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# A Mini-Review on Functional Near-Infrared Spectroscopy (fNIRS): Where Do We Stand, and Where Should We Go?

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**Abstract:** This mini-review is aimed at briefly summarizing the present status of functional near-infrared spectroscopy (fNIRS) and predicting where the technique should go in the next decade. This mini-review quotes 33 articles on the different fNIRS basics and technical developments and 44 reviews on the fNIRS applications published in the last eight years. The huge number of review articles about a wide spectrum of topics in the field of cognitive and social sciences, functional neuroimaging research, and medicine testifies to the maturity achieved by this non-invasive optical vascular-based functional neuroimaging technique. Today, fNIRS has started to be utilized on healthy subjects while moving freely in different naturalistic settings. Further instrumental developments are expected to be done in the near future to fully satisfy this latter important aspect. In addition, fNIRS procedures, including correction methods for the strong extracranial interferences, need to be standardized before using fNIRS as a clinical tool in individual patients. New research avenues such as interactive neurosciences, cortical activation modulated by different type of sport performance, and cortical activation during neurofeedback training are highlighted.

**Keywords:** functional near-infrared spectroscopy; functional neuroimaging; optical imaging; cortical activation

## 1. Introduction

Biophotonics is a bridging discipline located at a critical juncture between fundamental advances in science/technology and biomedicine. Optical technologies have been playing an increasingly big role in the study of living organisms—the brain, in particular. Neurophotonics is an exploding research field that spans the intersection of light and neurons for fundamental discovery and clinical translation [1]. Neurophotonics employs a range of optical methodologies, from microscopies to spectroscopies, to achieve a multiscale understanding of the structure and function of normal and diseased brains as well as the nervous system. In particular, neurophotonics has employed photons to: (1) Interrogate the cellular processes of the nervous systems, (2) manipulate neurons to modulate function, and (3) detect diseases for clinical diagnosis and surgical guidance. This transdisciplinary field bridges the disciplines of optical physics, biochemistry, biomedical engineering, physiology, neuroscience, and neurosurgery. In 2005, Tanner et al. [2] published the first article including the term "neurophotonics" in the title. The results reported in that article were obtained by near-infrared (NIR) spectroscopy (NIRS). The discovery of this technique, now named medical NIRS, goes back to 1977 [3], when Frans Jöbsis, Professor of Physiology at Duke University (Durham, NC, USA), reported that the relatively high degree of transparency of brain tissue in the 650–900 nm NIR range ("optical window"), and the characteristic hemoglobin (Hb) absorption spectra in this wavelength region enable real-time non-invasive detection of Hb oxygenation using transillumination spectroscopy.

In medical NIRS measurements, the source (laser or light emitting diode) and detector probes are positioned over the scalp surface to detect the change in optical density caused by the hemodynamic changes mainly expected in the cortical grey matter [4]. Consequently, the light needs to pass through different extracranial and intracranial tissues (superficial layers, skull, cerebrospinal fluid, meninges, cortical grey matter) both before and after passing through the brain. At the end, the detected emerging NIR signal (as a result of the absorption and scattering phenomena) comes mainly from oxygenated Hb ($O_2$Hb) and deoxygenated Hb (HHb) located in small vessels (<1 mm diameter). A schematic sketch representing the NIR light travelling through the different intracranial tissues is reported in Figure 1.

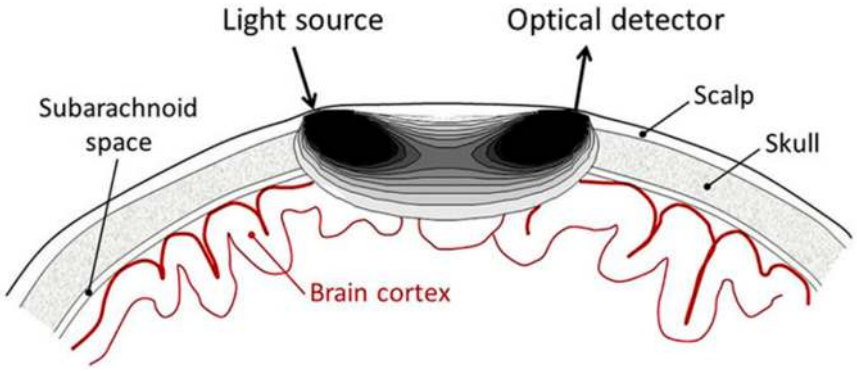


**Figure 1.** Schematic representation of the optical region of sensitivity (banana-shaped shaded area) in non-invasive near-infrared (NIR) studies of the human brain. The illumination and collection points (which are coupled to a light source and optical detector, respectively) are located on the scalp at a relative distance of the order of 3 cm. Light propagation is affected by the heterogeneity in the optical properties of tissues. Therefore, the sensitivity of the optical signal to the probed tissue is not spatially uniform (as indicated by the different grey levels within the region of sensitivity) and is maximal in the most superficial tissue layers (scalp and skull). Reproduced with permission from [5] © 2018 licensed under a Creative Commons Attribution (CC BY) license.

NIR photons propagate simultaneously in the entire illuminated volume of the head, and, due to multiple scattering, the photon paths have all possible shapes and lengths. The light intensity in the head cannot be non-invasively measured. Therefore, the light propagation in the head has been predicted by simulations using realistic head models and the Monte Carlo method [6]. The most meaningful way to characterize the variety of paths is to use the statistical quantities such as the mean total pathlength (typically 5–10 larger than the source–detector distance) and the partial pathlength—regions of the head, in particular. The partial pathlength in the brain of the adult subjects is small compared to the total pathlength (~10% of the total pathlength at a 3 cm separation).

It is important to obtain the sensitivity of the NIRS signal to the absorption change in the volume of sampled tissue, in particular in the cortical grey matter, with a particular source–detector pair. For this purpose, Sakakibara et al. [7], using Monte Carlo simulations and a five-layered head model, elaborated the spatial sensitivity profile on the surface of the grey matter (Figure 2). The source–detector pair detects the absorption change in the broad region in the grey matter. The sensitivity of the source–detector pair is the greatest at the measurement point, but the sensitivity decreases with an increase in the distance from the measurement point. The black and white lines in the figure indicate 50% and 10% with respect to the maximum sensitivity. The spatial distribution of the sensitivity of the probe arrangements depends on the positions of the measurement points and the direction of the spatial sensitivity profiles. Using the Monte Carlo method and the diffusion theory, several previous studies demonstrated that functional near-infrared spectroscopy (fNIRS) signals are more sensitive to the surface areas immediately under the optodes, i.e., the scalp, for review [5]. This limitation is less significant in young children, since, with thinner skull, the partial pathlength in the brain increases.

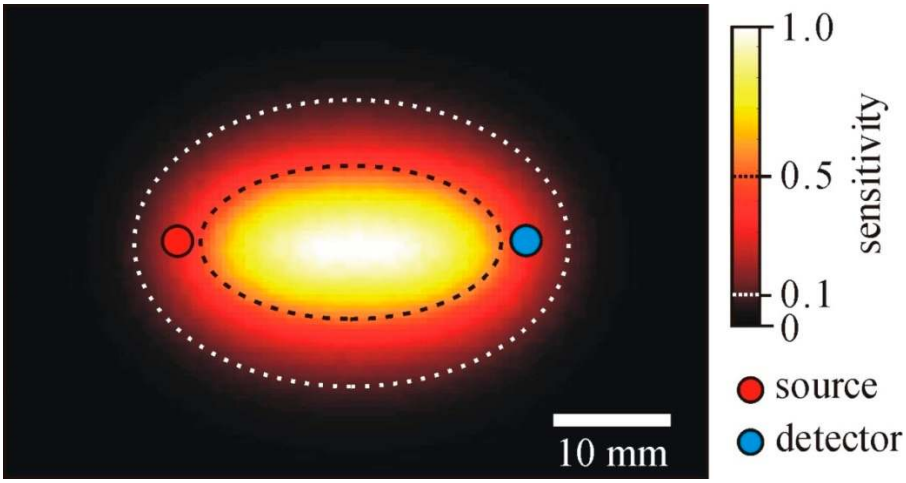


**Figure 2.** The spatial sensitivity profile on the grey matter surface. The black and white dotted lines indicate 50% and 10% with respect to the maximum sensitivity. This profile was obtained by a Monte Carlo simulation of a five-layered head model. Reproduced with permission from [7] © 2016 Springer.

In 2012, the *Journal of Near Infrared Spectroscopy Special Issue on Medical Application* nicely summarized the most important aspects of the medical NIRS in 16 articles (mainly review articles) [8,9]. Brain/muscle oximetry and functional NIRS (fNIRS) represented the most established clinical and/or basic research areas. The first brain oximeter measuring cortical Hb saturation (in %) was built in 1989 by Hamamatsu Photonics K.K. (Japan). Today, more than 10 brain oximeters with Food and Drug Administration (FDA) and/or European Union (EU) approval are commercially available and utilized worldwide mainly in cardiac surgery and neonatal intensive care units [10–13]. The present mini-review does not cover the present and future applications of oximetry. Instead, it wants to focus exclusively on fNIRS applied to different medical fields.

In the last 20 years, there have been exponential developments in the field of neuroimaging. This field includes mainly magnetic resonance imaging (MRI) and molecular imaging, and most of the changes have occurred in the latter with advances in positron emission tomography (PET). Now, it is possible to image the brain glucose consumption as well many different chemicals like dopamine, serotonin, and acetylcholine. Non-invasive vascular-based neuroimaging techniques, such as functional MRI (fMRI) and fNIRS, map brain activity through hemodynamic-based signals and are invaluable diagnostic tools in several neurological disorders. Cerebral blood flow (CBF), adequate for brain activity and metabolic demand, is maintained through the processes of neurovascular coupling. More particularly, when a specific brain region is activated, CBF increases in a temporally and spatially coordinated manner tightly linked to changes in neural activity through a complex sequence of coordinated events involving neurons, glia, arteries/arterioles, and signaling molecules. fNIRS and fMRI rely on this coupling to infer changes in neural activity that are mirrored by the changes in the blood oxygenation in the region of the activated cortical area.

fNIRS, applying an array of sources/detectors over the scalp, maps (typical sampling rate 1–10 Hz) the concomitant increase in $O_2$Hb and the decrease in HHb only at level of cortical microcirculation blood vessels by means of the characteristic Hb absorption spectra in the NIR range; fMRI only maps the decrease in HHb in all brain regions with a spatial resolution ten times higher than fNIRS does. fNIRS also maps the total Hb (tHb) (tHb = $O_2$Hb + HHb), though this is strictly related to cerebral blood volume. The hemodynamic signals are normally precisely related to the underlying neuronal activity through neurovascular coupling mechanisms that ensure the supply of glucose and oxygen to neurons [14] but also provide a heat sink to help cool the brain and removal of waste by-products [15,16]. In addition, the neurovascular coupling plays a key role in water dynamics inside the brain barrier [17]. As described recently in detail [18,19], the fNIRS signal includes six different components that can be classified according to their: (1) Source (cerebral versus

extra-cerebral); (2) stimulus/task relation (evoked versus non-evoked); and (3) physiological cause (neuronal versus systemic). The monitoring of the hemodynamic response due to neurovascular coupling is only one of these six components (i.e., the component neuronal/task-evoked/cerebral), while all the other components are the physiological noise that acts as confounders in fNIRS studies and must be removed by different methods [5,19]. While the strict relationship between CBF and neuronal activity forms a fundamental brain function, whether neurovascular coupling mechanisms are reliable across physiological and pathological conditions is still questionable; for instance, alterations of the brain vasculature compromise neurovascular coupling. The mechanisms that are involved in the neurovascular coupling are different in health and in diseases such as psychiatric disorders and stroke. In addition, neurovascular coupling mechanisms are probably affected by changing brain states like sleep, wakefulness, and attention. Though fMRI has been clinically utilized more extensively than fNIRS, in the last decade the functional activation of the human cerebral cortex has been successfully explored by fNIRS. The latest is also named: Optical topography, NIR imaging, diffuse optical imaging (DOI), or diffuse optical tomography (DOT). Unlike fMRI, fNIRS can be utilized on subjects while moving freely in naturalistic settings (such as face to face communications), in hyper-scanning studies, and in field studies on subjects practicing sports, playing a musical instrument, etc.

The present mini-review article is aimed at briefly summarizing the current status of fNIRS and at predicting where the technique should go in the next decade.

## 2. Where Do We Stand

In order to provide the readers with an update of the fNIRS methods, in Table 1 recent relevant references (33 articles published from 2012) are reported about several topics related to the fNIRS basics and technical developments. These articles were identified through the PubMed, Web of Science, and Scopus databases. The topics include: The basics of NIR photon migration, the state of the art of instrumentations/signal processing/statistical analysis, and the integration of fNIRS with other neuroimaging methods.

**Table 1.** Most relevant references about functional near-infrared spectroscopy (fNIRS): Basics and technical developments.

| Topic | Year | 1st Author [Ref] |
|---|---|---|
| Modeling near-infrared photon propagation in biological tissue | 2012<br>2016<br>2018 | Martelli [20]<br>Bigio [4]<br>Fantini [5] |
| History of fNIRS | 2012 | Ferrari [21] |
| State of the art of continuous-wave multispectral fNIRS instrumentation | 2014<br>2017 | Scholkmann [18]<br>Yücel [22] |
| State of the art of continuous-wave hyperspectral fNIRS instrumentation | 2016<br>2016<br>2018 | Nsorati [23]<br>Pham [24]<br>Giannoni [25] |
| State of the art of time-domain fNIRS instrumentation | 2014<br>2019 | Torricelli [26]<br>Yamada [27] |
| Clinical brain monitoring by time-domain fNIRS instrumentation | 2019 | Lange [28] |
| State of the art of diffuse optical imaging | 2016<br>2017<br>2018<br>2018 | Hoshi [29]<br>Lee [30]<br>Fantini [5]<br>Zhao [31] |
| State of the art of wearable fNIRS | 2018<br>2018 | Strangman [32]<br>Pinti [33] |
| State of the art of functional connectivity measurements | 2018 | Fantini [5] |

**Table 1.** *Cont.*

| Topic | Year | 1st Author [Ref] |
|---|---|---|
| Factors influencing fNIRS data and recommendations | 2010 | Orihuela-Espina [34] |
| Caps for long term fNIRS measurements | 2015 | Kassab [35] |
| Selection of the optimum source–detector distance | 2015 | Brigadoi [36] |
| Mayer waves interference | 2016 | Yücel [37] |
| Multiple components of the fNIRS signal | 2016 | Tachtsidis [19] |
| Signal pre-processing procedures | 2019 | Pinti [38] |
| Anatomical guidance for fNIRS | 2014 | Tsuzuki [39] |
| | 2015 | Aasted [40] |
| Statistical analysis of fNIRS data | 2014 | Tak [41] |
| Pattern of hemodynamic response in newborn < 1 month | 2018 | de Roever [42] |
| Pattern of hemodynamic response in infants | 2018 | Issard [43] |
| Integration of fNIRS with: | | |
| • Electroencephalography | 2017 | Chiarelli [44] |
| • Functional magnetic resonance imaging | 2017 | Scarapicchia [45] |
| • Transcranial magnetic stimulation | 2019 | Curtin [46] |
| Recent fNIRS general reviews including the advantages and limitations of fNIRS | 2018 | Fantini [5] |
| | 2018 | Pinti [47] |
| | 2019 | Quaresima [48] |

Ref: Reference number.

The advantages and disadvantages of fNIRS have been widely reported in several recent review articles [5,47,48]. Unlike other neuroimaging modalities, fNIRS has a very high experimental flexibility. fNIRS is silent, tolerant to movement artefacts, and allows for long-time continuous measurements. fNIRS can be easily integrated with fMRI, PET, electroencephalography (EEG) or event related potentials. A detailed critical comparison between fNIRS and fMRI has been recently reported [5]. Among the disadvantages, it is noteworthy to mention: (1) fNIRS does not provide anatomical information, and (2) fNIRS measurements are restricted to the outer cortex and have a low spatial resolution (2–3 cm).

Roughly twenty multi-channel fNIRS systems, which utilize arrays of multiple NIR sources and detectors arranged over the scalp, are so far commercially available [47,48]. Figure 3 shows one stationary system and two mobile wireless systems.

Multi-channel fNIRS systems utilize different NIRS techniques: (1) The continuous wave (CW) multispectral and CW hyperspectral (broadband) techniques, both based on constant tissue illumination, measuring the light attenuation; (2) the frequency-domain (FD) method, based on intensity-modulated light, measuring both the attenuation and phase delay of emerging light; and (3) the time-domain (TD) technique, based on short pulses of light, measuring the shape of the pulse after propagation through tissues [18]. The CW hyperspectral technique allows for a more accurate separation of the chromopores than the CW multispectral technique that utilizes few wavelengths [25]. The $O_2$Hb/HHb quantitation depends on the fNIRS adopted technology [5,18]. The most commonly used CW multispectral fNIRS instrumentation measures changes of $O_2$Hb and HHb (with respect to an initial value arbitrarily set equal to zero) that are calculated using a modification of the Lambert–Beer law. Considering that the tissue optical pathlength is longer than the distance between the source and the detector (Figure 1), the $O_2$Hb and HHb signal changes are expressed as μmolar*cm or mmolar*mm. CW multispectral systems offer the advantages of being low-cost and easily transportable (Figure 3). fNIRS analysis methods permit the monitoring of real-time cortical hemodynamic changes. fNIRS data from multiple simultaneous measurement sites are displayed by fNIRS systems in the form of $O_2$Hb/HHb map over a cortical area.

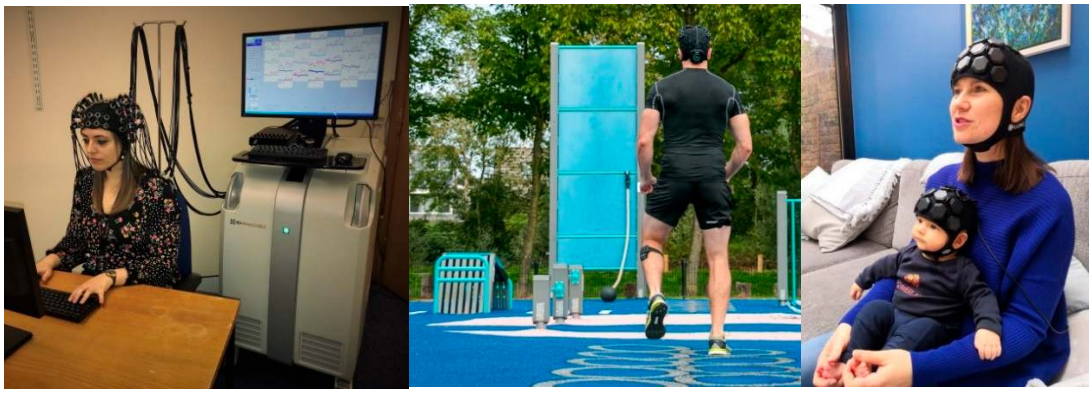

**Figure 3.** Continuous wave (CW) multispectral fNIRS instrumentations. Left panel: Stationary system in a conventional laboratory setting (LABNIRS, Shimadzu, Japan with three wavelengths and 52 channels) (year of release in USA 2015) (Photo courtesy of University College London, Department of Medical Physics and Biomedical Engineering). Central panel: Mobile wireless system in outdoor environment (Brite$^{24}$, Artinis Medical Systems, The Netherlands with two wavelengths and 24 channels) (year of release 2018) (Photo courtesy of Artinis). Right panel: Mobile wireless system (LUMO, Gowerlabs Ltd., UK) (year of release 2019) (Photo courtesy of Gowerlabs). The first commercially available modular, wearable, high-density diffuse optical tomography (DOT) system consisting of a series of hexagonal sensor modules ('tiles'), each of which provides two wavelength LED sources and four detectors. Channels are formed both within and across tiles with source–detector separations ranging from 10 to 40 mm. By connecting multiple tiles into the LUMO head cap, users can create lightweight, high-density fNIRS imaging arrays to cover any part of the cortex. We obtained permission from photographed subjects.

In 2014, the journal *Neuroimage* dedicated a Special Issue with 58 articles to celebrate the first 20 years of fNIRS research [49]. Thus far, fNIRS has lacked the combination of spatial resolution and wide field-of-view sufficient to map in detail distributed brain functions. The emergence of high-density DOT represents the last generation of multispectral CW fNIRS systems. Figure 3 depicts an example of a high-density DOT imaging system for children and adults. High-density DOT resolves the basic problem of the contribution from hemodynamic changes occurring in the scalp, skull, and other extra-cerebral tissue layers [5].

In order to provide the readers with an update on the fNIRS applications, in Table 2, 44 recent review articles (published from 2012) covering different applications are listed; the field of psychology/education is covered by 10 reviews, functional neuroimaging basic research by 13 reviews, and medicine by 18 reviews.

**Table 2.** Main reviews on the fNIRS applications in the fields of cognitive and social sciences, functional neuroimaging research, and medicine.

| Field of Application | Topic | Year | N. | Subjects | 1st Author [Ref] |
|---|---|---|---|---|---|
| ***Psychology/education*** | Cognition and food | 2015 | 39 | A | Val-Laillet [50] |
| | Cognition in infants | 2015 | 171 | C | Aslin [51] |
| | Development (typical and atypical) | 2014<br>2015 | 29<br>149 | C<br>C | Vanderwert [52]<br>Wilcox [53] |
| | Development of mathematics/language skills in children | 2018 | 7 | C | Soltanlou [54] |
| | Emotion | 2016 | 11 | A | Bendall [55] |
| | Influence of exercise on cognition | 2018 | 35 | A | Herold [56] |
| | Interhemispheric organization | 2014 | 32 | A | Homae [57] |
| | Psychology general review | 2012 | 106 | A | Cutini [58] |
| | Social development during infancy | 2018 | 29 | C | McDonald [59] |

**Table 2.** *Cont.*

| Field of Application | Topic | Year | N. | Subjects | 1st Author [Ref] |
|---|---|---|---|---|---|
| ***Economics*** | Neuroeconomic research | 2014 | 15 | A | Kopton [60] |
| ***Linguistics*** | Language and its development | 2012 | 60 | A<br>C | Quaresima [61] |
| | Word and sentence processing | 2012 | 9 | C | Rossi [62] |
| ***Neuroergonomics*** | Neuroergonomics and fNIRS | 2018<br>2019 | 68<br>37 | A<br>A | Curtin [63]<br>Zhu [64] |
| ***Functional Neuroimaging Basic Research*** | Brain computer interface | 2015 | 33 | A | Naseer [65] |
| | Driving research | 2016<br>2019 | 10<br>13 | A<br>A | Liu [66]<br>Lohani [67] |
| | Hybrid fNIRS-EEG brain-computer interfaces | 2017<br>2018 | 11<br>43 | A<br>A | Ahn [68]<br>Hong [69] |
| | Hyperscanning with multi-subject measurements | 2013<br>2018<br>2018 | 7<br>15<br>18 | A<br>A<br>A | Scholkmann [70]<br>Minagawa [71]<br>Wang [72] |
| | Postural and walking tasks | 2017 | 57 | A | Herold [73] |
| | Resting-state functional brain connectivity | 2014 | 16 | A | Niu [74] |
| | Walking | 2017<br>2019 | 31<br>35 | A<br>A | Vitorio [75]<br>Pelicioni [76] |
| | Walking and balance tasks in older adults | 2018 | 24 | A | Stuart [77] |
| ***Medicine*** | Attention deficit disorder | 2018 | 11 | C | Mauri [78] |
| | Auditory cortex plasticity after cochlear implant | 2018 | 7 | A | Basura [79] |
| | Autism spectrum disorder | 2019<br>2019 | 15<br>30 | C<br>C | Liu [80]<br>Zhang [81] |
| | Cognitive aging | 2017 | 34 | A | Agbangla [82] |
| | Developmental age attention deficit/hyperactivity disorder | 2019 | 13 | C | Grazioli [83] |
| | Eating disorders | 2015 | 11 | A | Val-Laillet [50] |
| | Epilepsy | 2016 | 23 | A | Peng [84] |
| | Gait disorders | 2017 | 12 | A | Gramigna [85] |
| | Mild cognitive impairment | 2017 | 8 | A | Beishon [86] |
| | Neurofeedback training | 2018 | 127 | A | Ehlis [87] |
| | Pain assessment in infants | 2017 | 9 | C | Benoit [88] |
| | Parkinson's disease and walking balance tasks | 2018 | 5 | A | Stuart [77] |
| | Prolonged disorder of consciousness | 2018 | 7 | A | Rupawala [89] |
| | Psychiatry | 2014 | 168 | A | Ehlis [90] |
| | Robot-assisted gait training | 2019 | 2 | A | Berger [91] |
| | Schizophrenic disorders | 2017 | 17 | A | Kumar [92] |
| | Stroke therapy/recovery/rehabilitation | 2019 | 66 | A | Yang [93] |

A: Adults; C: Children; EEG: Electroencephalography; N: Number of reviewed articles; Ref: Reference number.

The total number of the articles quoted by the 44 reviews is 1675. A detailed analysis of the very different fields of applications is beyond the aim of this mini-review. It is noteworthy to mention in the last five years, there has been an increasing number of clinical studies on psychiatric disorders and basic studies using the hyper-scanning approach. Hyper-scanning, which consists of the measurement of brain activity simultaneously on two or more people, has been adopted by fNIRS for investigating

inter-personal interactions in a natural context. fNIRS, more than any other neuroimaging modality, is suitable for investigating real social interactions by using the hyper-scanning approach.

Table 3 lists five recent video articles showing different applications; these videos very carefully illustrate different studies performed in a laboratory or outdoor area utilizing stationary or mobile/wireless instrumentations.

**Table 3.** Recent fNIRS video articles.

| Topic | Year | 1st Author [Ref] | Device, Company, Country | Number of Channels |
|---|---|---|---|---|
| Brain development. Language processing study (rhyme judgment task) on primary school aged children. | 2018 | Jasińska [94] | LightNIRS, Shimadzu, Japan | 47 |
| Hyper-scanning. Parent–child dyads for analyzing brain-to-brain synchrony during a cooperative and a competitive computer task. | 2019 | Reindl [95] | ETG-4000, Hitachi, Japan | 44 |
| Motor cortex activation during different motor tasks (cycling, walking) on adults. | 2014 | Sukal-Moulton [96] | CW6, TechEn, Milford, MA, USA | 24 |
| Temporal cortex activation during a dance video game task revealed by fNIRS and fMRI on adults. | 2015 | Noah [97] | LABNIRS, Shimadzu, Japan | 22 |
| Wearable fNIRS. Real-world ecological prospective memory tasks on adults. | 2015 | Pinti [98] | WOT-100, NeU Corporation, Japan | 16 |

fMRI = functional magnetic resonance imaging; Ref = reference number.

The top 10 cited articles on fNIRS [21,99–106], ranked according to their citations, account for between approximately 500 to over 1000 studies and (data from Scopus, Elsevier, Amsterdam, The Netherlands, June 2019) provide an insight into the historical developments and allows for the recognition of the important advances in the fNIRS field since 1993, the year of the first five fNIRS publications [21].

## 3. Where Should We Go?

The main question is: Might fNIRS improve people's lives? Imagining the future of the fNIRS instrumentations and applications is quite difficult. Considering that a significant portion of the optical pathlength of the detected photons lies within the extra-cerebral tissue (Figure 1), the "vital" main requirement of all commercial fNIRS instrumentations (using different fNIRS methods) should be their capability to correct the skull/scalp blood flow/systemic effects. For this purpose, the ideal fNIRS instrumentation should be equipped with different source–detector distances that can provide the fNIRS data necessary for adopting the different strategies to disentangle the cerebral/extra-cerebral contributions of the NIRS signals. These strategies have been recently reviewed [5,19].

The sector of wearable health technology is gaining endless interest. The use of low-cost wearable monitoring devices or wearable biosensors that allow for the constant monitoring of physiological signals, such as fNIRS signals, is essential for the advancement of both the diagnosis and treatment of diseases, as well as for monitoring active life styles [32,107].

Since the first fNIRS studies in 1993, there has been a vast improvement in CW multispectral fNIRS systems. TD-fNIRS (the most quantitative methodology) is still not at its final stage; broadband or multi-wavelength laser sources and new detectors can be further miniaturized [108], and the signal to noise ratio can be consistently improved [109,110].

New developments in fNIRS technology will further allow for the monitoring, at least on newborns, of the cytochrome-c-oxidase redox state (CCO), which is also a metabolic marker of oxidative metabolism [111]. The hyperspectral CW NIR technique is currently used by some research groups to monitor in vivo human brain metabolism via measurements of the concentration changes in $O_2$Hb, HHb and the oxidation state of CCO to achieve the quantification of cerebral metabolic activation in different situations from functional stimulation to response during oxygen-dependent conditions [23,24]. An increase of the CCO signal, typically corresponding to an increment in cerebral metabolism, was found, for instance, during the functional activation induced by simulated driving [23], the Stroop task [24] or working memory tasks [112]. Unlike the hemodynamic changes that are strongly affected by scalp blood flow changes, the changes in the CCO signal more specifically reflect the brain cortex activation. Therefore, the CCO measurement could represent an additional and more robust marker of cortical brain activation, thus allowing for the better identification of false positives and negatives [19].

The fNIRS integration with multimodal physiological monitoring and neuro-stimulation methodologies has already been demonstrated [46], but it needs to be better designed and defined. Very recently, Scholkmann et al. [113] introduced systemic-physiology-augmented functional near-infrared spectroscopy; SPA-fNIRS), which consists of a combination of fNIRS with physiological measurements. These measurements, obtained by a gas analyzer, a continuous noninvasive blood pressure monitor, and a skin conductance measuring device, can give an important integrative view because any brain stimulation could provoke systemic effects, which, in turn, could affect cerebral hemodynamics. Therefore, these effects should be investigated because the concept that cerebral hemodynamic changes are purely associated with brain activation is probably wrong, and it should be correctly revisited [113].

Considering that fNIRS has no age limitation, it is difficult to predict which would be the most useful clinical and basic science applications. Table 2 already includes some very useful clinical and basic science applications to be further investigated. The most important challenge is to improve patient care by translating the new technologies from basics science into clinical practice.

The FDA, industries and several research groups have become increasingly involved in efforts to develop international consensus standards that can facilitate the development of fNIRS devices with the potential to improve the related regulatory processes. Recommendations for conducting and reporting fNIRS findings should be also generated.

To extract and analyze the fNIRS information at single-subject level, novel methods should be conceived. Ideally, all clinical applications would require a single-subject analysis, even on-line in the case of, for example, the neurorehabilitation field. These new methods should be capable to identify the cortical circuitry and the brain function/dysfunction. For instance, several psychiatric and neurological symptoms are best explained by network-level changes rather than focal alterations. Given the broad range of related diseases and methodological variability, defining procedural clinical standards could be difficult. However, developing recommendations for patient and methodological challenges is highly desirable to move fNIRS into the clinical realm [114].

The multi-modal integrations of EEG-fNIRS seem to be promising in different fields [44]. For example, EEG-fNIRS can characterize the neurovascular coupling in the brain network dynamics induced by robot-assisted gait training [91]. In order to guide non-invasive brain stimulation protocols, a feedback of cortical activations patterns could be useful for the identifications of regions of hypo- or hyperactivity. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that involves the application of low intensity direct currents at the scalp for the modulation of central nervous system excitability [115]. tDCS is an increasingly important tool that is being used in a wide range of applications, including as a potential adjunct therapy for neurological/ psychiatric disorders. The integration of tDCS with EEG-fNIRS holds great promise for shedding light on the underlying neural mechanisms of stimulation effects [115].

A recent review article summarized the vast potential and bright future of all neuroimaging techniques [116]. Several advances in functional neuroimaging technologies offer promising opportunities to answer clinical questions and to address some of the most fundamental aspects of how the brain works. Local fluctuations in brain physiologic signals are highly correlated across brain regions organized within functional networks. Functional connectivity maps could also provide clear guidance for pre-surgical planning for the resection of brain tumors and epileptogenic lesions. In the future, such connectivity maps may allow clinicians to interrogate functionally perturbed networks controlling attention, memory, and other key cognitive domains. In addition, fNIRS will absolutely have a unique role in fields such interactive neurosciences [71], cortical activation in sport performance [117], and cortical activation during neurofeedback training [87].

Moreover, over the last 20 years, a complementary optical technique—NIR diffuse correlation spectroscopy (DCS)—has been developed for the continuous measurement of blood flow in tissue. Applications to the human brain cortex have been successfully demonstrated [118]. DCS uses the temporal fluctuations of diffusely-reflected light to quantify the motion of tissue scatterers (which are primarily red blood cells) and provides a non-invasive estimate of deep tissue microvascular blood flow. By combining oximetry and DCS flow measures, the tissue regional oxygen metabolic rate—a parameter closely linked to underlying physiology and pathological states—could finally be quantified [119,120]. Therefore, the combination of fNIRS with DCS could provide a very interesting tool for functional neuroimaging studies because it could give information about how surface/cortical blood flow changes affect the hemodynamic signals that are measured by fNIRS.

## 4. Conclusions

fNIRS technology continues to evolve, and the nature of this approach provides distinct advantages when studying human cortical activation. Despite the current limitations that are largely isolated to a limited depth of penetration, a low spatial resolution, and strong extra-cranial interference, in our view, the feasibility and the success of applying fNIRS in some branches of medicine, neuroimaging basic research, and social sciences have been well documented. The development of fNIRS has strongly gained from the advances in microelectronics, computer technology, and optical engineering. With the advent of further miniaturization and integration such as integrated optics, wearable and even disposable fNIRS technology can be envisioned. The fNIRS systems that will emerge from these developments would further enlarge the number of fNIRS applications and make fNIRS findings more easily comparable with the other ones obtained by using other technologies. Before reaching the final goal, consisting of the use of fNIRS as a clinical tool in individual patients, fNIRS procedures need to be standardized.

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