was regarded as an indication of increased oxygen consumption. However, it was not possible to evaluate the strength of the initial dip or the possibility of different kinds of initial dips. Yoshino and Kato [32] classified initial dips in the language area by phase according to their particular combinations of ΔO, ΔD, ΔCBV, and ΔCOE.

- Phases 1 through 5 on the vector plane were dip phases, showing increases in ΔD or ΔCOE; the presence of an event-related vector in these phases defined an initial dip.

- Phase 1 ($0 < \Delta D < \Delta O$, $\Delta COE < 0 < \Delta CBV$) and Phase 2 ($0 < \Delta O < \Delta D$, $0 < \Delta COE < \Delta CBV$) are canonical dips [79], in which both ΔD and ΔO increase.

- Phase 3 ($\Delta O < 0 < \Delta D$, $0 < \Delta CBV < \Delta COE$) is a hypoxic-hyperemic dip, in which ΔO decreases and ΔCBV increases.

- Phase 4 ($\Delta O < 0 < \Delta D$, $\Delta CBV < 0 < \Delta COE$) and Phase 5 ($\Delta O < \Delta D < 0$, $\Delta CBV < 0 < \Delta COE$) are hypoxic–ischemic dips, in which ΔCOE increases and ΔCBV decreases.

- Phases -1 through -3 are non-dip phases, in which ΔD and ΔCOE decrease.

Regarding oxygen metabolism, responses in the dip phases may indicate stronger brain activity than those in the non-dip phases. It is necessary to verify the strongest dip phases during the evaluation of the regulation between the oxygenation axis (ΔCOE) and the blood volume axis (ΔCBV) in the vector plane. The typical response corresponds to Phases -1 and -2, interpreted as brain activity with a low degree of oxygen exchange. The responses in other phases should be evaluated in the same manner and the frequency of their occurrence should be investigated based on phase classifications. The percentage of dips in Wernicke's area in Phases 1 and 2 was low (total: 15–21%). However, in Phases 4 and 5, this percentage was higher (total: 62–68%) [32]. Differences in the frequency of phase depending on the brain site and the task may have different physiological implications. The ratio between the decrease and increase in the levels of deoxyHb and oxyHb, respectively, in a typical response is not constant. The quantitative values of the phase angle k may be used to investigate such differences in typical responses.

In **Figure 8**, time course data for previously reported initial dips are reproduced on a vector plane using the vector-based technique. **Figure 8A** and **8B** show two different types of dip in different phases, depending on the observed change in the ΔCBV. In both fMRI and OIS, the canonical initial dip has been considered to be a response
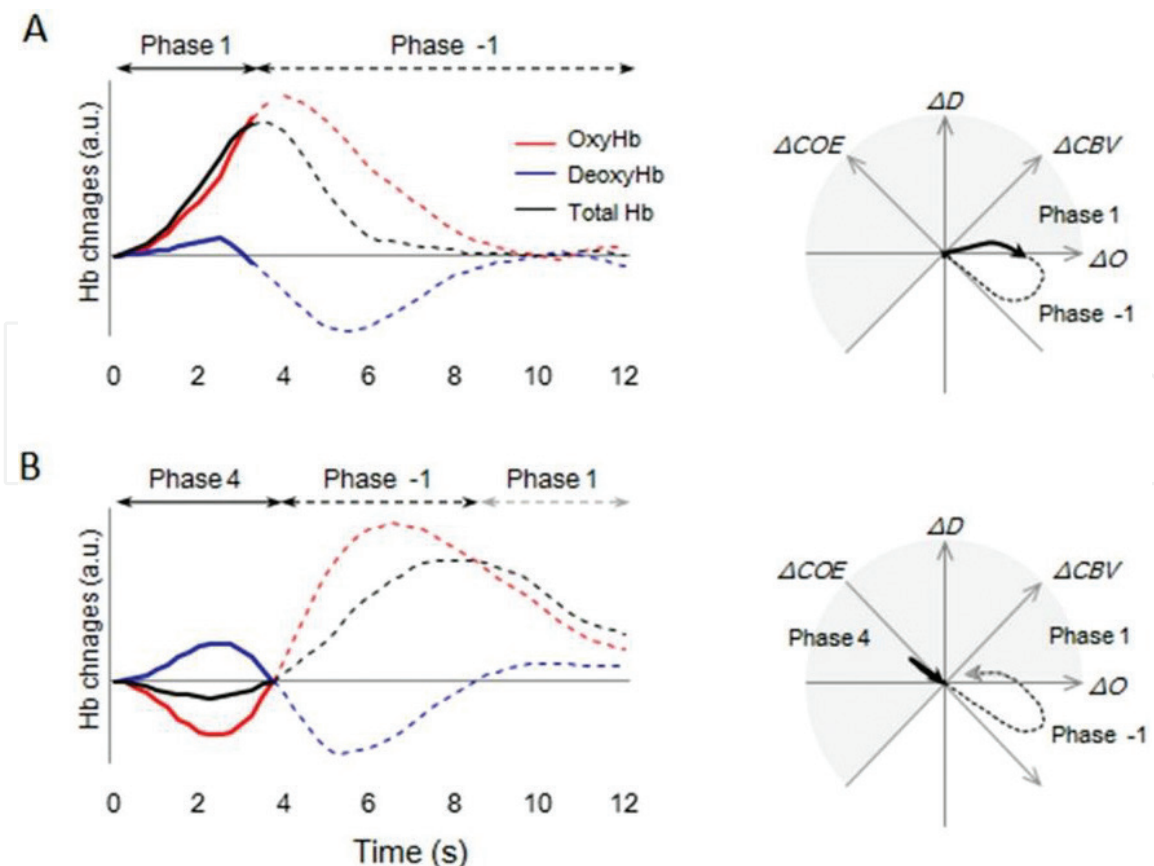
Figure 8.
Two kinds of initial dips [32]. Representative patterns of two types of initial dips when data from (A) and (B) were converted into vectors on a vector plane. (A) In a study using optical intrinsic signals, ΔD increased during the early part of a task [94]. The vector in this time course is in Phase 1 during the initial dip and subsequently progresses into Phase −1, indicating a typical response. (A) Initially, the vector is in Phase 1 and subsequently rotates in a clockwise direction into Phase −2. (B) The vector initially rotates in a clockwise direction into Phase 4, followed by rotation in a counterclockwise direction into Phase −1 and subsequently into Phase 1.

induced by increased levels of deoxyHb. **Figure 8B** shows an fNIRS initial dip (an increased ΔD accompanying a decreased ΔO), indicating Phase 4 [18, 32, 67, 68]. Recently, fNIRS was used to observe this new type of initial dip in primates [109].

As shown in **Figure 8A**, if this canonical initial dip detected by Malonek and Grinvald using OIS [94] corresponds to that of fMRI [95, 104], this would mean that the a blood oxygenation level-dependent (BOLD) signal from fMRI was able to differentiate between Phase 1, as a signal decrease, and Phase −1, as a signal increase. However, Phase 1 is an increased ΔCBV dip, in which ΔCOE decreases while the levels of deoxyHb increase. Thus, there is a discrepancy between the results from the two modalities. A theory bridging fNIRS and fMRI has been proposed, suggesting that a BOLD signal influenced by changes in ΔCBV closely resembles an increase in the levels of oxyHb [24]. In this model, the fMRI signal in the increased ΔCBV phase depends on the observed change in ΔO (not ΔD). Theoretically, this change may be considered to be a BOLD signal increase rather than a dip. Indeed, the use of the vector plane may explain the fact that the OIS initial dip does not correspond to that of fMRI.

In present, initial dips could be reliably detected with OIS [92–97] and fNIRS [31–36, 109]. On the other hand, the occurrence of the initial dip in fMRI has been doubted and its mechanism is still controversial [21–24, 105]. Logothetis et al. [86] reported a period of latency, when the increase in the BOLD signal was flat for a few seconds at the beginning of the task. This shows the difficulty in detecting changes in phases during passage through the capillaries from those in the BOLD

signal. Of note, the sensitivity of fMRI declines at detecting activities with high oxygen consumption. During early research on the combination of fMRI and fNIRS [9, 110], the concept of phases had not been introduced and the differences between these methods were not understood clearly.

Collectively, research has shown that these two modalities are physiologically inconsistent in their sensitivity to the initial dip, with significant differences between them. Moreover, animal studies have demonstrated the variation of ratios between changes in the levels of deoxyHb and oxyHb occurring simultaneously with neural activity (i.e., diversity of phase) [103, 109]. Using the concept of phases, it is also possible to re-evaluate the results of a previous fNIRS study [8] (**Figure 2**) and confirm that the results indicate Phase 1 in areas where oxygen consumption is high or in the time zone. The vector-based evaluation was able to show a short initial dip and sustained oxygen metabolism because the period of the task was long in this study. On the other hand, investigations that followed this previous study [8] may have evaluated the intensity of brain activity only (similar to L) in the Phase -1 and -2 typical responses.

9. Quantification of brain activity in time series

Local brain activity was quantified for the first time in 1993 using continuous-wave fNIRS, by substituting optical differential path length factors [8]. At that time, mmol•mm (or mmol•cm) was commonly used as the unit expressing the degree of change in the levels of Hb, taking the differential path length factor as 1 [111, 112]. The phase angle k expresses oxygen metabolism quantitatively in degrees. This offers the advantage of being independent of the actual levels of Hb. **Figure 9** shows image displays from a verbal task [29, 30]. Local increases in the angle k were detected in Broca's area (channel 4) and the surrounding area during the task, with almost no change observed in ΔCBV. Thus, the use of the angle k may permit the high-sensitivity detection of local brain activity occurring simultaneously with a task (regardless of the duration of the task) that has been undetected in previous studies against the background of slow hemodynamic change. On the other hand, intensity (L) is strongest in channels 4 and 5 during and after the task, respectively. After the task, the angle k decreases approaching zero. These findings indicate the variable behavior of different indices in spatiotemporal imaging. In the past, the differences in spatiotemporal imaging had been largely ignored, with researchers focusing exclusively on typical responses. The differences in local brain activity of this kind were equally ignored, particularly when they occurred simultaneously with short tasks.

It has been shown that vector-based NIRS is able to quantitatively evaluate differences in the oxygen load in the prefrontal cortex arising from different breathing routes (**Figure 10** [113]). In that study, although there were no significant differences in L, differences in the time series of the angle k were apparent between nasal and mouth breathing. This may have potentially useful practical applications, such as the provision of an earlier and more reliable diagnosis of a patient's habitual breathing route compared with a patient interview. The use of an index combining both deoxyHb and oxyHb may lead to new interpretations of previous fNIRS data. Previous brain imaging studies have been based on the intensity of response.

In usage of this vector-based approach, it may not be possible to obtain the correct phase value by conventional data processing. For example, if the deoxyHb and oxyHb data are processed independently (e.g., when normalization or statistical parametric mapping has been performed on only the oxyHb data) [114], this will change the ratios, and there is a risk that the values of k will be distorted.
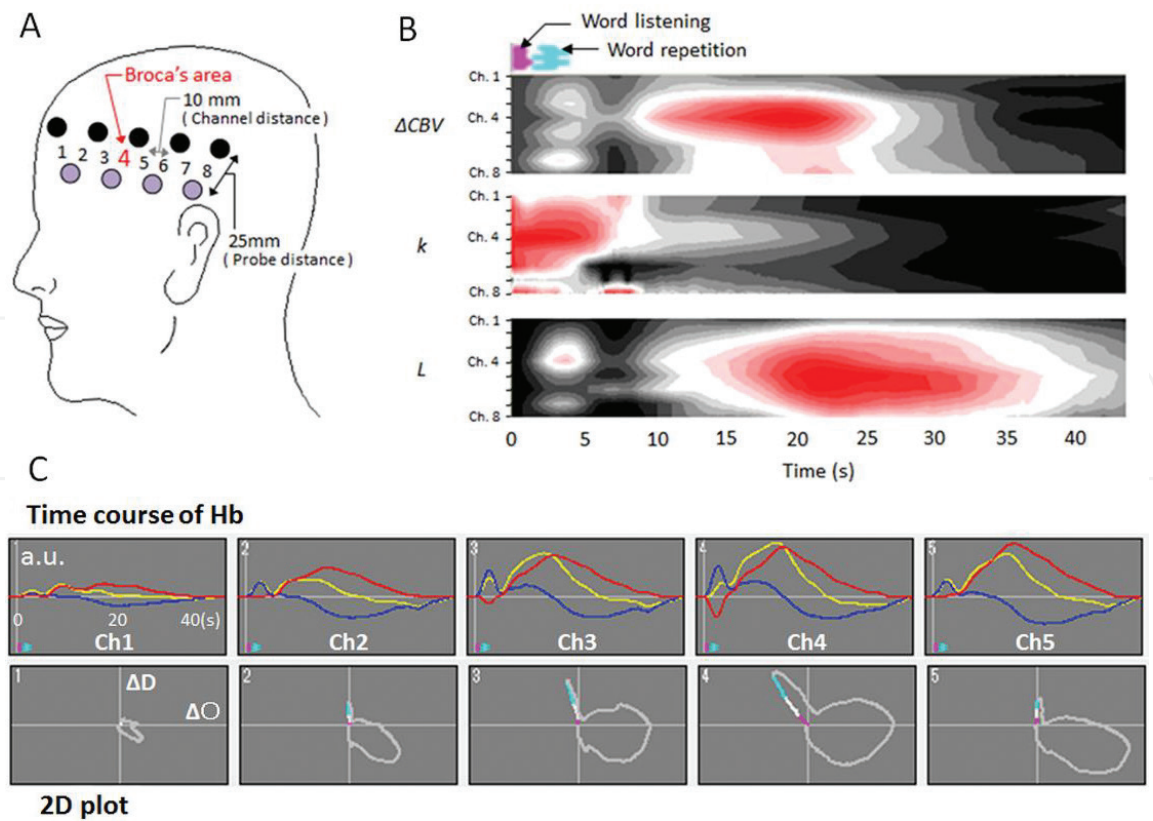
Figure 9.
Spatiotemporal imaging of cerebral oxygen exchange for a verbal task [29, 30]. (A) Channel positions. Broca's area corresponds to channel 4. (B) Pink shows the duration of word listening (average 1.2 seconds) and blue shows the duration of word repetition (average 1.1 seconds). For ΔCBV, red indicates positive vector changes, whereas black indicates negative vector changes. For the angle k, black indicates k = 0, whereas red indicates the maximum angle k (180°). For L, black indicates 0, whereas red indicates the peak value. (C) Time courses of hemoglobin components and their two dimensional vector coordinates. Oxyhemoglobin (OxyHb; red), deoxyhemoglobin (deoxyHb; blue), and total hemoglobin (total Hb; yellow). Arbitrary unit (a.u.).
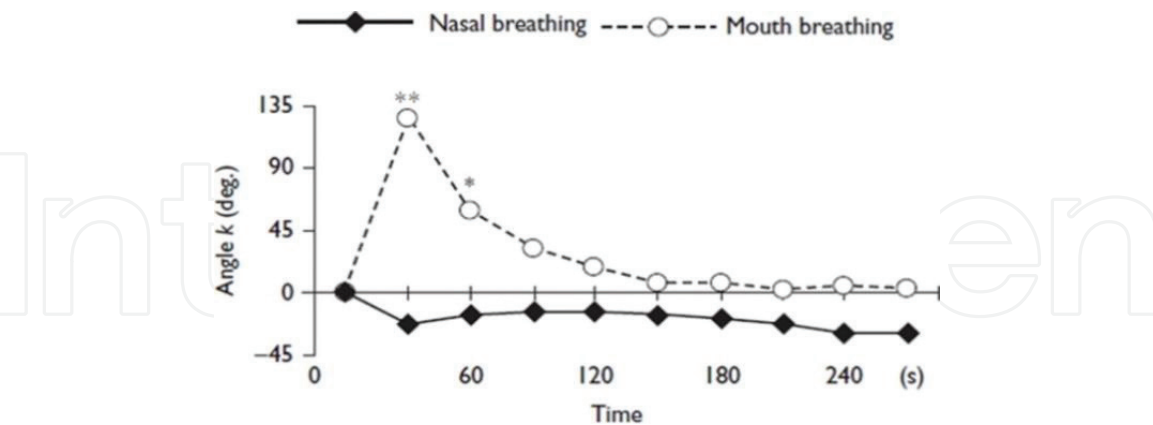

Figure 10.
Time courses of the angle k for nasal and mouth breathing ($^{**}P < 0.05$; $^{*}P < 0.1$) [113].

In addition, a method of baseline correction, in which linear regression connecting the pre- and post-task period is used to emphasize the typical response, is available [115]. This may affect the angle k and L (intensity of response). By moving forward with quantitative analysis of this kind—designed to clarify differences between oxygenation and blood volume while taking care to avoid distortion from the initial processing of the data—fNIRS will be able to meet the challenges of quantitatively and accurately identifying localized brain activity.

10. Conclusion

The precise detection of local brain activity was the original purpose of fNIRS. Nowadays, because of the vector-based approach, investigators can measure initial dips from the scalp. Progress has been achieved in the quantitative detection of local brain activity and the development of spatiotemporal imaging. However, some fNIRS studies are actually task-related studies using NIRS, never intended for the spatial localization of brain function. This together with other factors has introduced doubts regarding the validity of fNIRS. The historical background described earlier in this review may be useful as we attempt to erase these doubts and improve the spatial and temporal accuracy of fNIRS. Studies are warranted to examine the physiological significance of the different combinations of changes in the levels of the different Hb and changes in the characteristics of mapping depending on the selection of indices.

Local brain activity induces local oxygen consumption and demand for oxygen supply. Further research is required to investigate the relationship between the consumption of oxygen and the spatial distribution of oxygen supply accompanying local brain activity. The indices angle k and L, indicating the phase of hemoglobin response and its intensity, respectively, are new indices for the detection of local brain activity. In addition, the simultaneous measurement of composite indices of this kind may improve the detection of local brain activity. The application of methods for the simultaneous evaluation of these composite indicators is one of the challenges for future research on the new fNIRS method.

Author details

Toshinori Kato
Department of Brain Environmental Research, KatoBrain Co., Ltd., Tokyo, Japan

*Address all correspondence to: kato@katobrain.com

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References

[1] Ferrari M, Quaresima V. A brief review on the history of human functional near-infra-red spectroscopy (fNIRS) development and fields of application. NeuroImage. 2012;**63**:921-935. DOI: 10.1016/j.neuroimage.2012.03.049

[2] Mihara M, Miyai I. Review of functional near-infrared spectroscopy in neurorehabilitation. Neurophotonics. 2016;**3**:031414. DOI: 10.1117/1.NPh.3.3.031414

[3] Yoshino K, Oka N, Yamamoto K, Takahashi H, Kato T. Functional brain imaging using near infrared spectroscopy during actual driving on an expressway. Frontiers in Human Neuroscience. 2013;**7**:882. DOI: 10.3389/fnhum.2013.00882. eCollection 2013.

[4] Yoshino K, Oka N, Yamamoto K, Takahashi H, Kato T. Correlation of prefrontal cortical activation with changing vehicle speeds in actual driving: A vector-based functional near-infrared spectroscopy study. Frontiers in Human Neuroscience. 2013;**7**:895. DOI: 10.3389/fnhum.2013.00895

[5] Oka N, Yoshino K, Yamamoto K, Takahashi H, Li S, Sugimachi T, et al. Greater activity in the frontal cortex on left curves: A vector-based fNIRS study of left and right curve driving. PLoS One. 2015;**10**(5):e0127594. DOI: 10.1371/journal.pone.0127594

[6] Orino Y, Yoshino K, Oka N, Yamamoto K, Takahashi H, Kato T. Brain activity involved in vehicle velocity changes in a sag vertical curve on an expressway: Vector-based functional near-infrared spectroscopy study. Journal of the Transportation Research Board. 2015;**2518**:18-26. DOI: 10.3141/2518-03

[7] Takashima S, Kato T, Hirano S, Mito T. Observation of activation in local cerebral blood flow by means of near-infrared spectroscopy. Comprehensive research report concerning medical care for children (people) with disabilities. Japan. Ministry of Health & Welfare. 1992:179-181

[8] Kato T, Kamei A, Takashima S, Ozaki T. Human visual cortical function during photic stimulation monitoring by means of near-infrared spectroscopy. Journal of Cerebral Blood Flow and Metabolism. 1993;**13**:516-520. PMID: 8478409 DOI: 10.1038/jcbfm.1993.66

[9] Kato T, Takashima S, Kamada K, Kishibayashi J, Sunohara N, Ozaki T. Advantage of near-infrared spectroscopy in the human functional MR imaging in brain. In: 12th Annual Scientific Meeting of the Society of Magnetic Resonance in Medicine. Proceedings of the International Society for Magnetic Resonance in Medicine. New York; Aug 14-20 1993;**1993**(S3):1409. https://onlinelibrary.wiley.com/doi/epdf/10.1002/mrmp.22419930308

[10] Wyatt JS, Cope M, Delpy DT, Wray S, Reynolds EO. Quantification of cerebral oxygenation and haemodynamics in sick newborn infants by near infrared spectrophotometry. Lancet. 1986;**2**:1063-1066

[11] Togari H. Noninvasive cerebral blood volume monitoring in premature infants. Journal of Clinical and Experimental Medicine. 1987;**142**:907-909

[12] Golubic SJ, Susac A, Grilj V, Ranken D, Huonker R, Haueisen J, et al. Size matters: MEG empirical and simulation study on source localization of the earliest visual activity in the occipital cortex. Medical & Biological Engineering & Computing. 2011;**49**(5):545-554. DOI: 10.1007/s11517-011-0764-9

[13] Hillebrand A, Barnes GR. A quantitative assessment of the sensitivity of whole-head MEG to activity in the adult human cortex. NeuroImage. 2002;**16**:638-650

[14] Stancák A, Wackermann J. Spatial EEG synchronisation over sensorimotor hand areas in brisk and slow self-paced index finger movements. Brain Topography. 1998;**11**:23-31

[15] Kato T, Sancak A. Distinction of regional cerebral FORCE (fast-oxygen response in capillary event) effect by unilateral and bilateral finger movements. In: 11th Annual Meeting of the Organization for Human Brain Mapping, Toronto, Ontario, Canada. Jun 12-16, 2005. Presentation No. 1582

[16] Shin J, Kim DW, Müller KR, Hwang HJ. Improvement of information transfer rates using a hybrid EEG-NIRS brain-computer interface with a short trial length: Offline and pseudo-online analyses. Sensors (Basel). 2018;**18**(6). pii: E1827. DOI: 10.3390/s18061827

[17] Huppert T, Barker J, Schmidt B, Walls S, Ghuman A. Comparison of group-level, source localized activity for simultaneous functional near-infrared spectroscopy-magnetoencephalography and simultaneous fNIRS-fMRI during parametric median nerve stimulation. Neurophotonics. 2017;**4**(1):015001. DOI: 10.1117/1.NPh.4.1.015001

[18] Wylie GR, Graber HL, Voelbel GT, Kohl AD, DeLuca J, Pei Y, et al. Using co-variations in the Hb signal to detect visual activation: A near infrared spectroscopic imaging study. NeuroImage. 2009;**47**:473-481

[19] Heinzel S, Haeussinger FB, Hahn T, Ehlis AC, Plichta MM, Fallgatter AJ. Variability of functional hemodynamics as measured with simultaneous fNIRS and fMRI during intertemporal choice. NeuroImage. 2013;**71**:125-134

[20] Tian F, Sharma V, Kozel FA, Liu H. Functional near-infrared spectroscopy to investigate hemodynamic responses to deception in the prefrontal cortex. Brain Research. 2009;**1303**:120-130

[21] Buxton RB. The elusive initial dip. NeuroImage. 2001;**13**:953-958

[22] Iadecola C. Intrinsic signals and functional brain mapping: Caution, blood vessels at work. Cerebral Cortex. 2002;**12**:225-233

[23] Pouratian N, Sicotte N, Rex D, Martin NA, Becker D, Cannestra AF, et al. Spatial/temporal correlation of BOLD and optical intrinsic signals in humans. Magnetic Resonance in Medicine. 2002;**47**:766-776

[24] Yamamoto T, Kato T. Paradoxical correlation between signal in functional magnetic resonance imaging and deoxygenated haemoglobin content in capillaries: A new theoretical explanation. Physics in Medicine and Biology. 2002;**47**:1121-1141

[25] Takahashi T, Takikawa Y, Kawagoe R, Shibuya S, Iwano T, Kitazawa S. Influence of skin blood flow on near-infrared spectroscopy signals measured on the forehead during a verbal fluency task. NeuroImage. 2011;**57**:991-1002

[26] Kirilina E, Jelzow A, Heine A, Niessing M, Wabnitz H, Bruhl R, et al. The physiological origin of task-evoked systemic artefacts in functional near infrared spectroscopy. NeuroImage. 2012;**61**(1):70-81

[27] Cyranoski D. Thought experiment. Nature. 2011;**469**:148-149

[28] Takizawa R, Fukuda M, Kawasaki S, Kasai K, Mimura M, Pu S, et al. Neuroimaging-aided differential

diagnosis of the depressive state. Neuroimage. 2014;**85**(Pt 1):498-507. DOI: 10.1016/j.neuroimage.2013.05.126

[29] Kato T. Apparatus for evaluating biological function. 2006;WO/2003/068070. Available from: http://www.wipo.int/patentscope/search/en/WO2003068070

[30] Kato T. Biofunctuon diagnosis device, biofunction diagnosis method, bioprobe, bioprobe wearing tool, bioprobe support tool, and bioprobe wearing assisting tool. 2007;WO/2006/009178. Available from: http://www.wipo.int/patentscope/search/en/WO2006009178

[31] Kato T. Principle and technique of NIRS imaging for human brain FORCE: Fast-oxygen response in capillary event. In: Proceedings 15th World Congress of the International Society of Brain Electromagnetic Topography. 2004;**1270**:88-99. by Elsevier B.V. journal ISSN: 0531-5131. DOI: 10.1016/j.ics.2004.05.052

[32] Yoshino K, Kato T. Vector-based phase classification of initial dips during word listening using near-infrared spectroscopy. Neuroreport. 2012;**23**(16):947-951. DOI: 10.1097/WNR.0b013e328359833b

[33] Akiyama T, Ohira T, Kawase T, Kato T. TMS orientation for NIRS-functional motor mapping. Brain Topography. 2006;**19**(1-2):1-9. DOI: 10.1007/s10548-006-0007-9

[34] Hong KS, Naseer N. Reduction of delay in detecting initial dips from functional near-infrared spectroscopy signals using vector-based phase analysis. International Journal of Neural Systems. 2016;**26**(3):1650012. DOI: 10.1142/S012906571650012X

[35] Zafar A, Hong KS. Detection and classification of three-class initial dips

from prefrontal cortex. Biomedical Optics Express. 2017;**8**(1):367-383. PMCID: PMC5231305. DOI: 10.1364/BOE.8.000367

[36] Zafar A, Hong KS. Neuronal activation detection using vector phase analysis with dual threshold circles: A functional near-infrared spectroscopy study. International Journal of Neural Systems. 24 Jun 2018:1850031. PMID: 30045647. DOI: 10.1142/S0129065718500314

[37] Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science. 1977;**198**:1264-1267

[38] Takashima S, Ando Y. Reflectance spectrophotometry, cerebral blood flow and congestion in young rabbit brain. Brain & Development. 1988;**10**:20-23

[39] Koyama K, Mito T, Takashima S, Suzuki S. Effect of phenylephrine and dopamine on cerebral blood flow, blood volume, and oxygenation in young rabbits. Pediatric Neurology. 1990;**6**:87-90

[40] Mito T, Koyama K, Houdou S, Takashima S, Suzuki S. Response on near-infrared spectroscopy and of cerebral blood flow to hypoxemia induced by N_2 and CO_2 in young rabbits. Brain & Development. 1990;**12**:408-411

[41] Takashima S, Kudou H, Cho H, Houdou S, Hasegawa M. Monitoring of Oxygenation and Cerebral Blood Volume and Respiratory Abnormality of Children with Cerebral Palsy. Comprehensive Research Report Concerning Medical Care for Children (People) with Disabilities. Japan: Ministry of Health & Welfare; 1990. pp. 199-201

[42] Abdel-Dayem HM, Bahar RH, Sigurdsson GH, Sadek S, Olivercrona H, Ali AM. The hollow skull: A sign of

brain death in Tc-99m HM-PAO brain scintigraphy. Clinical Nuclear Medicine. 1989;**14**:912-916

[43] Roland PE, Friberg L. Localization of cortical areas activated by thinking. Journal of Neurophysiology. 1985;**53**:1219-1243

[44] Brod J, Fencl V, Hejl Z, Jirka J. Circulatory changes underlying blood pressure elevation during acute emotional stress (mental arithmetic) in normotensive and hypertensive subjects. Clinical Science. 1959;**18**:269-279

[45] Nyberg G, Graham RM, Stokes GS. The effect of mental arithmetic in normotensive and hypertensive subjects, and its modification by beta-adrenergic receptor blockade. British Journal of Clinical Pharmacology. 1977;**4**:469-474

[46] Kitagawa Y, Meyer JS, Tachibana H, Mortel KF, Rogers RL. CT-CBF correlations of cognitive deficits in multi-infarct dementia. Stroke. 1984;**15**:1000-1009

[47] Roland PE, Eriksson L, Stone-Elander S, Widen L. Does mental activity change the oxidative metabolism of the brain? The Journal of Neuroscience. 1987;**7**:2373-2389

[48] Roland PE, Skinhøj E, Lassen NA, Larsen B. Different cortical areas in man in organization of voluntary movements in extrapersonal space. Journal of Neurophysiology. 1980;**43**:137-150

[49] Fox P, Raichle M. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. Journal of Neurophysiology. 1984;**51**:1109-1120

[50] Jöbsis FF. Method and apparatus for monitoring metabolism in body organs. U.S. Patent No.4,281,645. 1981

[51] Kato T, Okuyama K. Assessment of maturation and impairment of brain by I-123 iodoamphetamine SPECT and MR imaging in children. Showa University Journal of Medical Sciences. 1993;**5**:99-115

[52] Beauchamp MS, Beurlot MR, Fava E, Nath AR, Parikh NA, Saad SZ, et al. The developmental trajectory of brain-scalp distance from birth through childhood: Implications for functional neuroimaging. PLoS One. 2011;**6**(9):e24981. DOI: 10.1371/journal.pone.0024981

[53] Liao SM, Ferradal SL, White BR, Gregg N, Inder TE, Culver JP. High-density diffuse optical tomography of term infant visual cortex in the nursery. Journal of Biomedical Optics. 2012;**17**:081414. DOI: 10.1117/1.JBO.17.8.081414

[54] Minagawa-Kawai Y, Cristia A, Long B, Vendelin I, Hakuno Y, Dutat M, et al. Insights on NIRS sensitivity from a cross-linguistic study on the emergence of phonological grammar. Frontiers in Psychology. 2013;**16**(4):170. DOI: 10.3389/fpsyg.2013.00170 (eCollection 2013)

[55] Maki A, Yamashita Y, Ito Y, Watanabe E, Mayanagi Y, Koizumi H. Spatial and temporal analysis of human motor activity using noninvasive NIR topography. Medical Physics. 1995;**22**:1997-2005

[56] Strangman G, Franceschini MA, Boas DA. Factors affecting the accuracy of near-infrared spectroscopy concentration calculations for focal changes in oxygenation parameters. NeuroImage. 2003;**18**:865-879

[57] Hoshi Y, Tamura M. Detection of dynamic changes in cerebral oxygenation coupled to neuronal function during mental work in man. Neuroscience Letters. 1993;**150**:5-8

[58] Villringer A, Planck J, Hock C, Schleinkofer L, Dirnagl U. Near infrared spectroscopy (NIRS): A new tool to study hemodynamic changes during activation of brain function in human adults. Neuroscience Letters. 1993;**154**:101-104

[59] Chance B, Zhuang Z, UnAh C, Alter C, Lipton L. Cognition-activated low frequency modulation of light absorption in human brain. Proceedings of the National Academy of Sciences of the United States of America. 1993;**90**:3770-3774

[60] Kawaguchi H, Hayashi T, Kato T, Okada E. Theoretical evaluation of accuracy in position and size of brain activity obtained by near-infrared topography. Physics in Medicine and Biology. 2004;**49**:2753-2765

[61] Franceschini MA, Toronov V, Filiaci ME, Gratton E, Fantini S. On-line optical imaging of the human brain with 160-ms temporal resolution. Optics Express. 2000;**6**:49-57

[62] Okamoto M, Dan H, Sakamoto K, Takeo K, Shimizu K, Kohno S, et al. Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10-20 system oriented for transcranial functional brain mapping. NeuroImage. 2004;**21**:99-111

[63] Barbour RL, Lubowsky J, Aronson R. Method of imaging a random medium. U.S. Patent No. 5,137,355. 1989

[64] Zeff BW, White BR, Dehghani H, Schlaggar BL, Culver JP. Retinotopic mapping of adult human visual cortex with high-density diffuse optical tomography. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**:12169-12174

[65] Habermehl C, Holtze S, Steinbrink J, Koch SP, Obrig H, Mehnert J, et al. Somatosensory activation of two fingers can be discriminated with ultrahigh-density diffuse optical tomography. NeuroImage. 2012;**59**:3201-3211

[66] Kato T, Wang P, Kim S-G, Kamba M, Kawaguchi F, Ichikawa N. Selectivity, sensitivity and connectivity due to somatosensory stimulation in rats investigated by noninvasive subcentimeter-fNIR. NeuroImage. 2001;**13**:S22

[67] Kato T, Endo A, Fukumizu M, Kato T, Takashima S, Kawaguchi F, et al. Initial cerebral metabolism due to short visual stimulation using human functional ear-infraredgraphy (fNIR): How it correlates with fMRI? In: Proceedings of the International Society for Magnetic Resonance in Medicine, 7th Annual Meeting. Philadelphia, Pennsylvania, USA; May 24-28 1999;**762**. Poster No. 762. https://www.ismrm.org/99prog/program.htm

[68] Kato T, Endo A, Fukumizu M, Kato T, Takashima S, Kawaguchi F, et al. Real-time imaging of "initial cerebral metabolism" using human functional near-infraredgraphy (fNIR). NeuroImage. 1999;**9**(6):S309

[69] Obrig H, Kleinschmidt A, Merboldt KD, Dirnagl U, Grahm J, Villringer A. Monitoring of cerebral blood oxygenation during human brain activation by simultaneous high-resolution MRI and near-infrared spectroscopy. In: Second Meeting of the Society of Magnetic Resonance. Proceedings of the International Society for Magnetic Resonance in Medicine. San Francisco, California USA; 6-12 August 1994;**1994**(S1):67. https://onlinelibrary.wiley.com/doi/epdf/10.1002/mrmp.22419940103

[70] Nakajima T, Fujita M, Watanabe H, Kuwabara T, Takeo K, Iwamoto S, et al. Functional mapping of the human visual system with near-infrared spectroscopy and BOLD

functional MRI. In: Second Meeting of the Society of Magnetic Resonance. Proceedings of the International Society for Magnetic Resonance in Medicine. San Francisco, California USA; Aug 6-12 1994;**1994**(S2):687. https://onlinelibrary.wiley.com/doi/epdf/10.1002/mrmp.22419940204

[71] Kleinschmidt A, Obrig H, Requardt M, Merboldt KD, Dirnagl U, Villringer A, et al. Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. Journal of Cerebral Blood Flow and Metabolism. 1996;**16**:817-826

[72] Kameyama M, Fukuda M, Yamagishi Y, Sato T, Uehara T, Ito M, et al. Frontal lobe function in bipolar disorder: A multichannel near-infrared spectroscopy study. NeuroImage. 2006;**29**:172-184

[73] Sumitani S, Tanaka T, Tayoshi S, Ota K, Kameoka N, Ueno S, et al. Activation of the prefrontal cortex during the Wisconsin card sorting test as measured by multichannel near-infrared spectroscopy. Neuropsychobiology. 2006;**53**:70-76

[74] Hibino S, Mase M, Shirataki T, Nagano Y, Fukagawa K, Abe A, et al. Oxyhemoglobin changes during cognitive rehabilitation after traumatic brain injury using near infrared spectroscopy. Neurologia Medico-Chirurgica (Tokyo). 2013;**53**:299-303

[75] Telkemeyer S, Rossi S, Nierhaus T, Steinbrink J, Obrig H, Wartenburger I. Acoustic processing of temporally modulated sounds in infants: Evidence from a combined near-infrared spectroscopy and EEG study. Frontiers in Psychology. 2011;**1**:62. DOI: 10.3389/fpsyg.2011.00062 (eCollection 2011)

[76] Leon-Dominguez U, Izzetoglu M, Leon-Carrion J, Solís-Marcos I, Garcia-Torrado FJ, Forastero-Rodríguez A, et al. Molecular concentration of deoxyHb in human prefrontal cortex predicts the emergence and suppression of consciousness. Neuroimage. 2014;**85**:616-625. DOI: 10.1016/j.neuroimage.2013.07.023

[77] Hoshi Y, Kobayashi N, Tamura M. Interpretation of near-infrared spectroscopy signals: A study with a newly developed perfused rat brain model. Journal of Applied Physiology. 2001;**90**:1657-1662

[78] Roy C, Sherrington C. On the regulation of the blood-supply of the brain. The Journal of Physiology. 1890;**11**:85-158

[79] Kety SS, Schmidt CF. The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. The American Journal of Physiology. 1945:153-166

[80] Leenders KL, Perani D, Lammertsma AA, Heather JD, Buchingham P, Healy MJR, et al. Cerebral blood flow, blood volume and oxygen utilization: Normal values and effect of age. Brain. 1990;**113**:27-47

[81] Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proceedings of the National Academy of Sciences. 1986;**83**:1140-1144

[82] Buxton RB, Frank LR. A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. Journal of Cerebral Blood Flow and Metabolism. 1997;**17**:64-72

[83] Vafaee MS, Gjedde A. Model of blood-brain transfer of oxygen explains nonlinear flow-metabolism coupling

during stimulation of visual cortex. Journal of Cerebral Blood Flow and Metabolism. 2000;**20**:747-754

[84] Hudetz AG, Biswal BB, Fehér G, Kampine JP. Effects of hypoxia and hypercapnia on capillary flow velocity in the rat cerebral cortex. Microvascular Research. 1997;**54**:35-42

[85] Mintun MA, Lundstrom BN, Snyder AZ, Vlassenko AG, Shulman GL, Raichle ME. Blood flow and oxygen delivery to human brain during functional activity: Theoretical modeling and experimental data. Proceedings of the National Academy of Sciences of the United States of America. 2001;**98**:6859-6864

[86] Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature. 2001;**412**:150-157

[87] Gratton G, Fabiani M, Corballis PM, Hood DC, Marsha R, Wood G, et al. Fast and localized event-related optical signals (EROS) in the human occipital cortex: Comparisons with the visual evoked potential and fMRI. NeuroImage. 1997;**6**:168-180

[88] Sheth SA, Nemoto M, Guiou M, Walker M, Pouratian N, Toga AW. Linear and nonlinear relationships between neuronal activity, oxygen metabolism, and hemodynamic responses. Neuron. 2004;**42**:347-355

[89] Vanzetta I, Hildesheim R, Grinvald A. Compartment-resolved imaging of activity-dependent dynamics of cortical blood volume and oximetry. The Journal of Neuroscience. 2005;**25**:2233-2244

[90] Mihara M, Miyai I, Hattori N, Hatakenaka M, Yagura H, Kawano T, et al. Neurofeedback using real-time near-infrared spectroscopy enhances

motor imagery related cortical activation. PLoS One. 2012;**7**:e32234. DOI: 10.1371/journal.pone.0032234

[91] Lee CH, Sugiyama T, Kataoka A, Kudo A, Fujino F, Chen YW, et al. Analysis for distinctive activation patterns of pain and itchy in the human brain cortex measured using near infrared spectroscopy (NIRS). PLoS One. 2013;**8**:e75360. DOI: 10.1371/journal.pone.0075360

[92] Ances BM. Coupling of changes in cerebral blood flow with neural activity: What must initially dip must come back up. Journal of Cerebral Blood Flow and Metabolism. 2003;**24**:1-6

[93] Frostig RD, Lieke EE, Ts'o DY, Grinvald A. Cortical functional architecture and local coupling between neuronal activity and the microcirculation revealed by in vivo high-resolution optical imaging of intrinsic signals. Proceedings of the National Academy of Sciences of the United States of America. 1990;**87**:6082-6086

[94] Malonek D, Grinvald A. Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: Implications for functional brain mapping. Science. 1996;**272**:551-554

[95] Vanzetta I, Grinvald A. Increased cortical oxidative metabolism due to sensory stimulation: Implications for functional brain imaging. Science. 1999;**286**:1555-1558

[96] Hess A, Stiller D, Kaulisch T, Heil P, Scheich H. New insights into the haemodynamic blood oxygenation level-dependent response through combination of functional magnetic resonance imaging and optical recording in gerbil barrel cortex. The Journal of Neuroscience. 2000;**20**:3328-3338

[97] Jones M, Berwick J, Johnston D, Mayhew J. Concurrent optical imaging spectroscopy and laser-doppler flowmetry: The relationship between blood flow, oxygenation, and volume in rodent barrel cortex. NeuroImage. 2001;**13**:1002-1015

[98] Suh M, Bahar S, Mehta A, Schwartz T. Blood volume and hemoglobin oxygenation response following electrical stimulation of human cortex. NeuroImage. 2006;**31**:66-75

[99] Kato T, Endo A, Fukumizu M, Furusho J, Takashima S, Kawaguchi F, et al. Single finger movement trial using human functional near-infraredgraphy (fNIR). NeuroImage. 1999;**9**(6):S430

[100] Kato T, Yamashita Y, Maki A, Yamamoto T, Koizumi H. Temporal behavior of human functional near-infraredgraphy (fNIR) using single-word speaking trial. NeuroImage. 1999;**9**(6):S1025

[101] Jasdzewski G, Strangman G, Wagner J, Kwong KK, Poldrack RA, Boas DA. Differences in the hemodynamic response to event-related motor and visual paradigms as measured by near-infrared spectroscopy. NeuroImage. 2003;**20**:479-488

[102] Ances BM, Buerk DG, Greenberg JH, Detre JA. Temporal dynamics of the partial pressure of brain tissue oxygen during functional forepaw stimulation in rats. Neuroscience Letters. 2001;**306**:106-110

[103] Thompson J, Peterson M, Freeman R. High-resolution neurometabolic coupling revealed by focal activation of visual neurons. Nature Neuroscience. 2004;**7**:919-920

[104] Menon RS, Ogawa S, Hu X, Strupp JS, Andersen P, Ugurbil K. BOLD based functional MRI at 4 Tesla includes a capillary bed contribution: Echo-planar imaging mirrors previous optical imaging using intrinsic signals. Magnetic Resonance in Medicine. 1995, 1995;**33**:453-459

[105] Hu X, Yacoub E. The story of the initial dip in fMRI. NeuroImage. 2012;**62**:1103-1108

[106] Watanabe E, Maki A, Kawaguchi F, Takashiro K, Yamashita Y, Koizumi H, et al. Non-invasive assessment of language dominance with near-infrared spectroscopic mapping. Neuroscience Letters. 1998;**256**:49-52

[107] Bisconti S, Di Sante G, Ferrari M, Quaresima V. Functional near-infrared spectroscopy reveals heterogeneous patterns of language lateralization over frontopolar cortex. Neuroscience Research. 2012;**73**:328-332

[108] Molteni E, Contini D, Caffini M, Baselli G, Spinelli L, Cubeddu R, et al. Load-dependent brain activation assessed by time-domain functional near-infrared spectroscopy during a working memory task with graded levels of difficulty. Journal of Biomedical Optics. 2012;**17**:056005. DOI: 10.1117/1.JBO.17.5.056005

[109] Zaidi AD, Birbaumer N, Fetz E, Logothetis N, Sitaram R. The hemodynamic initial-dip consists of both volumetric and oxymetric changes correlated to localized spiking activity. bioRxiv.2018. https://www.biorxiv.org/content/biorxiv/early/2018/02/22/259895.full.pdf

[110] Kato T, Kamada K, Segawa F, Sunohara N, Takashima S, Shimizu K, et al. Effects of photo stimulation on the anisotropic diffusion of the visual fibers. In: 11th Annual Scientific Meeting of the Society of Magnetic Resonance in Medicine. Proceedings of the International Society for Magnetic Resonance in Medicine. Berlin, Germany; Aug 8-14 1992;**1992**(S3):1029. https://

onlinelibrary.wiley.com/doi/
epdf/10.1002/mrmp.22419920303

[111] Hirano S, Hasegawa M, Kamei A, Ozaki T, Takashima S. Responses of cerebral blood volume and oxygenation to carotid ligation and hypoxia in young rabbits: Near-infrared spectroscopy study. Journal of Child Neurology. 1993;**8**:237-241

[112] Kamei A, Ozaki T, Takashima S. Monitoring of the intracranial hemodynamics and oxygenation during and after hyperventilation in newborn rabbits with near-infrared spectroscopy. Pediatric Research. 1994;**35**:334-338

[113] Sano M, Sano S, Oka N, Yoshino K, Kato T. Increased oxygen load in the prefrontal cortex from mouth breathing: A vector-based near-infrared spectroscopy study. Neuroreport. 2013;**24**(17):935-940. DOI: 10.1097/WNR.0000000000000008

[114] Ye JC, Tak S, Jang KE, Jung JW, Jang JD. NIRS-SPM: Statistical parametric mapping for near-infrared spectroscopy. NeuroImage. 2009;**44**:428-447

[115] Tsujimoto S, Yamamoto T, Kawaguchi H, Koizumi H, Sawaguchi T. Prefrontal cortical activation associated with working memory in adults and preschool children: An event-related optical topography study. Cerebral Cortex. 2004;**14**:703-712