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Review

A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application

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ABSTRACT

This review is aimed at celebrating the upcoming 20th anniversary of the birth of human functional near-infrared spectroscopy (fNIRS). After the discovery in 1992 that the functional activation of the human cerebral cortex (due to oxygenation and hemodynamic changes) can be explored by NIRS, human functional brain mapping research has gained a new dimension. fNIRS or optical topography, or near-infrared imaging or diffuse optical imaging is used mainly to detect simultaneous changes in optical properties of the human cortex from multiple measurement sites and displays the results in the form of a map or image over a specific area. In order to place current fNIRS research in its proper context, this paper presents a brief historical overview of the events that have shaped the present status of fNIRS. In particular, technological progresses of fNIRS are highlighted (i.e. from single-site to multi-site functional cortical measurements (images)), introduction of the commercial multi-channel systems, recent commercial wireless instrumentation and more advanced prototypes.

Contents

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Introduction

This review is aimed at reporting the main steps of the progresses, over the last two decades, of the human functional near-infrared spectroscopy (fNIRS) instrumental development, and at highlighting the explosion of its application in several medical fields. fNIRS reveals noninvasively and in a natural environment human infant and adult cortical activation in response to diverse stimuli. The chronology of the major events leading up to human functional cortical imaging by fNIRS is reported in Table 1. Although, in the meanwhile fNIRS methodological development and data analysis made wonderful progress, these important topics are beyond the goal of this article.

Considering that fNIRS exploits the principles of near-infrared spectroscopy (NIRS), the principles of NIRS, the three different NIRS techniques (each based on a specific type of illumination) and the main feature of the NIRS instrumentation are briefly reviewed. The principles of fNIRS are reported. The development of fNIRS instrumentation from 1992 (single channel system with a low temporal resolution and poor sensitivity) up to the multi-channel systems (the first 10-channel system was introduced in 1995) is reported in detail and sketched in Fig. 1. The present high temporal resolution multi-channel systems, using the three different NIRS techniques and complex data analysis systems, provide simultaneous multiple measurements and display the results in the form of a map or image over a specific cortical area. The potential that exists for fNIRS more than for any other neuroimaging modality is represented by the realization of multi-channel wearable and/or wireless systems that allow fNIRS measurements even in normal daily activities.

The discovery and basics of near-infrared spectroscopy for monitoring brain oxygenation

fNIRS, a neuroimaging technology for mapping the functioning human cortex, exploits the principles of near-infrared (NIR) spectroscopy (NIRS). Therefore, it is appropriate to start with the discovery and principles of NIRS.

The discovery

The development of optical methods originated from the muscle oximeter invented by Glenn Millikan in the forties (for a review: Chance, 1991). It is well known that brain activity is associated with a number of physiological events; some of which are associated with changes in the optical properties of brain tissue, and can be assessed by optical techniques. The major advantages of optical methods include the biochemical specificity; temporal resolution in the millisecond range; the potential to measure intracellular/intravascular events simultaneously; and the ease with which devices can be transported.

Frans Jöbsis, the founder of in vivo NIRS, was educated in the field of non-invasive optical techniques for monitoring intact tissues of laboratory animal, as post-doctoral fellow in the Britton Chance laboratory, University of Pennsylvania (Philadelphia) from 1962 to 1964 (Chance et al., 1962). In 1964, he moved to the Department of Physiology of Duke University (NC) and, in 1977, reported that the relatively high degree of brain tissue transparency in the NIR range enables real-time non-invasive detection of hemoglobin (Hb) oxygenation using transillumination spectroscopy (Jöbsis, 1977). The details of

Table 1
Overall chronology of the major events leading up to human functional cortical imaging by fNIRS. (The details are in the text).

Year	Major events
1977	Jöbsis demonstrates the possibility to detect changes of adult cortical oxygenation during hyperventilation by near-infrared spectroscopy.
1985	First NIRS clinical studies on newborns and adult cerebrovascular patients (Brazy; Ferrari)
1989	First commercial single-channel CW clinical instrument: NIRO-1000 by Hamamatsu Photonics, Japan
1991/1992	First fNIRS studies carried out independently by Chance, Kato, Hoshi, and Villringer by using single-channel instruments
1993	Publication of the first 6 fNIRS studies
	Simultaneous monitoring of different cortical areas by 5 single-channel instruments (Hoshi)
1994	First application of fNIRS on subjects affected by psychiatric disorders by using a single-channel system (Okada)
	Hitachi company (Japan) introduces a 10-channel CW system (Maki)
	First simultaneous recording of positron emission tomography and fNIRS data (Hoshi)
1995	First evidence of a fast optical signal related to neuronal activity (Gratton)
	First two-dimensional image of the adult occipital cortex activation by a frequency domain spectrometer (Gratton)
1996	First simultaneous recording of fMRI and CW fNIRS data (Kleinschmidt)
	First simultaneous recording of fMRI and TRS fNIRS data (Obrig)
1998	First application of fNIRS on newborns using a commercial single-channel CW system (Meek)
	First images of the premature infant cortex upon motor stimulation by using a CW-fNIRS prototype (Chance)
	First application of the Hitachi 10-channel system in clinics (Watanabe)
1999	First introduction of a 64-channel TRS system for adult optical tomography (Eda)
	First introduction of a 32-channel TRS system for infant optical tomography (Hebden)
	First optical tomography TRS images of the neonatal head (Benaron)
	Introduction of the first compact 8-channel TRS system (Cubeddu)
	TechEn company (USA) starts to release its first fNIRS commercial system
2000	Hitachi company starts to release its first commercial system: (ETG-100, 24 channels)
2001	First fNIRS study using a single-channel CW portable instrument and telemetry (Hoshi)
	Shimadzu company (Japan) starts to release its first commercial system: (OMM-2001, 42 channels)
	ISS Inc.(USA) starts to release the frequency domain system: Imagent (up to 128 channels)
	First three-dimensional CW tomographic imaging of the brain (DYNOT, NIRx Medical Technologies, US) (Bluestone)
2002	Hitachi company starts to release the ETG-7000 (68 channels)
2003	Hitachi company starts to release the ETG-4000 (52 channels)
	Artinis company (The Netherlands) starts to release the Oxymon MkIII (up to 96 channels)
2004	Shimadzu company (Japan) starts to release the NIRStation (64 channels)
	First simultaneous recording of DC-magnetoencephalography and CW fNIRS data (Mackert)
2005	Hitachi company starts to release the ETG-7100 (72 channels)
2007	Shimadzu company starts to release the FOIRE-3000 (52 channels)
2009	fNIR Devices company (USA) starts to release a wearable 16-channel system for adult PFC measurements
	Hitachi company starts to release a battery operated wearable/wireless 22-channel system for adult prefrontal cortex measurements
2011	NIRx Medical Technologies company (USA) starts to release a battery operated wearable/wireless 256-channel system for adult frontal cortex measurements

CW = continuous wave; TRS = time resolved spectroscopy

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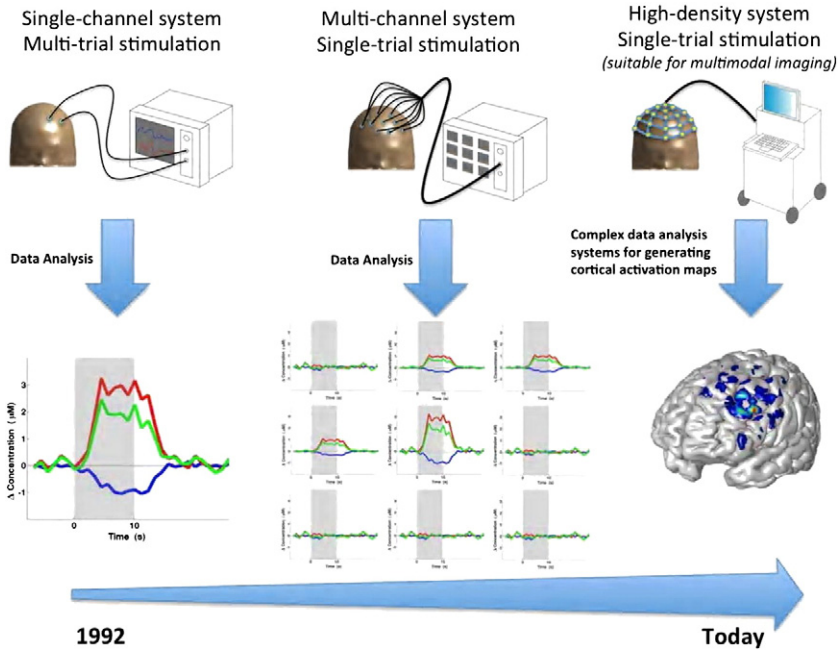

Fig. 1. Sketch of the development of fNIRS instrumentation from 1992 (single channel with a low temporal resolution and poor sensitivity) up to the multi-channel systems.

this discovery have been reviewed previously (Piantadosi, 2007). Following several demonstrations concerning the applications of NIRS in laboratory animals (Jöbsis, 1999), Jöbsis and his colleagues used this technique to study cerebral oxygenation in sick newborn infants (Brazy et al., 1985).

In 1980, Marco Ferrari, at that time working at the "Istituto Superiore di Sanità" (Rome, Italy) (before moving in 1988 to the University of L'Aquila — Italy), started to utilize prototype NIRS instruments to measure changes in brain oxygenation in experimental animal models (Ferrari et al., 1980; Giannini et al., 1982) and human adults (Ferrari et al., 1982, 1985). In 1985, he presented the data on the effects of carotid artery compression on regional cerebral Hb oxygenation and volume of cerebrovascular patients at the 13rd Meeting of the International Society on Oxygen Transport to Tissue (Ferrari et al., 1986b) together with the data on newborn brain measurements (Ferrari et al., 1986a).

In 1984, David Delpy (University College London, UK) started to develop several NIRS instruments and reported, three years later, the first quantitative measurement of various oxygenation and hemodynamic parameters in sick newborn infants including changes in oxygenated (O_2Hb), deoxygenated (HHb) and total hemoglobin (tHb; tHb = $O_2Hb + HHb$) concentrations, cerebral blood volume, and cerebral blood flow (Wyatt et al., 1986; for a review: Reynolds et al., 1988). A four-wavelength system was described by Cope and Delpy (1988) and used as the basis of the single-channel continuous wave (CW) NIRO-1000, the first commercial system built in 1989 by Hamamatsu Photonics K.K. (Hamamatsu City, Japan). This instrument represents the first fruit of a long lasting collaboration between University College London and Hamamatsu Photonics.

From 1980 to 1995, a further 9 companies were involved in developing NIRS prototypes: 1) American Edwards Laboratories in collaboration with Duke University (NC); 2) Critikon (UK) and Johnson & Johnson (Bridgewater, NJ) with Zurich University (Switzerland), 3) Hitachi Ltd. Central Research Laboratories (Tokyo, Japan); 4) Near Infrared Imaging Inc. with the University of Pennsylvania (both in Philadelphia, PA); 5) NIRSystems, Inc. (Laurel, MD) and Edwards Lifesciences Corp. (Irvine, CA) with Johns Hopkins University (Baltimore, MD); 6) Radiometer (Copenhagen, Denmark) with Copenhagen University (Denmark); 7) Sclavo (Siena, Italy) with the "Istituto Superiore di Sanità" (Rome, Italy); 8) Shimadzu (Kyoto, Japan) with Hokkaido University (Sapporo, Japan); and 9) Somanetics Corporation (Troy, MI).

Basics of near-infrared spectroscopy

The basics and main characteristics of NIRS are summarized as follows. NIRS is based on the fact that: 1) human tissues are relatively transparent to light in the NIR spectral window (650–1000 nm); 2) NIR light is either absorbed by pigmented compounds (chromophores) or scattered in tissues; 3) NIR light is able to penetrate human tissues, since the dominant factor in its tissue transport is scattering, which is typically about 100 times more probable than absorption (for a review: Delpy and Cope, 1997); and 4) the relatively high attenuation of NIR light in tissue is due to the main chromophore hemoglobin (the oxygen transport red blood cell protein) located in small vessels (<1 mm in diameter) of the microcirculation, such as capillary, arteriolar and venular beds. NIRS is weakly sensitive to blood vessels >1 mm because they completely absorb the light. Given the fact that arterial blood volume fraction is approximately 30% in humans brain (Ito et al., 2005), the NIRS technique offers the possibility to obtain information mainly concerning oxygenation changes occurring within the venous compartment.

The absorption spectrum of hemoglobin depends on its level of oxygenation. NIRS is a non-invasive safe technique that utilizes 1) laser diode and/or light emitting diode light sources spanning the optical window between 650 and 1000 nm, and 2) flexible fiber optics to carry the NIR light to (source) and from (detector) tissues. Fiber optics are very suitable for any head position and posture. NIRS measurements can be performed in natural environments without the need for restraint or sedation. Adequate depth of NIR light penetration (almost one half of the source-detector distance) can be achieved using a source-detector distance around 3 cm. The selection of the optimal source-detector distance depends on NIR light intensity and wavelength, as well as the age of the subject and the head region measured. As a consequence of the complex light scattering effect by different tissue layers, the length of the NIR light path through tissue (optical pathlength) is longer than the physical distance between the source and detector.

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The spatial distribution of NIR light through the tissue layers is rather complex. A series of photon migration simulation studies led by Eiji Okada (Keio University, Japan) and other groups provided the theoretical basis on whether fNIRS actually measures cortical activation (Custo et al., 2006; Okada and Delpy, 2003a,b; Okada et al., 1997). Briefly, as injected light diffuses in all directions inside the tissues of the head (scalp, skull, and subarachnoid space filled with cerebrospinal fluid) both before and after passing through the brain tissue, the sensitivity of each source-detector pair exhibits a banana-shaped profile. This profile is characterized by the following characteristics of spatial sensitivities: two narrow ends and a curved inward toward the center. The distortion of the spatial sensitivity is caused by the optical heterogeneity in the head (especially the low scattering subarachnoid space). Nevertheless, this distortion does not reduce the partial optical pathlength in the gray matter (NIRS sensitivity to brain activity); then the spatial sensitivity tends to distribute along the gray matter.

NIRS permits semiquantitative/quantitative monitoring of important physiological parameters including: a) O_2Hb; b) HHb; c) tHb, (tHb is strictly proportional to cerebral blood volume by the hematocrit); and d) O_2Hb saturation.

NIRS instrumentation and brain oximetry

Different NIRS instruments with related key features, advantages and disadvantages, and parameters measurable by using different NIRS techniques have been reviewed in detail elsewhere (Ferrari et al., 2004; Wolf et al., 2007) and summarized in Table 2. Briefly, three different NIRS techniques are used, each based on a specific type of illumination: 1) the CW modality which, based on constant tissue illumination, simply measures light attenuation through the head; 2) the frequency-domain (FD) method which, illuminating the head with intensity-modulated light, measure both attenuation and phase delay of emerging light; and 3) the time-domain (TD) technique which, illuminating the head with short pulses of light, detects the shape of the pulse after propagation through tissues.

The quantitation of NIRS parameters depends on the NIRS technology adopted (for a review: Delpy and Cope, 1997). The most commonly used CW-based NIRS instrumentation measures only oxygenation changes of O_2Hb and HHb (with respect to an initial value arbitrarily set equal to zero) calculated using a modification of the Lambert–Beer's law. Considering that the tissue optical pathlength is longer than the distance between the source and the detector (because of the scattering effects of different tissue layers are unknown), the unit of O_2Hb and HHb signal changes is expressed as μmolar∗cm or mmolar∗mm (Maki et al., 1995). Furthermore, CW-based systems offer the advantages of low-cost and ease of transport. In ascending order, CW-, FD-, and TD-based instruments increase in cost and technological complexity. Only the FD and TD techniques offer the possibility to absolutely characterize the optical properties of tissues (absorption and reduced scattering coefficients), from which it is possible to retrieve absolute O_2Hb and HHb concentrations.

Subsequently the preliminary prototypes, several commercial two-channel brain oximeters (utilizing spatially resolved CW spectroscopy) have been made available in the nineties for monitoring adults and newborns at risk of brain hypoxia/ischemia, permitting clinicians to detect and correct a variety of life threatening complications and improve clinical outcomes (for a review: Drayna et al., 2011; Ferrari and Quaresima, 2012; Greisen et al., 2011; Smith, 2011; Wolf et al., 2012). Of these, the INVOS 3100 (Somanetics Corporation) was the first cerebral oximetry device to be approved by the United States Food and Drug Administration in May 1993. The first commercial single-channel spatially resolved spectroscopy oximeter (OM-200) was introduced by Shimadzu, Japan in 1997. In 1998, two-channel spatially resolved spectroscopy oximeters (NIRO-300 (Hamamatsu, Japan) and INVOS-4100 (Somanetics)) were commercialized and in 1999 Shimadzu introduced a two-channel oximeter (OM-220). To date, it is estimated that approximately 10,000 brain oximeters have been utilized worldwide, mostly on adults. In addition, several more quantitative oximeter prototypes are under development in several University research groups. It is worthy of note that the "Japanese Society on Medical NIRS" was founded in 1994 and continues to hold annual meetings.

The discovery of functional NIRS (fNIRS)

The basics principles of fNIRS

Although the image intensity that varies with HHb content, termed "blood oxygenation level dependent" (BOLD), was suggested for potential use in functional studies of the brain in 1990 (Ogawa et al., 1990), the era of BOLD-based functional MRI (fMRI) initiated two years later (for a review: Raichle, 2000) with the publication of three exciting papers (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992). Interestingly, the discovery of human fNIRS goes back to 1992. fNIRS or optical topography or NIR imaging mainly detects changes in optical properties of the human cortex simultaneously from multiple measurement sites and the results can be displayed either in the form of a map or image over a specific area. The basic principles of fNIRS including features, strengths, advantages, and limitations have been recently summarized in several review articles (Elwell and Cooper, 2011; Gervain et al., 2011; Lloyd-Fox et al., 2009;

Table 2
fNIRS techniques: main characteristics and measurable parameters.

Main characteristics	fNIRS techniques-based instrumentation		
	Continuous wave	Frequency-domain	Time-domain
Sampling rate (Hz)	≤100	≤50	≤10
Spatial resolution (cm)	≤1	≤1	≤1
Penetration depth with a 4 cm source-detector distance	Low	Deep	Deep
Discrimination between cerebral and extra-cerebral tissue (scalp, skull, CSF)	n.a.	Feasible	Feasible
Possibility to measure deep brain structures	Feasible on newborns	Feasible on newborns	Feasible on newborns
Instrument size	Some bulky, some small	Bulky	Bulky
Instrument stabilization	n.r.	n.r.	Required
Transportability	Some easy, some feasible	Feasible	Feasible
Instrument cost	Some low, some high	Very high	Very high
Telemetry	Available	Difficult	Not easy
Measurable parameters			
[O_2Hb], [HHb], [tHb]	Yes, changes	Yes, absolute value	Yes, absolute value
Scattering and absorption coefficient and pathlength measurement	No	Yes	Yes
Tissue O_2Hb saturation measurement (%)	No	Yes	Yes

CSF = cerebrospinal fluid, HHb = deoxyhemoglobin, n.a. = not available, n.r. = not required, O_2Hb = oxyhemoglobin, tHb = O_2Hb + HHb.

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Minagawa-Kawai et al., 2008; Quaresima et al., 2012). A typical single-site cortical activation, as revealed by fNIRS, is shown in Figs. 1 and 2. The increase in O_2Hb and the concomitant decrease in HHb reflect an increase in local arteriolar vasodilatation, which increases local cerebral blood flow and cerebral blood volume, a mechanism known as neurovascular coupling. The increased oxygen transported to the area typically exceeds the local neuronal rate of oxygen utilization, resulting in an overabundance of cerebral blood oxygenation in active areas. The precise neuronal origin of the hemodynamic responses measured by fNIRS, fMRI and other techniques is still relatively unknown, despite its importance (for review: Figley and Stroman, 2011; Vanzetta and Grinvald, 2008). It is beyond the scope of this article to cover these important issues.

The first single-site fNIRS human adult studies

The first fNIRS human studies, adopting single-site measurements, were performed in the latter part of 1991 and in 1992, and published in 1993 by four research groups belonging to the: 1) Hokkaido University (Sapporo, Japan); 2) Tokyo National Institute of Neuroscience (Japan); 3) University of Munich (Germany); and 4) University of Pennsylvania (Philadelphia, PA). The two Japanese groups, in collaboration with Japanese industries Hamamatsu Photonics and Shimadzu, submitted their findings to international scientific journals earlier than the other two.

One fNIRS study was submitted in June 1992 by the group of Tamura (Institute for Electronic Science, Hokkaido University) to Neuroscience Letters and was accepted two months later (Hoshi and Tamura, 1993a). They observed bilateral prefrontal cortex (PFC) oxygenation changes (evidenced as an increase in O_2Hb and decrease in HHb) in 14 volunteers during a mental task using two CW-instruments, each equipped with a single-channel (OM-100A, Shimadzu, Japan). In order to quantitatively detect the small absorption change in the brain, they employed the three-wavelength method (Hazeki and Tamura, 1988) for eliminating scattering artifacts during functional studies. Moreover, the Hokkaido University group, by using the OM-100A, demonstrated gender- and handedness-related differences of PFC oxygenation in 72 volunteers (Okada et al., 1993).

Although, another fNIRS study was submitted earlier to The Lancet journal (December 1991) by Toshinori Kato (from the Tokyo National Institute of Neuroscience), it was not published as the journal "was not able to find room for it". The study, performed in collaboration with Takeo Ozaki of the Application Systems Division of Hamamatsu Photonics (Japan), investigated human visual cortical function for the first time during and after photic stimulation, utilizing the single-channel CW instrument NIRO-1000. Preliminary results were published in the Proceedings of a national conference (Takashima et al., 1992) and submitted as a "Letter" to the Journal of Cerebral Blood Flow and Metabolism, in February 1992. Finally, the manuscript was accepted for publication in October 1992 (Kato et al., 1993). During photic stimulation, O_2Hb increased in the occipital region of five subjects, whereas no oxygenation changes were observed in the PFC. The O_2Hb changes were reproducible following repeated photic stimulations. These preliminary observations were confirmed and refined later by the groups from the University College London (Meek et al., 1995) and the Humboldt University of Berlin (Wenzel et al., 1996), with both groups using the single-channel CW instrument NIRO-500 (Hamamatsu Photonics, Japan).

In August 1992, Arno Villringer (in close cooperation with Ulrich Dirnagl), at that time working at the University of Munich (Germany) (before moving to the Neurologische Klinik, Charité — Humboldt University of Berlin), presented the first of a long list of fNIRS studies at the 20th Meeting of the International Society on Oxygen Transport to Tissue held in Mainz (Germany) (Villringer et al., 1994). A PFC increase in O_2Hb and tHb (measured by the NIRO-500) was observed in most (10 out of 12) subjects during cognitive stimulation (calculation task); the same pattern was observed even in the occipital region during visual stimulation (picture watching). Afterward, the same group carried out an interesting fNIRS study on epileptic patients during spontaneously occurring complex-partial seizures. Extremely large increases in O_2Hb and tHb were measured during these seizures. A part of these data was published in Neuroscience Letters (Villringer et al., 1993). Interestingly, this study pointed out that PFC oxygenation changes were not accompanied by alterations in skin blood flow.

A different fNIRS approach, adopted by Britton Chance (University of Pennsylvania), was presented in October 1992 at the Society for Neuroscience Conference held in Anaheim (CA) (Chance et al., 1992b) and published the following year (Chance et al., 1993). Cognition-activated low-frequency modulation of light absorption was demonstrated in the PFC, utilizing a very simple CW single-channel prototype. The observed oxygenation changes were associated with brain activity in response to problem solving of analogies presented visually that require an associative function in the frontal region. It is worthy of note to consider that in 1992 Chance, a renowned biophysicist (pioneer in several fields including cellular energy metabolism and in vivo magnetic resonance spectroscopy), was 80 years old and, for the following years, he was continuing to work actively and successfully in several aspects of NIRS/fNIRS research.

The necessity to simultaneously map cortical oxygenation in different areas of the brain was suggested by the first single-site fNIRS studies as well as by the previous brain oximetry clinical studies. Fig. 3 shows a drawing of the patent made by the Rome group to point out the relevance of the simultaneous mapping of different cortical areas (Giannini et al., 1988).

The usefulness of measuring by fNIRS simultaneously different cortical regions was demonstrated in 1993 (Hoshi and Tamura, 1993b) by using at the same time 5 single-channel instruments (OM-100A, Shimadzu). These authors first succeeded in detecting region-specific changes in both O_2Hb and tHb during various mental tasks, in addition to visual and auditory stimulations. The time course of increases in cortical oxygenation varied with each brain region and depended on the type of internal operations occurring during the mental tasks. However, actual fNIRS mapping, whether it is continuous image construction or discrete channel-wise representation, needs to solve the problem of light interference among different channels. This was first solved by Maki et al. (1995) who introduced the frequency encoding method.

Detailed evidence of cortical oxygenation changes in response to motor tasks was obtained for the first time by using the CW single-

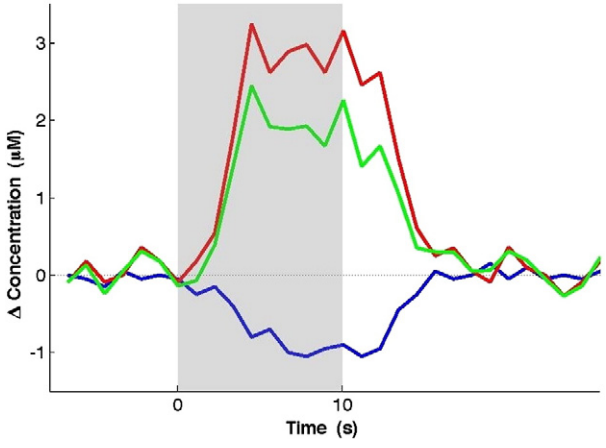

Fig. 2. Sketch of the typical cortical activation as revealed by fNIRS. The increase in oxygenated hemoglobin (red line) and the concomitant decrease in deoxygenated hemoglobin (blue line) reflect an increase in local arteriolar vasodilatation which increases local cerebral blood flow and total hemoglobin (green line) that is strictly related to cerebral blood volume. The shadow indicates the stimulus duration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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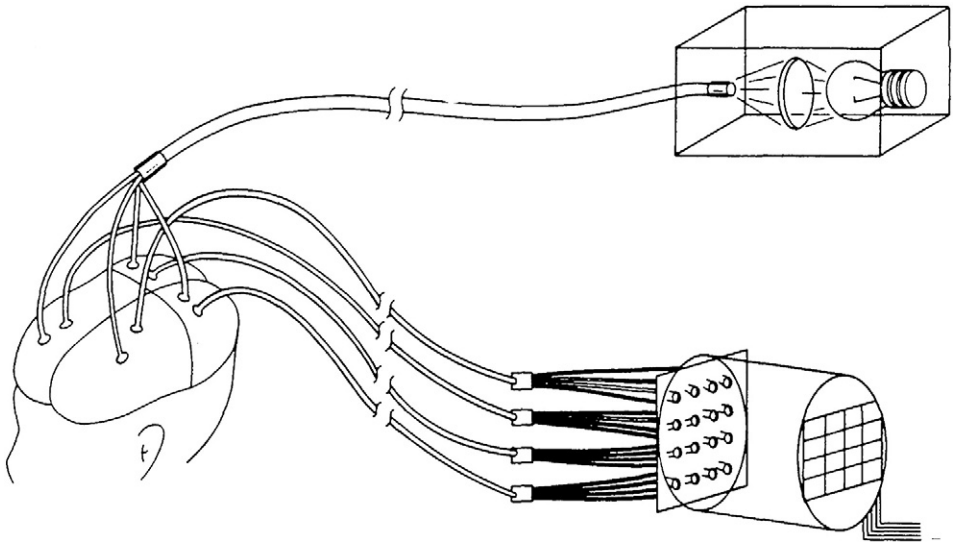

Fig. 3. A drawing of the 1985 Patent made by the Rome group to point out the relevance of the simultaneous mapping of different cortical areas.

channel prototype which was developed at the Radboud University of Njimegen (The Netherlands) (Colier et al., 1997). The high temporal resolution (10 Hz) of this prototype showed evidence of the heart beat in the O_2Hb signal. Moreover, the same instrument was utilized for detecting reproducible motor-cortex oxygenation patterns in response to single cycles (20 s) of cyclic coupled movements of hand and foot (Colier et al., 1999).

The Neuroimage journal, created in 1992, started to publish fNIRS studies in 1997 with the paper by Hoshi and Tamura (1997a) in which the sequential PFC activation during mental tasks was described, and the potential of fNIRS for imaging the sequence of brain activation was first suggested. Moreover, Hoshi and Tamura (1997b) reported for the first time the PFC fluctuations of O_2Hb and HHb during the resting period and demonstrated that those fluctuations were unrelated to alterations in the systemic circulatory system. Afterward, several other researchers started to investigate the physiological fluctuations observable by fNIRS.

The results achieved over of the first early years of fNIRS research have been nicely reviewed (Hebden and Delpy, 1997; Tamura et al., 1997; Villringer and Chance, 1997).

The first single-site fNIRS human infant studies

A few years after the first fNIRS studies on human adults, the group from University College London published the first fNIRS study carried out on infants (Meek et al., 1998). A visual stimulation-induced (checkerboard with a 5-Hz pattern reversal) increase in O_2Hb was found on the visual cortex of awake infants by utilizing the single-channel CW instrument NIRO-500. Whereas in the early infant fNIRS studies the main aim was to detect the primary cortical areas response to basic stimuli, such as acoustic tone in the auditory cortex (Sakatani et al., 1999; Zaramella et al., 2001), odor stimulation in the olfactory cortex (Bartocci et al., 2000), stroboscopic flashing light in the visual cortex (Hoshi et al., 2000a), in more recent studies researchers have focused their attention on infant cortical responses to more complex stimuli (i.e. object processing, social communication, biological motion processing, face processing) which are supposed to activate multiple cortical regions (for a review: Lloyd-Fox et al., 2009).

The first single-site fNIRS human clinical studies

The earliest clinical application of fNIRS goes back to 1994 (Okada et al., 1994). This study, performed on 38 subjects affected by chronic schizophrenia by the group at Hokkaido University, aimed at finding and qualifying disturbances in inter-hemispheric integration in brain oxygenation changes during a mirror drawing task. In response to this task, normal subjects showed distinct and well-integrated patterns of changes in O_2Hb and HHb. On the other hand, one half of the subjects affected by schizophrenia showed deregulated patterns between hemispheres, which never appeared in normal subjects. These results demonstrated for the first time the usefulness of fNIRS in psychiatry. The age dependency of changes in PFC oxygenation and the small activation observed in subjects affected by Alzheimer's disease during a calculation task were demonstrated by the group from Munich (Hock et al., 1995, 1996). In 1997, Fallgatter from the University Clinic of Würzburg (Germany) published the first of his long list of fNIRS clinical studies demonstrating the loss of functional hemispheric asymmetry in subjects affected by Alzheimer's dementia (Fallgatter et al., 1997).

The first simultaneous fNIRS-fMRI and fNIRS-PET studies

It is well known that the combination of the data from different techniques allows a description of human brain activity with a combination of spatial and temporal precision and contrast mechanisms that are impossible to achieve using any single imaging modality. The group from Humboldt University of Berlin in collaboration with Frahm (Max Planck Institute for Biophysical Chemistry, Göttingen, Germany) carried out the first simultaneous fMRI and fNIRS recording of cerebral blood oxygenation changes during human brain activation (Kleinschmidt et al., 1996). Specifically, changes in cortical oxygenation due to functional activation of the primary sensorimotor cortex during a unilateral finger opposition task were mapped simultaneously by fMRI and fNIRS (NIRO-500). Activation foci along the contralateral central sulcus displayed task-associated increases in MRI signal intensity, indicating a concomitant decrease of the focal concentration of HHb. This interpretation was confirmed by the simultaneous decrease in HHb, as measured by fNIRS. Several combined fMRI and fNIRS studies have been performed in the following years to validate the correlation of the BOLD signal with the cortical hemodynamic changes, as measured by fNIRS (for a review: Steinbrink et al., 2006).

The first study on the simultaneous measurement of regional cerebral blood flow by positron emission tomography (PET) and cortical hemodynamic changes by fNIRS during a mental task was performed on two subjects by Hoshi et al. (1994). The second study was performed on subjects affected by Alzheimer's disease and controls

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demonstrating a significant correlation during the performance of a verbal fluency task (Hock et al., 1997). So far, very few simultaneous PET and fNIRS studies have been carried out due to the different temporal resolution of the two techniques.

From single-point CW fNIRS measurements to CW multi-channel functional cortical near-infrared topography

The first near-infrared images of human tissues

The first transillumination (diaphanoscopy) using white light of the larynx, the paranasal sinuses and testis goes back to the eighteen-century. Later, transillumination was adopted as a means of diagnosing lesions of the female breast, as described by Cutler (1929). The first one-dimension transillumination of the human hand oxygenation was realized by Jarry et al. (1989) using two pulsed NIR lasers and concluded that "these results could be applied to imaging".

Brain optical imaging was the main topic of the conference on "Optical imaging of brain function and metabolism" organized by Chance, Villringer, Dirnagl, and Einhäupl, which was held in Garmisch-Partenkirchen (Germany) on October 21–22, 1991 (Chance et al., 1992a).

The first in vivo NIR images were obtained from the human forearm during ischemia by Araki and Nashimoto (1992) using a 2-wavelength CW-NIRS prototype. These researchers from Saitama University (Japan) measured NIR projection images at 700 and 800 nm, and they obtained two-dimensional images of Hb oxygenation in the forearm of about 5 cm thickness. Forearm occlusion caused an increase in the two-dimensional optical density image at 700 nm, and a slight decrease in the image at 800 nm.

Continuous wave multi-channel instrumental development in Japan

At the end of the eighties, the Japanese companies Hamamatsu Photonics, Hitachi and Shimadzu started to make tremendous contributions to the development of fNIRS instrumentation. From 1988 to 1996, Hideaki Koizumi and Atsushi Maki (from the Tokyo Hitachi Ltd. Central Research Laboratories) developed the first optical computerized tomography system for the rat head using the TD technique, also named time resolved spectroscopy (TRS). This prototype was built using Hamamatsu components. A 3-dimensional reconstruction method, based on the partial pathlength distribution calculated by Monte-Carlo simulation, was utilized (Maki and Koizumi, 1996). Then, the feasibility of using NIR light for obtaining in vivo Hb oxygen-saturation images of the rat brain by a time-gating technique was demonstrated (Kawaguchi et al., 1991; Shinohara et al., 1991).

Hitachi introduced the first 10-channel CW system in 1994 (Watanabe et al., 1994). The topographic imaging system concept was for the first time introduced in the article by Maki et al. (1995). Cortical mapping, also called optical topography, represents a means of acquiring multiple reflectance measurements at small source-detector separations (usually 3 cm) over a large area of the head simultaneously. In the same article, the concept of the frequency encoding method, which is the principle of the Hitachi multi-channel technology, was also introduced. In order to bear out the hypothesis that NIRS can measure brain activity, those authors employed block-designed paradigms and compared the difference of the hemodynamic responses in the motor area induced by different stimulations (i.e., left and right finger tapping). By mapping the static topograms of the changes in HbO_2, HHb and tHb and comparing them with an anatomical image of MRI, it was found that the particular activated area was located on the motor cortex along the central sulcus. These results demonstrated for the first time that functional NIR topography (fNIRT) can be used to effectively map human brain activity. The temporal resolution (images generated per second) of fNIRT systems depends on the number of source-detector pairs and the required signal-to-noise ratio. The Hitachi system was able to provide images with an acquisition rate of 2 Hz (Maki et al., 1995). The results of the first clinical application of fNIRT as serial maps of tHb were published by Watanabe et al. (1998) (Fig. 4). The hemispheric dominance for language was demonstrated on healthy volunteers and on subjects affected by epilepsy using a word-generation task. Very recently, the use of word-generation tasks in fNIRS studies has been nicely reviewed (Dieler et al., 2012). The first commercial Hitachi CW 24-channel instrument, named ETG-100, was released in 2000 (Yamashita et al., 1999). The results achieved by Hitachi over the first years of its fNIRS research activity were previously reviewed by Koizumi et al. (1999, 2003). The ETG-7000 (a 68-channel system), ETG-4000 (a 52-channel system) and ETG-7100 (a 72-channel system) were released by Hitachi in 2002, 2003 and 2005, respectively. Only the last two instruments are presently on the market (ETG-4000: commercialized worldwide, and ETG-7100: commercialized only in Japan). So far, almost 300 instruments have been sold by Hitachi. From 2000 to today, several milestone functional studies have been published using the Hitachi systems. It is worthy of note to mention the first two fNIRT studies performed on newborns. Specifically, Mehler's group in Trieste (Italy) investigated language recognition at birth (Peña et al., 2003), and Taga's group in Tokyo studied the response of the occipital cortex to brief changes in the luminance contrast of visual stimulation (Taga et al., 2003). More recently, the latter group has investigated, by using a 94-channel NIRS system (ETG-7000), developmental changes in the global cortical networks from several days to 6 months after birth by examining spontaneous fluctuations in brain activity (Homae et al., 2010). The first decade of the use of fNIRS on infants, the potential of the technology, and the future prospects in the field of developmental neuroscience have been reviewed (Lloyd-Fox et al., 2009). Moreover, a video article was realized to illustrate the running of a typical CW fNIRS study performed on an infant (Shalinsky et al., 2009).

In 1998, Shimadzu started to work on the development of multi-channel CW systems. The first commercial 42-channel instrument, named multi-channel oxygen monitor OMM-2001, was released in 2001. In the same year, the first article reporting the use of this system was published (Miyai et al., 2001). These authors succeeded in visualizing cortical activation patterns of human gait; walking activities were bilaterally associated with increased levels of O_2Hb in the medial primary sensorimotor cortices and the supplementary motor areas. Alternating foot movements activated similar but less broad regions. Gait imagery increased activities caudally located in the supplementary motor areas. These findings indicated that fNIRT might be useful for evaluating cerebral activation patterns during pathological gait and rehabilitative intervention. In 2004, the OMM-3000 (a 52-channel system) and NIRStation (a 64-channel system) were launched by Shimadzu and they are currently present on the market exclusively in Japan. The 52-channel Functional Optical Imager for Research (FOIRE 3000) was launched in 2007 and commercialized worldwide in 2010. The latter system allows simultaneous fNIRS-EEG measurements and integrated analysis. So far, Shimadzu has sold over 100 instruments.

Continuous wave multi-channel instrumental development in America and Europe

Since 1985 Simon Arridge (University College London) started his research work on diffuse optical tomography (DOT) for imaging the optical properties of biological tissue (Arridge et al., 1985, 1991). DOT operates by measuring light transmission through the body between different points on the surface. The distribution of photons in these boundary measurements, as well as the temporal dispersion and spectral information, can be used to reconstruct images of the internal distribution of optical absorption and scattering coefficients. DOT is generally recognized as a nonlinear inverse problem. A physically accurate model, that describes the progress of photons from the source optodes through the media and to the detector optodes, is constructed. This is termed the forward problem. This model is parameterized by the

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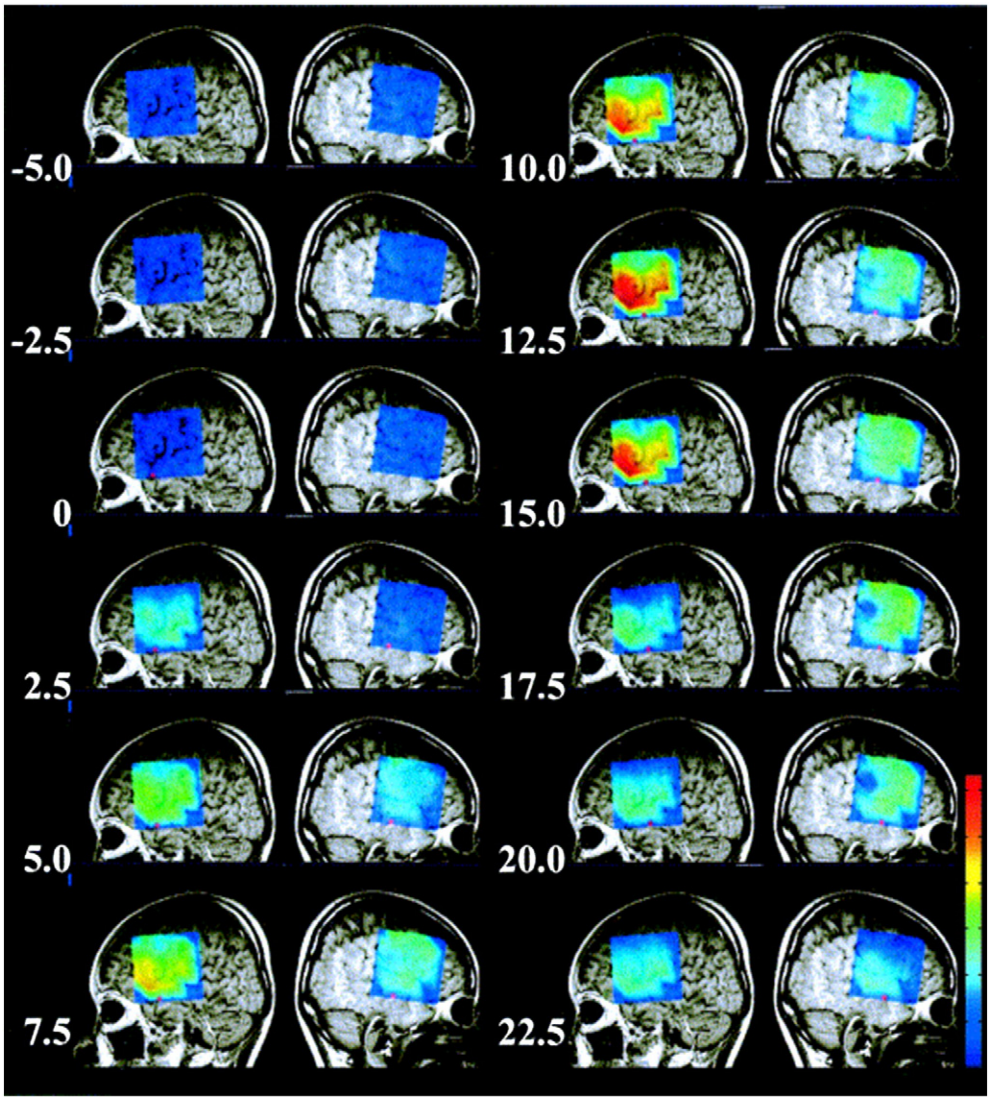

Fig. 4. Serial contour pseudo color maps of total hemoglobin changes obtained by a 24-channel (12 on each hemisphere) continuous wave system (Tokyo Hitachi Ltd. Central Research Laboratory). The maps are overlaid on the lateral MRI surface image of the subject. Total hemoglobin increased after the beginning of the task (a 17-s word generation) and gradually decreased at its end. The largest increase was observed in the left inferior frontal area which is in the vicinity of the Broca's area. The numbers indicate the time in s (being time 0 the beginning of the task).
Adapted from Watanabe et al. Neurosci. Lett. (1996).

spatial distribution of scattering and absorption properties in the media. These properties are adjusted iteratively until the predicted measurements from the forward model match the physical measurements from the device. This is termed the inverse problem (for reviews: Arridge, 2011; Arridge and Hebden, 1997; Boas et al., 2001a).

In the United States, David Boas (Harvard Medical School, Boston, MA) and Randall Barbour (SUNY Downstate Medical Center, Brooklyn, NY) gave a relevant contribution to the application of DOT in human fNIRS measurements. Boas was working (from 1998) on several theoretical, instrumental and clinical aspects of fNIRS. At the beginning, his research group investigated the accuracy of fNIRS for identifying focal activation (Boas et al., 2001b), and combined fNIRS with other neuroimaging techniques (such as EEG, magnetoencephalography and fMRI).

Specifically, Boas has contributed to the development of novel algorithms for obtaining dynamic space-time solutions of multimodal data to better understand the hemodynamic response during brain activity (Ou et al., 2009; Strangman et al., 2002). Boas led the development of several new medical optical imaging techniques. Since 1999, commercial CW fNIRS systems (with different number of sources and detectors) have been introduced by TechEn (Milford, MA) (Franceschini and Boas, 2004). The most recent system (CW6) can monitor signals from any combination of up to 32 lasers and 32 detectors. So far, over 50 units have been sold in the United States and worldwide by TechEn.

Randall Barbour started to work on NIRS in 1987. Throughout the nineties his principal focus dealt with improving numerical capabilities for image recovery. By the late 1990's Barbour and co-workers had identified that analysis of normalized data produced tomographic images with high stability sufficient to support time series studies. Based on this finding an instrument development effort was initiated in 1999.

The first application of the model-based approach to three-dimensional tomographic imaging of the adult brain was demonstrated by Bluestone et al. (2001), who acquired measurements on the adult forehead during a Valsalva maneuver using a multi-channel system (Schmitz et al., 2000). The images of the cortex were generated using a finite-element formulation of the three-dimensional, time-independent diffusion equation as a forward model. Since 1999, several commercial imaging systems, with different number of sources and detectors, have been introduced by NIRx Medical Technologies LLC. These systems provide three-dimensional tomographic and topographic investigations of the head. Recently, Koch et al. (2010), using a high-density diffuse-optical sensing array in conjunction with optical tomographic

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reconstruction, provided high-resolution functional mapping of the human somatosensory cortex. So far, over 50 units have been sold in the United States and worldwide.

From January 1993 to December 1998, the NIRS and NIR imaging research of different European Universities and companies were supported in part by the European Union. In those years, the European companies Philips, Siemens and Zeiss were developing optical imaging instrumentation for the human female breast. The building of the first two European CW multi-channel fNIRS systems, made by the Radboud University of Nijmegen (The Netherlands) and Humboldt University of Berlin, was supported in part by the project of the European Union on "Imaging of the language functions in the brain" (June 1999–May 2001). The 12-channel system, built by Colier and co-workers in Nijmegen, was utilized for collecting real time cortical oxygenation maps upon motor and cognitive stimuli (Quaresima et al., 2001). The same instrument was utilized for revealing the lateral frontal cortex oxygenation changes during translation and language switching (Quaresima et al., 2002). The results of the latter study confirmed that Broca's area is involved in the translation process and its activation is unaffected by the direction of the translation. Very recently, the results obtained by using fNIRT for language imaging studies in newborns and adults have been reviewed (Quaresima et al., 2012). The Artinis Medical System (founded in April 2002 as a spin-off of the Radboud University of Nijmegen) introduced in 2003 a multi-channel (up to 96) instrument (Oxymon MkIII). So far, Artinis is the only European-based commercial fNIRS company and has sold 80 systems worldwide.

In 1999, the Humboldt University of Berlin built a 22-channel CW instrument that was utilized successfully for human visual cortex studies (Obrig and Villringer, 2003).

The results obtained over the first years of fNIRT studies have been nicely reviewed by several groups (Hebden, 2003; Hoshi, 2003, 2005, 2007; Obrig and Villringer, 2003; Strangman et al., 2002). Since 1995, the results of fNIRS research have been presented mainly at the conferences of the Organization for Human Brain Mapping (OHBM) and the SPIE—The International Society for Optical Engineering. It is worthy of note that the "Japan Optical Functional Brain Imaging Society (JOFBIS)" was founded in March 2004 and continues to hold annual meetings. The first International fNIRS Conference was held in Boston (MA) in 2010 and biennial meetings are planned (www.fnirs.org).

Multi-channel functional near-infrared imaging by time resolved and frequency resolved systems. Towards optical tomography

The introduction of time resolved instrumentation

In vivo NIR TD and FD measurements were introduced in 1988 and 1990, respectively. To generate images that can discriminate between the effects of absorption and scattering in tissue, it is necessary to acquire more than just measurements of intensity. In fact, to evaluate changes in chromophore concentration in non-arbitrary units, it is necessary to determine the average pathlength of transmitted (or reflected) photons. The pathlength of individual photons can be recorded directly using a time-of-flight system, which employs a source of extremely short pulses of NIR laser light and a fast time-resolved detector. This was first demonstrated on rat head at the University College London (Delpy et al., 1988). From the time-of-flight measurements of pathlength across the rat head they reported a pathlength of 5.3 ± 0.3 times the head diameter. These data have been used to calculate the differential pathlength factor (DPF), defined as the mean distance traveled by the photons divided by the distance between the points where light entered and left the head. In the same year, Chance, utilizing the instrumental facilities of Coherent Laser Products Division (Palo Alto, CA), performed time-of-flight measurements to determine the kinetics of Hb deoxygenation in cat brain during mild ischemia/hypoxia (Chance et al., 1988). The DPF value was first measured on the head of preterm infants after death (Wyatt et al., 1990), and later on: 1) living newborn infants and adults (van der Zee et al., 1992), and 2) adults during hypoxic hypoxia (Ferrari et al., 1993).

The introduction of frequency resolved instrumentation

In 1990, Chance, Enrico Gratton (University of Illinois at Urbana-Champaign, Urbana, IL) and Lakowicz (University of Maryland, Baltimore, MD) reported for the first time the use of FD measurements to characterize time-dependent migration of NIR photons in tissues. This technique measures the phase shift and amplitude changes of intensity-modulated light after propagation through different tissue layers. By combining NIR intensity-modulated illumination with FD detection methods, Gratton obtained the first preliminary 2-dimensional images of the human hand (Gratton et al., 1993). In the following years, several portable FD prototypes were built by the groups from the University College London, the University of Illinois at Urbana-Champaign, the University of Pennsylvania, the University of Keele (UK), and others (for a review: Chance et al., 1998b). The instrument developed at the University College London was utilized to measure the optical pathlength on newborn and adult head (Duncan et al., 1995); the instruments developed at Urbana-Champaign and Philadelphia were utilized also to measure for the first time O_2Hb saturation on adult PFC (De Blasi et al., 1995; Levy et al., 1995). The first commercial single-channel FD oximeter, Oxiplex, was introduced in 1998 by the ISS Inc. (Champaign, IL) and even now it remains the only commercially available system.

Since 1995, FD instrumentation has been utilized to detect the neuronal signal related to optical changes directly associated with neuronal activity (Gratton et al., 1995). This signal (an increase in the phase) arises within 100 ms after the onset of the stimulation and has been studied at the cellular level, in experimental animal models and in human adults (for a review: Gratton and Fabiani, 2010). The non-invasive detection of the localized neuronal signal, although extremely interesting, is still controversial mainly because these fast signals are very much weaker than those of hemodynamic origin (for a review: Wolf et al., 2008).

The first attempts of fNIRT, using the FD approach, were performed using single-channel FD systems. The first functional 2-dimensional images of the human occipital cortex during visual stimulation were obtained by sequential measurements collected by a FD spectrometer with a spatial and temporal resolution of 0.5 cm and 50 ms, respectively (Gratton et al., 1995).

FD- and TD-based imaging systems have been developed by either Universities or companies (for a review: Wolf et al., 2007). Yodh (University of Pennsylvania) developed a FD imaging array consisting of 12 intensity-modulated sources and 4 detectors (Danen et al., 1998). The device was employed to reveal a shunt surgically inserted within the brain of a patient with hydrocephalus. Also the group from the University of Illinois developed a FD frequency domain system, consisting of 16 intensity-modulated sources and two detectors, that has been used to demonstrate real-time optical topography of the adult brain during activation of the motor cortex (Franceschini et al., 2000). Images were generated to exhibit the hemodynamic response over an area of 9×4 cm at a rate of 6.25 Hz enabling the arterial pulsation to be displayed. In 2001, the instrument Imagent was first commercialized by the ISS Inc.; this instrument, upgradeable to 128 channels, is the only commercially available multi-channel FD system. So far, over 70 units have been sold worldwide.

Towards optical tomography

Optical tomography is based on the general principle that a finite set of measurements of transmitted light between pairs of points on the surface of an object is sufficient to reconstruct a transverse slice or three-dimensional volume representing the distribution of internal

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scatterers and absorbers. At the end of the nineties, Benaron (Stanford University, Palo Alto, CA) demonstrated, for the first time, the feasibility of optical tomography of the neonatal head utilizing an imaging system based on TRS measurements of the photon flight times between points on the circumference of the infant head (Benaron et al., 2000). Because only a single detector was employed, transmitted light between each combination of source and detector position was recorded sequentially, resulting in scan times of 2–6 h. Using the same system, focal regions of low oxygenation were found in infants after acute stroke. The greater attenuation of NIR light across large heads prevents any optical system for imaging the center of the adult brain; however, partial tomographic reconstruction of the adult cortex is feasible. A localized contralateral oxygenation increase in the motor cortex of a healthy adult during hand movement was reported (Benaron et al., 2000).

From 1995 to 1999, in the framework of the realization of the project granted by the Wellcome Trust grant, a 32-channel TRS system, named as MONSTIR (Multi-channel Opto-electronic Near-infrared System for Time-resolved Image Reconstruction), was built by Hebden at the University College London (Schmidt et al., 2000). Newborn infant brain studies did not begin until a portable fiber laser became available about two years later. MONSTIR provided three-dimensional whole-head optical tomography of passive motor evoked responses in the neonate (Gibson et al., 2006). The system was rather slow to be very effective at imaging functional activation. Therefore, it was necessary to repeat the passive motor stimulus for each source position. Since 1992, the University College London's group has done extensive theoretical and experimental studies on behavior of photons in brain models. This has led to the development of image reconstruction methods which have been applied to fNIRS imaging (for a review: Gibson et al., 2005). The literature on the diffusion model of light transport in tissues has been recently reviewed (Durduran et al., 2010).

From 1992 to 1999, as one of the national research and development projects managed by the "New Energy and Industrial Technology Development Organization", Tamura (Hokkaido University) in collaboration with Shimadzu and Hamamatsu Photonics, and with the support of Yamada (Mechanical Engineering Laboratory, MITI, Tsukuba, Japan) and Hoshi (Hokkaido University), developed a 64-channel TRS tomographic imaging system (Eda et al., 1999). This prototype was utilized for example to demonstrate in healthy adult volunteers that: 1) the backward digit span task activated the dorsolateral PFC of each hemisphere more than the forward digit span task, and 2) higher performance of the backward digit span task was closely related to the activation of the right dorsolateral PFC (Hoshi et al., 2000b).

In 2003, Yamashita and his colleagues at Hamamatsu Central Research Laboratory (Japan) developed a more advanced 16-channel TRS system (Yamashita et al., 2003) that was utilized in some functional studies (Ueda et al., 2005). In the same laboratory, a 3-wavelength TRS system for brain oxygenation measurements was also developed (Oda et al., 1999; Ohmae et al., 2006). Since 2009, a two-channel commercial oximeter for brain measurements has been available (TRS-20 Hamamatsu, Japan); this is the sole commercially available TRS system.

In 1996, the researchers from the Physikalisch-Technische Bundesanstalt (PTB) (Berlin) in collaboration with the group from the Humboldt University of Berlin began to utilize single-channel TRS for fNIRS studies. This can be considered the first example of the use of TRS approach in human fNIRS studies. A decrease of mean time-of-flight was observed on the motor cortex during a unilateral finger opposition task (Obrig et al., 1996). These preliminary measurements inspired the development of a compact TRS experimental set-up suitable for bedside monitoring that was applied for motor-stimulation experiments (Steinbrink et al., 2001). This group was also the first one in combining DC-magnetoencephalography with CW NIRS to better investigate the temporal relation between vascular and neuronal responses of the brain to external stimuli (Mackert et al., 2004). More recently, modulation DC-magnetoencephalography and 4-channel TRS signals were recorded over the motor cortex during finger movement. The off-line averaged signals from both modalities showed distinct stimulation-related changes: i.e. the vascular signal increased significantly slower than the neuronal signal (Sander et al., 2007). Another application of the 4-channel TRS instrument is to assess perfusion in stroke patients by indocyanine green bolus tracking (Liebert et al., 2005). Based on the analysis of the variance of the time-of-flight, a delay of the bolus of the optical contrast agent over the affected, when compared to the unaffected hemisphere, was found in all patients who were suffering from acute unilateral ischemic stroke.

In 1998, Cubeddu, Torricelli and their co-workers at the Department of Physics, "Politecnico di Milano" (Italy) started to work on the medical applications of TRS (Torricelli et al., 1998). Initially, this group developed a compact 8-channel TRS system (Cubeddu et al., 1999; Torricelli et al., 2004) that was employed for investigating the bilateral PFC oxygenation responses to a verbal fluency task (Quaresima et al., 2005); a more complex instrument equipped with 16 sources and up to 64 collection points (minimum acquisition time 5 ms per channel) (Contini et al., 2006) was later utilized in different fNIRS studies (Butti et al., 2009).

The main commercially available transportable fNIRS systems are reported in Table 3.

Wearable/wireless fNIRT systems

The commercial fNIRS systems listed in Table 3 utilize fiber optic bundles. The disadvantage of using fiber optic bundles is that the fibers are often heavy and of limited flexibility, perhaps provoking discomfort (especially in patients). In addition, these fNIRS systems require that the subject's head position not move beyond the length

Table 3
Main commercially available transportable fNIRS systems.

Instrument	Technique	Year of release	No. of channels	Company	Web site
Dynot Compact	CW	2004	288–2049	NIRx, USA	www.nirx.net
ETG-4000[a]	CW	2003	52	Hitachi, Japan	www.hitachimed.com
ETG-7100	CW	2007	72–120	Hitachi, Japan	www.hitachimed.com
OXYMON MkIII	CW	2003	Up to 96	Artinis, The Netherlands	www.artinis.com
NIRO-200	CW	2008	10	Hamamatsu, Japan	www.hamamatsu.com
NIRS2 CE	CW	2007	16	TechEn, Inc., USA	www.nirsoptix.com
CW6	CW	2009	20–1024	TechEn, Inc, USA	www.nirsoptix.com
FOIRE-3000[a]	CW	2007	52	Shimadzu, Japan	www.med.shimadzu.co.jp
NIRScout	CW	2008	128–1536	NIRx, USA	www.nirx.net
HD-NI	CW	2009	Over 200	Cephalogics	www.alliedminds.com
Imagent	FD	2001	Up to 128	ISS, USA	www.iss.com

Channel (or measurement point): the midpoint between illuminating and detecting optical fibers.
CW = continuous wave, FD = frequency-domain.
[a] US Food and Drug Administration's approval.

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of the fiber optic bundles. Multi-channel wearable and/or wireless systems could make fNIRS measurements more comfortable. These advanced fNIRS systems would represent a useful tool for evaluating brain activation related to cognitive tasks performed in normal daily activities. This is a potential that exists for fNIRS more than for any other neuroimaging modality.

In 1996, Chance started to develop and test several low cost CW imaging devices for the PFC and the muscle (Chance et al., 1997). Optical topography of the premature infant cortex was performed using a system consisting of 9 sources and 4 detectors upon sensorimotor activation with an imaging time of 30 s (Chance et al., 1998a). Chance's company, called NIM (Near Infrared Monitoring) operated from 1996 to 2009 selling approximately 20 units of the device named LED imager (one half for brain imaging and one half for muscle oxygenation monitoring). In the meanwhile, researchers from the School of Biomedical Engineering of the Drexel University (Philadelphia, PA) started (in 1999) to collaborate with Chance. A wearable optical system for adult PFC fNIRS measurements was developed in 2004 and utilized in several studies (for a review: Izzetoglu et al., 2011). In August 2009, fNIR Devices (Potomac, MD), using the technologies licensed from Chance and the Drexel University, started shipping a 16-channel instrument for adult PFC fNIRS measurements (Model 1100). In 2011, a 4-channel wireless system for adults (Model 1100W) as well as a pediatric 2-channel probe was introduced in the market. So far, over 60 systems have been sold mainly in the United States by fNIR Devices.

In 1994, Nakase and Shiga (Omron Institute of Life Science, Kyoto, Japan) developed, in collaboration with Chance, a single-channel portable oximeter for muscle studies (HEO-100, Omron Ltd. Inc., Japan) (Shiga et al., 1995, 1997). In 1997, this instrument was equipped with a PFC probe (HEO-200) and utilized in several fNIRS studies. In 2001, Hoshi at the Tokyo Institute of Psychiatry combined for the first time the HEO-200 with a wireless telemetry system demonstrating the PFC activation of children during different cognitive studies (Hoshi and Chen, 2002, 2006; Hoshi et al., 2001). The children carried on their back a miniaturized instrument and the data were sent by a wireless telemetry system to a computer, without restricting movement of the children.

Recently, Hitachi has introduced two battery operated wearable/wireless systems suitable for performing fNIRS measurements on adult PFC; i.e. a 22-channel in 2009 (WOT) and a 2-channel in 2011 (HOT 121B) (Atsumori et al., 2009). Both instruments are currently commercially available only in Japan. In 2009, another Japanese company, the Spectratech, has introduced a 16-channel wireless system (OEG-16) for carrying out studies on adult PFC and has sold over 100 units (only in Japan).

A portable 16-channel system, suitable for performing adult fNIRS studies on adult PFC was developed by Huazhong University of Science and Technology (Wuhan, China) (Lv et al., 2008). A 4-channel wireless imager has been developed by Wolf (University of Zurich, Switzerland) (Muehlemann et al., 2008) and utilized on newborn and adult fNIRS studies (Holper et al., 2012; Wolf et al., 2007). More recently, 1) a wearable/wireless battery operated fNIRT system (NIRSport, up to 256 measurement points) has been introduced (in 2011) by NIRx Medical Technologies LLC, and 2) a wearable/wireless battery operated single-channel oximeter (PortaLite) has been introduced (in 2011) by Artinis.

The main commercially available wearable/wireless fNIRS systems are reported in Table 4.

The first 19 years of fNIRS research and perspectives

The summary of the results of almost two decades of fNIRS research goes beyond the goal of this article. From a search on the databases PubMed, Scopus and Web of Science, performed using the keywords: “NIRS”, “functional NIRS”, “functional near-infrared topography”, and “optical imaging”, about 400 articles have been published over the last 3 years. The main fields where fNIRS has been applied since its birth are listed in Table 5. Several recently published review articles summarize the fNIRS results obtained in some of these fields. In particular, five reviews were dedicated to the use of fNIRS in language processing in newborns/children and adults (Dieler et al., 2012; Minagawa-Kawai et al., 2008; Obrig et al., 2011; Quaresima et al., 2012; Rossi et al., 2012); other review articles were focused on: the fNIRS applications on newborn (Aslin, 2012; Gervain et al., 2011; Lloyd-Fox et al., 2009; Wolf and Greisen, 2009), the cognitive neuroscience (Cutini et al., 2012), the activation of the cerebral cortex during motor tasks (Leff et al., 2011), and the quality control in fNIRS studies (Orihuela-Espina et al., 2010).

Andreas Fallgatter (presently at the University of Tuebingen, Germany) and Masato Fukuda (presently at Gunma University, Japan) have been the driving force of the application of fNIRS in Psychiatry (for reviews: Ernst et al., 2012; Fallgatter et al., 2004; Fukuda, 2012). In 1997, Fallgatter (that time at the University Clinic of Würzburg, Germany) published the first of his long list of fNIRS clinical studies demonstrating the loss of functional hemispheric symmetry in subjects affected by Alzheimer's dementia (Fallgatter et al., 1997). In 2000, Fukuda and co-workers (that time at the University of Tokyo, Bunkyo, Japan), by using a one-channel portable instrument, published their first study evidencing that the hypofrontality in elderly depression was not due to altered vasodilator response (Matsuo et al., 2000). Suto et al. (2004), using a 48-channel system, found differences concerning the time course of prefrontal oxygenation during the verbal fluency task between groups of depressive and schizophrenic patients. This and other studies led by Fukuda represent the main experimental basis for the fNIRS approval as a diagnostic method for depression from the Japanese Ministry of Health, Labor and Welfare.

Although, it was not the goal of this article, it is worth of mentioning that the progresses of fNIRS over the years are also attributable to the giant development of fNIRS methodology and data analysis. In Fallgatter laboratory several test/retest reliability studies have been conducted by Plitcha et al. (2006, 2007) and Schecklmann et al. (2008). Although inter-individual differences in physical parameters (such as skull

Table 4
Main commercially available continuous wave wearable/wireless fNIRS systems.

Instrument	Year of release	Wireless	No. of channels	Company	Web site
fNIR 1100	2009	No	16	fNIR Devices, USA	www.fnirdevices.com
fNIR 1100w*	2011	Yes	2 or 4	fNIR Devices, USA	www.fnirdevices.com
HOT 121B	2011	Yes	2	Hitachi, Japan	www.hitachimed.com
NIRSport	2011	Yes	Up to 256	NIRx, USA	www.nirx.net
OEG-16	2009	No	16	Spectratech, Japan	www.spectratech.co.jp
OEG-SpO_2^	2011	Yes	16	Spectratech, Japan	www.spectratech.co.jp
PocketNIRS Duo	2010	Yes	2	DynaSense, Japan	www.dynasense.co.jp
PortaLite°	2011	Yes	1	Artinis, The Netherlands	www.artinis.com
WOT	2009	Yes	22	Hitachi, Japan	www.hitachimed.com

Channel (or measurement point): the midpoint between source and detector;
* = children probe available; ^ = measure of arterial O_2Hb saturation; ° = brain oximeter.

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Table 5
Main fields of fNIRS applications over 19 years.

Neurology	• Alzheimer's disease
	• Dementia
	• Depression
	• Epilepsy
	• Parkinson's disease
	• Post-neuro surgery disfunctions
	• Rehabilitation
	• Stroke recovery
Psychiatry	• Anxiety disorders
	• Childhood disorders
	• Eating disorders
	• Mood disorders
	• Personality disorders
	• Substances related disorders
	• Schizophrenic disorders
Psychology/education	• Attention
	• Body representation
	• Comprehension
	• Developmental disorders
	• Developmental psychology
	• Emotion
	• Functional connectivity
	• Gender differences
	• Language
	• Memory
	• Perception
	• Reasoning
	• Social brain
Basic research	• Brain computer interface
	• Fusion
	• Neuroergonomics
	• Pain research
	• Sleep research
	• Sports sciences research

thickness and the associated skull-to-cortex-distance) limit fNIRS signal interpretability in single trials (Haeussinger et al., 2011), it has been shown that on group level fNIRS results can be reliably reproduced even over time periods of one year. Schroeter et al. (2004) first introduced event-related design and general linear model (GLM)-based analyses. Both approaches are gaining increasing importance in recent fNIRS studies. This methodological step is important in the context of fNIRS history because the tendency of fMRI users and fNIRS users is to share the same analytical basis. In fact, the validity of the population analysis of fNIRS studies would be strengthened by data presentation on a common platform to facilitate both intra- and inter-modal data sharing among the neuroimaging community. Many efforts have been made to improve fNIRS data visualization and to better localize brain activations measured from the scalp. Introducing anatomical priors from subject-specific MRI volumes or MRI atlases, an anatomical-constrained data reconstruction can be established (Boas and Dale, 2005; Custo et al., 2010). Ippeita Dan (presently at Jichi Medical University, Japan and previously at National Food Research Institute, Tsukuba, Japan) proposed different probabilistic registration methods for the spatial registration of fNIRS maps onto the Montreal Neurological Institute (MNI) coordinate space through standardized 10/20 external reference positions (Jurcak et al., 2007) and MRI (Okamoto et al., 2004) and without MRI (Singh et al., 2005). These methods, however, require the careful measurement of scalp landmarks and fNIRS optode positions using a 3D-digitizer. Another registration method, based on simulations in place of physical measurements for optode positioning, has been proposed allowing the virtual spatial registration of completely stand-alone fNIRS data onto MNI space without the use of supplementary measurements (Tsuzuki et al., 2007).

In the recent years the validity of fNIRS measurements has been repeatedly confirmed by simultaneous fMRI measurements showing that fNIRS results are highly consistent with fMRI findings. The possibility of combining fNIRS with event-related EEG potentials has been also demonstrated in Fallgatter laboratory assessing auditory sensory gating (Ehlis et al., 2009) and emotional stimuli processing (Herrmann et al., 2008).

Although significant advances have been made also in the methods used to model light transport in brain tissue and to reconstruct images from optical data (Arridge, 2011), no standardized approach to the data analysis of the multi-channel systems is currently available for creating absolute DOT images or topographic maps, or for determining the statistical significance of cortical oxygenation changes (Elwell and Cooper, 2011).

Along with the ever-increasing applications, in terms of the future directions of fNIRS instrument development, it is expected that multi-channel TRS innovations will continue accompanied by robust data analysis standardization. So far, fNIRS has been promoted in a number of fields in which fMRI is limited due to the constraints induced by the scanning environment and the experimental measurements take place in a more comfortable and natural environment. One of the major strengths and future direction of fNIRS with respect to fMRI is represented by the availability of relatively low cost portable wireless instruments. Only these devices can be utilized for example in infant and children developmental studies, in neuro-rehabilitation assessment, and in simultaneous brain activation studies on multiple subjects.

In conclusion, over the years fNIRS has become a neuroimaging technique which contributes in making advances toward the understanding of the functioning human brain. Moreover, the fNIRS field is continuing to grow as more researchers from diverse fields engage the technology. It can be estimated that up to 700 fNIRS units, made by American (fNIR Devices, ISS, NIRx, TechEn), Dutch (Artinis) and Japanese (Hamamatsu, Hitachi, Shimadazu, Spectratech) companies, are utilized worldwide for human brain cortex fNIRS studies on adults and infants. In addition, several non-commercial multi-channel prototypes have been developed by University and industrial research groups.

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