Perspective: Prospects of non-invasive sensing of the human brain with diffuse optical imaging

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Abstract

Since the initial demonstration of near-infrared spectroscopy (NIRS) for noninvasive measurements of brain perfusion and metabolism in the 1970s, and its application to functional brain studies (fNIRS) in the 1990s, the field of noninvasive optical studies of the brain has been continuously growing. Technological developments, data analysis advances, and novel areas of application keep advancing the field. In this article, we provide a view of the state of the field of cerebral NIRS, starting with a brief historical introduction and a description of the information content of the NIRS signal. We argue that NIRS and fNIRS studies should always report data of both oxy- and deoxyhemoglobin concentrations in brain tissue, as they complement each other to provide more complete functional and physiological information, and may help identify different types of confounds. One significant challenge is the assessment of absolute tissue properties, be them optical or physiological, so that relative measurements account for the vast majority of NIRS and fNIRS applications. However, even relative measurements of hemodynamics or metabolic changes face the major problem of a potential contamination from extracerebral tissue layers. Accounting for extracerebral contributions to fNIRS signals is one of the most critical barriers in the field. We present some of the approaches that were proposed to tackle this challenge in the study of cerebral hemodynamics and functional connectivity. Finally, we critically compare fNIRS and functional magnetic resonance imaging (fMRI) by relating their measurements in terms of signal and noise, and by commenting on their complementarity.

Keywords

functional near-infrared spectroscopy; diffuse optics; cerebral hemodynamics; noninvasive brain monitoring

I. Introduction: Historical bits and broad overview of the state of the art

In 1977, Frans Jöbsis reported non-invasive optical measurements of oxygen saturation of hemoglobin and redox state of cytochrome aa3 in the cat brain (Jöbsis, 1977). This pioneering work, performed at dual wavelengths within the spectral range 740–865 nm, gave birth to the field of non-invasive cerebral near-infrared spectroscopy (NIRS). The 1980s saw
further validations on animal models (Giannini et al., 1982), preterm infants (Brazy et al., 1985) and adult human subjects (Ferrari et al., 1985). The clinical potential of non-invasive cerebral NIRS was explored in a number of areas, including Alzheimer’s disease, Parkinson’s disease, epilepsy, traumatic brain injury, stroke, schizophrenia, and other psychiatric disorders (for reviews, see Irani et al., 2007; Obrig, 2014).

The first functional NIRS (fNIRS) studies of brain activation were reported in 1993 (Chance et al., 1993; Villringer et al., 1993; Hoshi and Tamura, 1993; Kato et al., 1993). The following 20+ years saw growing research efforts and numerous significant achievements in instrumentation development, data analysis methods, and applications in a number of areas, including brain development, cognitive science, balance & gait assessment, psychiatry, neurology, aging, and anesthesia (Ferrari and Quaresima, 2012; Boas et al., 2014).

The main appeal of NIRS and fNIRS rests on the possibility of sensing the human brain non-invasively and continuously, using compact and cost-effective instrumentation that can be portable and even wearable. These features allow for the realization of diagnostic monitoring in real-time or functional assessment in every-day environments that are beyond the capabilities of more powerful and established neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). However, non-invasive optical techniques for human brain studies suffer from a limited penetration depth, a relatively low spatial resolution, and a strong sensitivity to extracerebral tissue. While limitations in penetration depth and spatial resolution may not negatively impact the study of spatially extended hemodynamic features in superficial cortical regions, the high sensitivity to extracerebral hemodynamics needs to be taken into consideration and properly accounted for.

In this article, we describe and comment on the sources of noninvasive NIRS signals (Section II), the importance of exploiting the NIRS sensitivity to both oxygenated and reduced forms of hemoglobin (Section III), modeling optical propagation in tissues (Section IV), approaches to account for extracerebral tissue contributions (Section V), and the topic of functional connectivity (Section VI). Finally, both fMRI and fNIRS are hemodynamic-based neuroimaging techniques, and they are closely related since they are both sensitive to blood flow, blood volume, and blood oxygenation changes associated with neuronal activation. These two techniques are critically compared in Section VII.

II. The sources of NIRS signals

Noninvasive, diffuse optical measurements of biological tissue probe a macroscopic tissue volume that typically has a size of several cubic centimeters. Of course, the shape and size of the optically probed tissue volume depends on the geometrical and optical properties of tissue, as well as the size and relative distance of the illumination and collection areas on the tissue surface. Typical configurations for NIRS studies of the brain call for source-detector distances of the order of 3 cm, resulting in a banana-shaped probed volume (Feng et al., 1995; Sassaroli et al., 2014) that extends to a maximum tissue depth of about 2–2.5 cm (Martelli et al., 2016). The key optical properties of tissue that determine the measured NIRS signal are the absorption coefficient ($\mu_a$) and the reduced scattering coefficient ($\mu'_s$).
In the near-infrared spectral region of interest (600–900 nm), brain tissue absorption is mostly determined by hemoglobin, in its oxygenated (HbO$_2$) and reduced (Hb) forms, with smaller contributions from water, lipids, and cytochrome c oxidase. Tissue scattering results from spatial discontinuities and gradients, on a length scale comparable to the optical wavelength, in the refractive index. While tissue scattering properties may be impacted by hemodynamic, metabolic, and functional events, NIRS signals are more strongly sensitive to absorption changes associated with blood volume, blood flow, and metabolic changes.

It is very important to recognize two facts. The first fact, already mentioned above, is that the NIRS signal results from the spatial distribution of optical absorbers and scatterers within the entire optically probed region. The second fact is that the sensitivity of the NIRS signal is not uniform throughout the optically probed region. This means that the same optical absorber (say, a blood vessel) or a dynamic optical absorber (say, a dilating blood vessel) will result in different NIRS signals depending on where they are located in the optically probed volume.

The question we want to consider in this section refers to dynamic NIRS signals, which are almost exclusively considered in fNIRS studies, and it is the following: “What are the possible sources of a dynamic change in the noninvasive NIRS signal measured from the tissue surface (scalp) on a subject’s head?” By taking into account the above considerations, here are the possible sources of fNIRS signals:

1. A tissue scattering change occurring within the optically probed volume.
2. A spatially distributed absorption change occurring within the optically probed volume: for example a change in the microvascular amount of Hb and/or HbO$_2$, a change in the redox state of cytochrome c oxidase, or a change in water or lipids content.
3. A spatially localized absorption change within the optically probed volume: for example the dilation or constriction of a blood vessel, or the change in the amount of Hb and/or HbO$_2$ in a localized vascular compartment.
4. A spatial displacement of a localized absorber: for example the displacement of a blood vessel within the optically probed volume (this would result in a NIRS signal because of its non-uniform sensitivity over the probed volume).
5. A change in the optical coupling between tissue and the light source or optical detector (this may be a result of subject movement, tissue motion, or a mechanical instability of the optical probe on the subject’s head).

These five possible sources of noninvasive NIRS signals describe the nature of the physiological and functional origins of the NIRS signals (1: cell swelling, water or ion transport, cellular density, tissue architecture, etc.; 2: microvascular blood volume and blood oxygenation, blood flow, metabolic rate of oxygen, cellular metabolism, tissue composition; 3: macrovascular blood volume and blood oxygenation, focal hemodynamic or metabolic changes; 4: vascular displacement), or possible artifacts (5: subject’s motion, unstable optical coupling with tissue, etc.).
One needs to consider that the optically probed region includes the most superficial tissue regions located directly underneath the illumination and collection areas on the tissue surface. Furthermore, the sensitivity of the NIRS signal to these superficial, extracerebral tissue layers (scalp, skull, subarachnoid space, etc.) is greater than to the deeper cortical tissue. Therefore, the biological origins of the NIRS signals (1–4, above) may originate within either or both of the extracerebral and cerebral tissue regions that fall within the optical probed volume. This important point is illustrated in Fig. 1 and is further considered in Section V.

III. The importance of reporting both [Hb] and [HbO₂] in NIRS

The strongest sensitivity of the NIRS signal is to hemoglobin, given its relatively high concentration in brain tissue (~0.1 mM, resulting from the ~2.3 mM concentration of hemoglobin in blood and the ~4% blood volume fraction in the brain cortex), and its relatively high molar extinction coefficient (~2×10³ M⁻¹ cm⁻¹ at 800 nm, for the four-heme-group hemoglobin molecule and an extinction coefficient defined in base e). Furthermore, the different near infrared absorption spectra of Hb and HbO₂ allow for their spectral separation from NIRS measurements at multiple (at least two) wavelengths. The ability to separately measure Hb and HbO₂ concentrations in tissue is of paramount importance, because it provides critical information on the relative contributions from blood volume, blood flow, and metabolic changes to the measured NIRS signals, the blood oxygenation level, and may help identify confounding contributions from a variety of artifacts (Quaresima et al., 2013). In fact, the relative Hb and HbO₂ concentration changes reflect the nature of the driving physiological process. For example: (A) a blood volume increase results in a concurrent increase of both [Hb] and [HbO₂] with a relative amount that reflects the oxygen saturation of the associated vascular compartment(s); (B) a blood flow increase shortens the time spent by red blood cells in the smaller arterioles and capillaries where blood-to-tissue oxygen exchange occurs, resulting in a concurrent microvascular increase in [HbO₂] and decrease in [Hb]; (C) a metabolic rate of oxygen increase results in a higher rate of oxygen diffusion from blood to tissue, and therefore a concurrent microvascular decrease in [HbO₂] and increase in [Hb]. In addition to the relative amounts of [Hb] and [HbO₂] changes, their relative timing also provides valuable indications on the dynamics of cerebral blood volume (CBV), cerebral blood flow (CBF), and cerebral metabolic rate of oxygen (CMRO₂), as recently quantified with a mathematical model [Fantini, 2014a; Fantini 2014b].

The importance of measuring both [Hb] and [HbO₂] dynamics in NIRS and fNIRS studies of the brain has been recognized for some time. For example, measurements of the relative phase of cerebral [Hb] and [HbO₂] oscillations were performed in infants [Taga et al., 2000; Watanabe et al., 2017] and adults [Obrig et al., 2000; Reinhard et al., 2006; Tian et al., 2011]. In functional brain imaging, the co-registration of [Hb] and [HbO₂] led to a vector-based representation in the [Hb]-[HbO₂] plane to help discriminate blood volume and oxygen extraction contributions to the signals [Wylie et al., 2009; Yoshino and Kato, 2012]. More recently, it was proposed to consider a particular kind of cerebral hemodynamics, those that are coherent with a particular physiological or functional process (arterial blood pressure, brain activation, etc.), to allow for a more robust and reliable analysis of...
covariations of [Hb] and [HbO₂] (coherent hemodynamics spectroscopy) [Fantini et al., 2014a; Kainerstorfer et al., 2014].

Despite the powerful ability of NIRS to measure the tissue concentrations of both oxygenated and reduced forms of hemoglobin, and the recognized importance of reporting results for both [Hb] and [HbO₂], there are still research articles and presentations that opt to only report data on either [Hb] or [HbO₂]. Such choice should be explicitly justified, but we think that it is always appropriate to report results for both hemoglobin species to convey a more complete picture of the studies performed.

IV. Modeling light propagation in biological tissue: Standard transport theory, diffusion theory, and more

The two challenges faced by NIRS for the quantification of the optical properties of tissue and their spatial distribution relate to the description of light propagation in tissue (forward problem) and methods for image reconstruction (inverse problem). The forward problem aims to determine the light distribution within tissue and the optical intensity exiting the tissue boundary for any given distribution of light sources and optical properties. The inverse problem aims to recover the absorption and scattering properties of tissue from optical measurements at the tissue boundary. These two problems are challenging due to the prevalence of scattering over absorption events in tissue: on average, a near-infrared photon traveling in brain tissue is scattered every 100 μm, whereas it may travel 10 cm before being absorbed. Such dominant scattering complicates quantitative spectroscopy of tissue and is the reason for the intrinsic blurring of the images obtained by NIRS. Here, we focus our attention on the forward problem.

In order to understand the complexity of modeling light propagation in biological tissue, we start from the basic and most relevant phenomenon of light scattering. Scattering in biological tissues is due to refractive index discontinuities and gradients on a length scale comparable with the light wavelength (Mourant et al., 1998). Maxwell’s equations provide a rigorous framework to treat scattering, but solutions for the scattered field are complex even for the simple case of an incident plane wave on a single spherical particle (Mie theory). The problem of calculating the scattered field becomes significantly more complicated in the presence of a collection of scattering particles (multiple scattering). Historically, two methods were proposed for studying this problem on the basis of an analytical theory (Ishimaru 1978; Chapter 14) or transport theory (Ishimaru 1978; Chapters 7–13). The analytical, or multiple scattering, theory was developed by introducing multi-particle interactions starting from Maxwell’s equations for a single particle. Transport theory deals directly with the transport of optical energy in a random medium. It considers diffraction and interference effects at a single particle level, but neglects interference effects from the electric fields scattered by multiple particles, which are considered to be uncorrelated. Therefore, optical energies, rather than optical fields, are superimposed.

In most NIRS applications, biological tissue is assumed to be a random isotropic medium, for which one may apply the standard transport equation (Case and Zweifel, 1967; Duderstadt and Martin, 1979; Ishimaru 1978; Martelli et al., 2009; Bigio and Fantini, 2016).
The standard radiative transport equation is an integro-differential equation for the optical radiance, expressed in terms of the absorption coefficient ($\mu'_a$), the scattering coefficient ($\mu_s$), and the scattering phase function (which is the angular, and the probability density of photon scattering). Isotropic media are characterized by a phase function that only depends on the scattering angle, and by absorption and scattering coefficients that are independent of the light direction of propagation. Note that even if a medium is isotropic, its phase function can have an angular dependence, i.e. scattering itself may not be isotropic. When collected photons have undergone a large number of scattering events, one can use the standard diffusion equation as an approximation to transport theory (Patterson et al., 1989; Martelli et al., 2009; Bigio and Fantini, 2016). The standard diffusion equation has been extensively used in NIRS studies of breast, skeletal muscle, and brain tissues in vivo. However, the diffusion approximation breaks down close to the illumination point(s) in tissue, in cases where scattering processes do not dominate over absorption processes, and in proximity of tissue boundaries. In the case of non-invasive brain studies, light must propagate through the subarachnoid space that contains the cerebrospinal fluid (see Fig. 1), a clear fluid where light propagation does not fulfill the conditions of diffusion theory. As a result, transport theory, rather than diffusion theory, has sometimes been considered as a more accurate modeling tool for cerebral NIRS.

Usually, the radiative transport equation is solved with Monte Carlo simulations. In the last fifteen years, the NIRS community has witnessed a tremendous increase in Monte Carlo codes that are capable of dealing with realistic head geometries (Boas et al., 2002), and even include the effects of the vasculature on photon migration (Dehaes et al., 2011). The advent of Graphics Processing Units (GPU) has made Monte Carlo calculations orders of magnitudes faster (Alerstam et al., 2008; Ren et al., 2010; Fang and Boas, 2009), to a point that it is now possible to use them as forward solvers for the solution of the inverse problem (Selb et al., 2014). Furthermore, Monte Carlo simulations may provide a validation of simplified analytical methods used for chromophore concentration measurements, such as the modified Beer-Lambert law or diffusion theory.

Solving the standard radiative transport equation with Monte Carlo methods for realistic geometrical and anatomical conditions (possibly including a full atlas of brain and scalp vasculature) may provide the ultimate model of photon migration in the human brain. An accurate description of light propagation in brain tissue may be further complemented by physiological models to properly account for hemodynamic, metabolic, functional, and autoregulatory processes.

However, there may be more to photon migration modeling in tissues. For example, the hypothesis of random isotropic media for biological tissues may not always be correct. Some tissues are characterized by elongated fibers or cellular components that result in directional microstructures. For example, this is the case for skin (Nickell et al., 2000), dentin (Kienle and Hibst, 2006), tendons (Kienle et al., 2007), muscles (Marquez et al., 1998), the cerebral cortex (McKinstry et al., 2002; Heiskala et al., 2007), and the myelin sheath surrounding axons. In noninvasive cerebral NIRS, the strongly inhomogeneous and layered structure of the tissue (scalp, skull, dura mater, subdural space, subarachnoid space, brain cortex) may further limit the validity of the assumption of isotropy. Anisotropic light propagation and
birefringent tissue properties require the introduction of a dependence of absorption and scattering coefficients, as well as the scattering phase function, on the photon direction of propagation. This is beyond the limits of applicability of standard diffusion theory. Attempts to address this issue include an anisotropic diffusion equation that led to the definition of a directional reduced scattering coefficient (Heino et al., 2003), and a Monte Carlo code based on anatomical and structural information from diffusion tensor MRI (McKinstry et al. 2002) that solves a non-standard radiative transport equation for anisotropic media to study light propagation in the infant brain (Heiskala et al. 2007).

The above considerations point to the fact that absolute measurements of brain optical properties may require more refined forward models than standard transport and diffusion models. Instead, relative optical measurements that reflect differences between states (rest vs. activation in functional studies, normocapnia vs. hypercapnia vs. hypocapnia in cerebral blood flow studies, normoxia vs. hyperoxia vs. hypoxia in oxygenation studies, low vs. high arterial blood pressure in autoregulation studies, etc.) are typically more robust than absolute measurements, and are commonly employed in cerebral NIRS.

The case of relatively short (<1 cm) source-detector separations may be particularly sensitive to the inaccuracies of standard transport and diffusion theory and the assumption of tissue isotropy. Such measurements are commonly used to sense the superficial extracerebral tissue to account and potentially correct for extracerebral tissue contributions to the NIRS signals that are collected at larger source-detector separations (>2.5 cm). This approach is discussed in the following section, and it may benefit from a more accurate model of NIRS signals collected at short source-detector separations.

V. The impact of extracerebral tissue to the noninvasive optical signals

One of the most basic problems in noninvasive NIRS studies of the brain is the confounding contribution from hemodynamics occurring in the scalp, skull, and other extracerebral tissue layers. In fact, a significant portion of the optical path of detected photons lies within extracerebral tissue (see Fig. 1). A number of strategies have been adopted to disentangle the contributions to the NIRS signals that originate from cerebral and extracerebral tissues. Most of these strategies rely on some kind of assumption, for example that the tissue hemodynamics have a one-dimensional, layered-like spatial distribution, or that hemodynamics occurring in the brain are uncorrelated with those occurring in the extracerebral tissue. One basic strategy is to collect optical measurements at short (<1 cm) and long (>2.5 cm) source-detector distances. Saager and Berger proposed a least square algorithm where intensity measurements at a short source-detector separation are regressed out from the ones at a long source-detector separation (Saager and Berger, 2005). Of course, only brain tissue hemodynamics that are uncorrelated with those occurring in the extracerebral tissue can be recovered with this algorithm. In a follow-up work, the assumption of layered-like hemodynamics was validated, and the method was applied to the cases of a Valsalva maneuver and visual activation. The results demonstrated the systemic physiological changes associated with the Valsalva maneuver, and the expected cerebral hemodynamic response to functional activation following the correction for extracerebral contributions (Saager and Berger, 2008).
The method proposed by Saager and Berger has been widely adopted in the field. A conceptually similar, but more flexible method employs an adaptive filter that dynamically updates the residuals between the short and long source-detector distance signals (Zhang et al., 2007). The requirement that cerebral and extracerebral hemodynamics be uncorrelated may not always be fulfilled. For example, scalp blood flow fluctuations, measured with laser Doppler flowmetry, were found to be temporally correlated with a verbal fluency task (Takahashi et al., 2011). It is reasonable to expect that superficial tissue hemodynamics may not always be uncorrelated to cerebral hemodynamics depending on the experimental protocol, anatomical conditions, cortical region, etc. Therefore, the goal of cerebral NIRS to selectively measure hemodynamics in the brain can be achieved to a greater extent by monitoring extracerebral tissue hemodynamics, as well as systemic physiological dynamics, in relation to the functional or physiological experimental protocol.

A powerful method, albeit not practical in general, to monitor scalp hemodynamics is to use specific fMRI measurements designed to be sensitive to the scalp. A study of the spatial, physiological, and compartmental origin of the NIRS signal during continuous semantic categorization and N-back tasks involved a multi-modal approach including time-resolved NIRS and fMRI, the latter with sensitivity to both cerebral and extracerebral tissue, as well as laser Doppler flowmetry, skin conductance, arterial blood pressure, and heart rate measurements to monitor systemic signals concurrently with the task (Kirilina et al., 2012). It was found that skin blood flow, which was consistent with a task-evoked sympathetic arterial vasoconstriction followed by a delayed decrease in venous volume, mainly affected the oxyhemoglobin concentration, which also strongly correlated with the extracerebral fMRI signal. On the contrary, changes in deoxyhemoglobin concentration strongly correlated with the cerebral fMRI signal. The significance of the deoxyhemoglobin change as a marker of brain activation was also supported by a more rigorous analysis based on the general linear model (GLM) and t test applied to NIRS data.

A more sophisticated method to suppress superficial contributions, also relying on one short and one long source-detector separation, is based on state-space modelling and Kalman filter (Gagnon et al., 2011). In a follow-up work, the authors tackled the question of whether the superficial hemodynamics are global or local, and reported results that showed a local nature of superficial hemodynamic signals, especially at lower frequencies (0.01–0.2 Hz) (Gagnon et al., 2012). This is an important question to consider, especially when mapping an extended area of the brain. A possible approach to take into account inhomogenous superficial hemodynamics is to employ two short source-detector channels for each long distance channel (Gagnon et al., 2014).

To avoid the strong assumption of uncorrelated cerebral and extracerebral hemodynamics, a weighted independent component analysis was proposed on the basis of weaker assumptions (Funane et al., 2014). More computationally challenging methods for separating extracerebral and cerebral hemodynamics are based on the solution of the diffusion equation in more complex geometries such as a spherical two-layered medium (Gregg et al., 2010).

Addressing the issue of extracerebral contamination in noninvasive cerebral NIRS remains one of the most critical questions in the field. Many of the methods developed to date...
perform well with simulated data and phantom experiments, but due to the anatomical, functional, physiological (and optical) complexity of the adult human head, they cannot fully explain the features of *in vivo* human data. It is still unclear what the most effective method to account for extracerebral hemodynamics may be. However, it is in general advisable to measure NIRS signals at both long and short source-detector separations to verify that there is indeed a difference between the non-cerebral signal collected at the short distance and the brain-sensitive signal collected at the long distance. It is also advisable to always collect relevant physiological quantities (heart rate, respiratory rate, arterial saturation, arterial blood pressure, etc.) concurrently with optical signals to identify systemic sources of hemodynamic changes that may contribute to both cerebral and extracerebral hemodynamics.

### VI. Measurement of functional connectivity

Functional connectivity is a term coined by Karl Friston to describe a fundamentally mathematical concept – it is “the observed temporal correlations between spatially remote neurophysiological events” (Friston et al., 1993a). It is purely an observational definition (despite the somewhat suggestive nature of the word “functional”) – there is no attribution of causality or directionality, simply an observed association. This is distinct from “effective connectivity”, which he defines as “the influence one neural system exerts over another” (Friston et al., 1993b). While we generally are interested in effective connectivity, traditionally, functional connectivity is what we can measure with hemodynamic imaging methods such as fNIRS and fMRI – effective connectivity can only be inferred or perhaps ruled out with these analysis methods, rather than asserted as fact. This is because there is a temporal disconnect between the timescales of hemodynamic imaging, which images changes that happen over seconds, and underlying neuronal processes, which typically happen on the timescale of milliseconds. It is important to note that the higher temporal resolution of fNIRS relative to fMRI does not provide better resolution of activation timing – the hemodynamic response is a physiological property, not an instrumental one.

Not only does the hemodynamic response waveform feature much lower frequencies than the driving neuronal activity – the exact timing of the hemodynamic response is spatially variable, and may in fact change over time. Because the neuronal activations in connected regions differ by time delays of 50 ms or less, it is therefore not possible to use hemodynamic data to determine the sequence of activations using standard correlational methods with any reliability (Smith et al., 2011). Very recently, however, there is some evidence from fMRI that considering connectivity as a dynamic process that changes over time yields additional information that can be used to determine the directionality of coupling in small networks (Schwab et al., 2018). To date there have been very few dynamic connectivity studies in fNIRS (Li et al., 2015), but this will undoubtedly change as the value of these methods are established. Connectivity analysis is rapidly increasing in the field of fNIRS – a Pubmed search (using the query “(NIRS OR (near infrared)) AND ((resting state) or (resting connectivity))” returns an average of 35 results per year in 2016–2017, but 16 results so far in the first 3 and a half months of 2018 alone (see Fig. 2).
A. Resting state connectivity

By far the most common type of connectivity analysis in recent years is so-called “resting state” analysis, which quantifies functional connectivity between regions in the absence of a task, to probe how different parts of the brain communicate information and work together to perform higher functions, or as a means to compare brain activity patterns between groups or conditions. In fMRI, this has led to the Human Connectome Project, a study of connectivity in the resting state (and during tasks), along with detailed structural measurements, in a cohort of 1200 healthy adults between the ages of 22 and 37. To date, adoption in fNIRS has been slower, due in large part to the fact that high resolution cortical mapping with fNIRS is a fairly recent development. In order to have interpretable results between subjects, it is critical to either have very careful probe placement to make sure the channel locations being correlated are comparable between subjects, or to perform a spatial reconstruction of the channels in order to work in a registered anatomic, rather than channel, space. There are also some significant confounds unique to fNIRS that one needs to consider (more below). However, the potential for fNIRS to measure human subjects in naturalistic settings and during free behavior makes it an extremely attractive platform to explore brain connectivity.

B. Types of connectivity analysis

There are a number of techniques which are used to probe connectivity. We will focus here on correlational methods, as they are by far the most popular. There are two main types of connectivity analysis performed on fNIRS (and fMRI) data – seed correlation and independent component analysis.

B.1 Seed correlation analysis—The first, and most basic form of connectivity analysis is the so called “seed correlation” method, where the correlation properties are measured between a signal extracted from a “seed” region (for example, a single fNIRS channel) and other regions to determine how much variance they share. This is simple to implement, and is well suited to fNIRS data, especially where the number of channels (N) is small, so all possible correlations \[\frac{N(N-1)}{2}\] can be examined if desired. A strong argument in favor of seed correlation is that it has the benefit of being hypothesis driven (generally you are examining connectivity between regions of interest you expect to be related), and the results are generally straightforward to analyze and interpret as representing the connection between two parts of a neuronal circuit. Finally, there is an increased statistical power of limiting the analysis only to hypothesized channel pairs.

B.2 Independent component analysis—Independent component analysis, or ICA, is fundamentally different, in that it is a data driven, rather than a hypothesis-driven approach. It is a special case of a “blind source separation” problem – there are an unknown number of “signals” (and these signals are unknown) being recorded by some number of detectors, each of which records some mixture of the signals. To be more concrete, this is often called “the cocktail party problem.” Imagine a crowded cocktail party with many people speaking at once. There are a number of microphones distributed around the room, each of which records the sound of multiple speakers at once. The blind source separation task is to separate these sounds into the speech of individual speakers, without knowing what they had
said or how many speakers there are at the outset. In the fNIRS case, there is an unknown number of correlated hemodynamic fluctuation signals (resulting from presumed correlated neuronal activity in various networks), which are shared by unknown sets of brain regions. These signals are measured by the individual channels of the fNIRS device (along with noise); the task is to recover the temporal fluctuations, and determine which sets of brain regions share them. ICA is a method for solving this problem, which works assuming a number of conditions are met, namely: 1) there are at least as many channels of data as there are signals being sought (i.e. the problem is exactly determined or overdetermined), 2) the signals are statistically independent, and 3) the statistical distribution of the values of each signal is not Gaussian.

The second and third conditions are easily met by fNIRS data. This is partly definitional; since we are looking to find regions of the brain that talk to each other, any pattern of shared variance between regions (i.e. the variance that is not independent) defines a network, and any orthogonal variance is considered to belong to other networks (or to be noise). Furthermore – it can be seen by inspection that the intensity values of hemodynamic time courses are generally not Gaussian. The first constraint is a bit more troublesome. In fMRI ICA analyses, the system is clearly highly overdetermined – there are 10’s or 100’s of thousands of voxels in an fMRI dataset, and even though over short range these time courses are correlated due to smoothing, the number of measurements still greatly exceeds the 30–60 components that are typically found in fMRI datasets. fNIRS, in contrast, has far fewer channels – systems with more than 50 measurement channels are relatively rare. However, this is to some extent offset by the more limited spatial coverage – because a smaller cortical area is probed, there will be fewer independent networks in the field of view that need to be separated.

The data-driven nature of ICA offers both advantages and disadvantages. It can be and has been used to map functional connectivity in fMRI – work in the last several years has shown that there are in fact stereotypical patterns of connectivity that show up over and over in ICA analyses (with some changes across the lifespan), despite the unconstrained nature of the technique (Greicius et al., 2004; Beckmann and Smith, 2004; Damoiseaux et al., 2006; Betzel et al., 2014). These networks have been named and ascribed functions based on their anatomical structure and how they behave functionally (such as the “default mode network,” the “motor network,” the “salience network,” etc.). However, the rather complex nature of the detected networks of activation complicates the analysis of data; how to compare patterns of connectivity between networks of regions, which may change shape or size in different groups and conditions is in some ways still an open problem, and can make interpreting results difficult.

C. Dynamic connectivity

Conventional connectivity analysis assumes that the correlation properties of the brain are stationary, and performs correlations between regions over long time periods (several minutes) in order to estimate the mean connectivity between regions, with fluctuations being treated as noise. However, “evidence from both task-based fMRI studies and animal electrophysiology suggests that functional connectivity may exhibit dynamic changes within
time scales of seconds to minutes” (Chang and Glover, 2010). The more recently developed dynamic connectivity treats the connectivity between regions as a parameter that evolves over time, as different parts of the brain come on- and off-line, and groups of regions switch tasks over timescales of tens of seconds, so correlations are performed with sliding windows, or other methods to limit the correlations to subsequences of the dataset to see how the correlations evolve over time, and as noted above, may provide extra information that can be used to determine connectivity direction (Schwab et al., 2018). However to date there seems to only have been one dynamic fNIRS connectivity study (Li et al., 2015).

D. Extracerebral contamination

One problem unique to connectivity analysis with fNIRS is extracerebral signal contamination (discussed at greater length in Section V). Because fNIRS signals must pass through the scalp, a significant amount of non-neuronal signal is included in the measurement of each channel. Worse, this signal is dominated by global systemic low frequency noise signals which propagate through the bloodstream, so they are highly correlated at all locations, which will cause apparent correlation between channels that has nothing to do with neuronal connectivity. This problem has long been recognized in fMRI and fNIRS, and various methods of regressing these signals out have been developed, such as global signal regression in fMRI (Desjardins et al., 2001) and short source-detector distance channel regression in fNIRS (Saager and Berger, 2005). However, these methods have their deficiencies, due to blood flow delay. Because this signal shows up in different locations at different times, the delay must be considered in order to properly remove the extracerebral signal, otherwise the regression itself may cause spurious correlations. In the NIRS case, this could be done by having short source-detector distance channels at every location, but a more practical method can be borrowed from the fMRI literature – estimating the systemic blood-borne noise signal either from peripheral NIRS recordings (in the fingertip, for example), or from the global average signal from all the channels, and then using cross-correlation to determine its delay at each point and regressing out a delayed copy of the signal (Frederick et al., 2012; Tong et al., 2015; Erdogan et al., 2016; Hocke et al., 2016). This method has recently been adapted to fNIRS, and has shown good promise for removing systemic noise without compromising neuronal signal (Hocke et al., 2018). This will likely become standard practice in the preprocessing of resting state fNIRS connectivity data.

VII. Critical comparison of fNIRS and fMRI

Comparisons of fNIRS and fMRI usually start and end with “the methods are complementary – fNIRS has high temporal resolution and low spatial resolution; fMRI has high spatial resolution and low temporal resolution”. While true to some extent (although becoming less so as high density probes for NIRS improve its spatial resolution, and simultaneous multislice fMRI has made whole brain acquisitions faster than the cardiac rate possible), the differences are somewhat more nuanced. Both imaging methods work by the same physiological mechanism; both detect and characterize signal changes arising from changes in blood oxygenation and volume in neuronal tissue. Both are extremely well suited for particular types of applications. However, the methodological differences in the
acquisitions affect the content and interpretation of the signals, and fundamentally circumscribe what can be learned with each technique.

A. The signal itself

The first major area of difference is that the photons used to generate fMRI data interact only weakly with tissue – brain tissue has a very low interaction cross-section to radiofrequency (RF) photons. Therefore, there is very little inherent difference between signals from tissue inside and outside the brain in terms of signal strengths and signal to noise ratio at the field strengths currently used for fMRI imaging. The mechanism by which the signals are spatially resolved in echoplanar MR imaging (the basis of most fMRI experiments), phase and frequency modulation using externally applied magnetic field gradients, further separates signals from adjacent locations. As a result, fMRI signals truly reflect the blood parameters at a given location in the brain, regardless of location. In contrast, fNIRS uses near infrared photons as signal carriers. While the NIRS band is relatively translucent to these photons compared to neighboring regions of the spectrum, the photons used to probe a location will always interact with intervening tissue through absorption and scattering; fNIRS at a basic level represents the blood parameters over a path through the brain that starts and ends on the surface of the head, rather than at a particular location within the head. While spatial locations can be isolated through time gating, phase analysis, back projection, or full-fledged solutions of the inverse problem, the effects of scattering and absorption of tissue in the head mean that different brain regions can never be equivalent in terms of detection sensitivity in fNIRS. Certain cortical regions can be probed with very high sensitivity and time resolution, whereas other brain regions (subcortical regions, or regions on the bottom of the brain) will always be difficult or impossible to monitor directly with NIRS.

The second difference is that while both fMRI and fNIRS signals reflect changes in blood oxygenation and concentration, fMRI is two steps further removed from these parameters than fNIRS. fNIRS allows direct and independent measurement of oxy and deoxy hemoglobin concentrations (and potentially other species, as discussed in Section II) through the optical properties of the hemoglobin molecule; independent optical measurements at multiple wavelengths allow for the discrimination of multiple unknowns (namely the concentrations of chromophores with different absorption spectra). The fMRI signal, in contrast, is modulated by changes in T2* relaxation times in tissue surrounding blood vessels, which in turn changes as the magnetic susceptibility in the vessel varies with the total amount and ratio of paramagnetic deoxy-hemoglobin and diamagnetic oxy-hemoglobin in the vessel\(^1\). It is therefore not possible to separate the effects of blood oxygenation and volume in the conventional fMRI signal – the signal is a composite measure that depends both on blood volume and oxygenation. This has important implications both for what can be detected with fMRI, and how it can be interpreted. Blood oxygenation and volume can change in ways that increase or decrease the fMRI signal in response to neuronal activation.

1\(^\text{T2* relaxation is a characteristic of tissue that summarizes how quickly the MR signal decays due to local magnetic field inhomogeneity. This affects the image intensity in a voxel – more inhomogeneity leads to decreased signal intensity. Because deoxyhemoglobin is paramagnetic and disrupts the local magnetic field, the amount of deoxygenated blood in a voxel has a strong effect on image intensity.}\)
in some cases even cancelling out completely (Seiyama et al., 2004). So fMRI signal changes are more removed from the degree of neuronal activity driving them than fNIRS, and should therefore not be over-interpreted.

B. Signal and noise

Much is made of the higher temporal resolution afforded by fNIRS relative to fMRI, but why this is advantageous is frequently misunderstood. At first glance, the fact that the hemodynamic response is so slow (~4–6 seconds time to peak activation for fNIRS, fMRI, and arterial spin labeling (ASL) activations (Huppert et al., 2006; Sassaroli et al., 2006)), it would seem that sampling rates much higher than 2–3 seconds per point, which for years was a standard acquisition rate for fMRI, would offer little advantage for recording the hemodynamic signal associated with neuronal activation (other than the SNR increase coming from more data points). While this is true, the noise is another matter. Hemodynamic signals are strongly contaminated by physiological noise; respiration (mostly in fMRI), and cardiac (in both fMRI and fNIRS) signals are large, often larger than the target activation. The cardiac signal in particular is at a relatively high frequency – the normal adult heart rate ranges from 60–100 beats per minute (1–1.6 Hz), and the waveform is complex, with significant energy in the first 2–3 harmonics (up to 4.8 Hz). This can only be reliably quantified with sample rates greater than 9.6 Hz, easily attainable with fNIRS, but currently out of range of routine fMRI. Sampling at this high rate allows these noise time courses to be removed with simple spectral filtering. Sampling at lower rates does not make this noise go away, it simply records it improperly (i.e. the signal is aliased-the signal energy shows up in the recorded data, but at incorrect frequencies.). The result is what appears to be additional noise power in the recorded signal which can be difficult or impossible to completely remove, greatly reducing the power to detect activations. So the primary advantage of high sampling rates in fNIRS is not to better record the signal, but to better record (and thus suppress) the noise.

C. Complementary information of multi-modal approaches

fMRI’s deficits in mapping the details of the hemodynamic changes resulting from neuronal activity are offset to a large degree by the numerous additional types of scans that can be performed in an MR exam. High resolution 3D anatomy, blood flow, levels of brain metabolites such as GABA and glutamate, vascular architecture, white matter tractography and myelin density, and other parameters can be acquired in the same session as fMRI examinations, complementing the fMRI data and providing a rich picture of brain structure and function. Recent advances in fNIRS, such as the development of diffuse correlation spectroscopy (DCS) for flow measurement, and the ease of integrating fNIRS with EEG acquisition (or with slightly more difficulty, MRI), also allow for complex multimodal examination of the brain to complement measures of hemoglobin concentration.

D. Portability

fMRI has always, and likely will always, require a subject to lie still within an enclosed scanner constructed at significant expense. The exquisite spatial resolution of fMRI comes at the cost of requiring the subject to remain unnaturally still in an awkward position for relatively long times. In contrast, fNIRS systems can be extremely portable – there is no
reason to believe that continuously wearable, low profile, high resolution systems will not be available at reasonable cost in the near future. Prototypes of these systems are in use today, and significant advances have been made in addressing motion artifacts, to the point where these systems can be used to record brain activity during normal behavior, not just in a laboratory or clinical setting, but out in the world (Metz et al., 2015), or during sleep (Pierro et al., 2012). Increasing numbers of fiberless and wireless NIRS systems are being developed to render them more easily wearable and portable. This makes NIRS the appropriate choice for brain monitoring in a naturalistic setting with a minimum of interference from the measurement itself. This also gives the ability to detect neuronal activity in response to rare events that may not happen during the course of an MRI exam due to timing, or at all, because of the environment itself. The ability to perform continuous monitoring also makes fNIRS well suited to clinical monitoring.

**Conclusions**

In summary, we have reported our views on noninvasive brain studies with near-infrared light, including some of its intrinsic limitations (penetration depth, spatial resolution), the key questions that it needs to address (full extraction of the information content of NIRS data, extracerebral contamination), its potential, once pitfalls are properly considered, for functional connectivity studies, and a critical comparison of fNIRS and fMRI. We have also discussed the challenge of performing absolute measurements of brain optical properties with NIRS. Absolute measurements of brain absorption and scattering properties may add an important research tool and diagnostic dimensions by allowing meaningful comparisons across subjects and within subjects for long-term monitoring and longitudinal studies. Furthermore, absolute measurements of baseline properties can enhance the accuracy and information content of dynamic, relative measurements performed during physiological challenges or brain activation protocols. Therefore, while the vast majority of cerebral NIRS and fNIRS studies rely on relative optical measurements, it is important to appreciate the potential information provided by absolute measurements despite the associated instrumentation and computational complexities.

Given the broad range of applicability of fNIRS, its user friendliness, and the rich information content of its data, the field of noninvasive optical sensing of the brain has a bright future ahead. The unique combination of detailed, independent measurements of hemoglobin species, portability, and the ability to monitor brain activity continuously and unobtrusively means that fNIRS will be a critical tool for studying the brain in naturalistic settings for the foreseeable future. It can have a substantial impact on basic, preclinical, and clinical research.

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Fig. 1.
Schematic representation of the optical region of sensitivity (banana-shaped shaded area) in noninvasive optical studies of the human brain. The illumination and collections 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. The sensitivity of the optical signal to the probed tissue is not spatially uniform (as indicated by the different gray levels within the region of sensitivity) and is maximal in the most superficial tissue layers (scalp and skull). The clear cerebrospinal fluid is found in the subarachnoid space.
Fig. 2.
Number of publications per year found on PUBMED in response to the query “(NIRS OR (near infrared)) AND ((resting state) or (resting connectivity))”