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Functional Near Infrared Spectroscopy: For BOLD Detection Only?

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Abstract

Functional near infrared spectroscopy (fNIRS) is a non-invasive imaging technology that has been developed to measure brain activity by means of the blood oxygenation level response (BOLD). Widespread interest in the technology has propelled its use for an increasing range of diagnostic and therapeutic applications in neurology and psychiatry. As a specific application of NIRS, however, the technology's theoretical analytical potential is greatly underserved, particularly in its compositional identification and spatial resolution dimensions. Technological improvements in light travel and component reduction as well as improved spatial resolution and data analysis can be expected to positively assist the technology's evolution and continued analytical promise.

Keywords: *Functional Near Infrared Spectroscopy (fNIRS); Blood Oxygenation Level Response (BOLD)*

Introduction

Functional near infrared spectroscopy (fNIRS) is a non-invasive imaging technology used for monitoring brain activity that is now widely used in neurology and psychiatry [1-3]. Originally employed for validation studies, the technology has since been exploited for an increasing range of diagnostic and therapeutic applications in neurology and psychiatry. Widespread interest in the technology has propelled its appearance in scientific reporting since the technology was originally developed in the early 1990's [4,5]. From a low of 5 articles per year in 1995, publication rate now exceeds 130 articles per annum in 2015, a roughly 25-fold increase and a confirmation of future interest in expanding the technology's use for the study of functional brain activity.

fNIRS represents a specific application of NIRS that has been developed to assess localized blood oxygenation changes occurring during neural activity [6,7]. Termed the hemodynamic or blood oxygenation level dependent (BOLD) response the application builds consecutively on Pauling and Coryell's 1936 observation that oxygenated and deoxygenated hemoglobin are chemically and physically distinguishable - due to the magnetic dipole difference between the two states - and Ogawa's extrapolation in 1990 that exploited these differences for measuring local neural activity, based on the amount of oxygen consumed. Although the hemodynamic response has since been chiefly used for fMRI, where hemoglobin oxygenation is related to the observed magnetic differences, Jobsis discovery in 1977 [8] of the relative tissue transparency in the near infrared spectrum also allowed the monitoring of hemoglobin's oxygenated states by means of absorption or reflectance spectra. This discovery and the progressive development of fNIRS from a continuous wave format to incorporate frequency and time domain formats have since expanded its diagnostic range in neurological and psychiatric applications.

In neurological evaluation, for example, fNIRS has largely replaced fMRI in circumstances where assessments require that patients be kept mobile. fNIRS, notably, is the preferred modality for monitoring the progress of rehabilitation following stroke, including the monitoring of upper and lower limb recovery and the restoration of cognitive function. fNIRS has also been used to monitor abnormal brain activity during psychiatric disturbances such as, for instance, fronto temporal activity in schizophrenia patients during facial emotional reactions. Major depressive disorder, SSRI inhibition, and sleep disturbances have also been assessed using the technology [1-3,9].

In its current stage of development, fNIRS chief advantages include monitoring of the hemodynamic response in mobile patients with both hemoglobin oxygenation states, as opposed to only one in fMRI, portability, and low cost. Whereas, for example, new formats have substantially increased in expense from tens of thousands of dollars for continuous wave configurations to hundreds of thousands for frequency and time domain applications, expenses of even the most expensive fNIRS units pale relative to fMRI, which can exceed 20 fold or more costs of upper end fNIRS units.

Despite the significant advantages of the technology and the increasing scope of its applications though, a number of shortcomings converge to restrict its further evolution. Chief factors include a) low spatial resolution, which is more than a magnitude less than fMRI, b) slow temporal response, which while comparable to fMRI, is nonetheless several orders of magnitude slower than the neural events that are the object of study, and c) an inability to assess compounds other than hemoglobin. These shortcomings have been mitigated in practice somewhat by combining fNIRS with other technologies, such as electroencephalographic (EEG) recording, that complement deficiencies of fNIRS with improved capabilities in other dimensions [10,11].

When considered alongside the chemomimetic analyses performed by NIRS, however, the analytic potential of the technology is clearly underserved in its fNIRS mode [12]. For example, the technology has been proposed for material analysis in nanoscale fabrication, requiring a spatial resolution some seven orders of magnitude better than that currently achieved by fNIRS. While it is generally agreed that such an enhanced scale of detection exceeds the theoretical diffraction width, this theoretical latter is nonetheless some 5 orders of magnitude greater than that achieved *in vivo*. Further, when not limited by the slow BOLD response, temporal resolution is equivalent to electrical recording [4]. Finally, by monitoring molecular vibrational events in the infrared spectral region, as opposed to the electronic transitions of the visible range, many more compounds are potentially distinguishable, a capability now being exploited for a vast number of compounds examined in industrial and other institutional settings [13].

These clear differences between the specialized use of NIRS for detecting functional, brain activity and its parent technology raise the obvious question of whether such theoretical capability is exploitable, that is, whether the greater analytical capability of the latter can be accessed for *in vivo* recording. To address this question the paper will review basic physical principles of near infrared spectroscopy and their use in chemomimetic analysis and the chief factors limiting their access in fMRI. The potential for overcoming these obstacles will then be framed from the perspective of NIRS successful use in chemomimetic analysis of tissue preparations and the likelihood for technology transference that may address or mitigate these limitations in clinical practice.

NIRS and Chemomimetic Analysis

Basic principles

The analytic use of NIRS predates its redeployment for functional medical diagnosis and involves a much broader scope of analytical objectives, providing a non-destructive, multi-constituent detection of nearly all physical matrices. Norris's use of this technique as a spectroscopic technique notably introduced its general application to industrial analytics in quality and processing control where it offered component specific qualitative and quantitative information that has since come to dominate similarly purposed technologies in the pharmaceutical industry. Much of NIRS analytical capacity therefore remains latent with respect to clinical evaluation.

The technique's analytical potential derives from the preponderance of compounds that absorb chiefly in the near infrared region of the electromagnetic spectrum, encompassing the wavelength range from about 700 nanometer to 2,500 nanometers. Absorbances in this spectral region are due to quantum mechanical vibration modes of the principal carbonyl and common hydrogen bonding elements found in cells, that is, NH, OH, and SH functional groups, which can be detected in both absorption and scattering modes. Within the higher wavelength range, from about 1100 to 2,500 nm, absorption is due to fundamental and largely asymmetric combinations of vibration modes, whereas absorption below this range includes many vibrational overtones. Consequently, these latter display absorption coefficients on the order of 10 or more fold lower than those of the fundamental vibration modes.

Due to the asymmetry of these chemical group combinations, unique spectra are in principal obtainable for a wide number of compounds. Moreover, several additional factors contribute to its analytical breadth. Vibrational combinations may be probed with intermolecular interactions, like that introduced through electronegativity of neighboring atoms or mechanical coupling with other vibrational modes, which generate detectable frequency shifts. Further, some vibrations are sited to particular chemical groups thereby providing characteristic narrow frequencies despite the remaining complexity of the molecule. By comparing these with empirical tables they can be relatively easily detected and identified. Finally, in the scanning regime used in infrared microspectroscopy it is capable of yielding per pixel a complete spectrum of several thousand intensity values, compared to the typical 8 bit color values in the visible range.

The spatial resolution of NIRS, significantly and moreover, is limited chiefly by optical diffraction giving the procedure microscopic access [14]. For resolution of minute objects this limit is mathematically described for microscopic observation by $\Delta x = 0.61 (\lambda/n \sin \Theta)$ where the separation between two points, Δx, is defined as the Airy disk zero crossing of a second Airy disk image; $n \sin \Theta$ represents the numerical aperture enabling observation at increased magnification and Θ is the angle of acceptance. Due to the direct relationship between diffraction and wavelength, therefore, probing stimuli with infrared radiation extends spatial resolution downward to several um. Nearly four orders of magnitude better than that obtained with fNIRS, this limit approximates the size of many smaller neurons and even axonal processes. Moreover, NIRS has also been proposed for the examination of nanoscaled devices, and so invites exploration with probing modalities that exceed even the diffraction limits of IR spectroscopy [15].

Obstacles to improved fNIRS analysis

Among the currently recognized chief obstacles to improved fNIRS imaging, Ferrari and Quaresima [6,7] and Boas and Franceschini [16] cite tissue complexity, with significant contributions from dominant infrared absorbers, light path obstructions, and photon scattering. These difficulties reflect the considerable hindrances intrinsic to *in vivo* and non invasive analysis. A growing range of methodologies and data treatments nonetheless indicate that substantial improvements in fNIRS can be achieved by improvements in component reduction methods [12], which involve physical accommodations [17] as well as established data processing procedures, and technical advances that improve light travel, delivery, and detection [18,19].

Due to the material complexity of tissue the detection of dominant infrared absorbers in tissue is favored in unfiltered spectra. Spectra of these compounds complicate analysis by modifying baseline and by overlapping with other absorbing species. Dominant absorbers of infrared radiation in the brain include hemoglobin in its oxygenated and deoxygenated forms and water. While the chief absorption of hemoglobin is in the visible range, there is also substantial absorption occurring between 750 and 850 nm for both states, with the isobestic point of the two states at about 800 nm. In principle measurements may be taken as the change in the absorbance difference at points above and below that of the isosbestic point. Water, additionally, absorbs strongly in the infrared region, generally above 900 nm, but there is considerable variation as a function of wavelength due to the lesser extinction of vibrational overtones in the near infrared, and the relatively discrete localization of absorbance to particular wavelengths that is related to the simplicity of water's molecular structure. Water, for example, possesses only three fundamental vibrations. Peak maxima lie in the mid to far infrared at 2898 nm, 2,766 nm, and 6,097 nm maxima. In the near infrared peak absorbance occurs at 970 nm, 1,200 nm, 1,450 nm and 1,950 nm. Absorption intensities for these latter maxima are comprised chiefly of the fundamental vibrational overtones, and so are considerably weaker than fundamental vibrations. The absorption band at 698 nm, for example, that gives water its light blue tint, is a third vibrational overtone.

Compositional analysis with NIRS

Due to the lower absorbance in regions close to and between near infrared bands, NIRS can and has been used for aqueous solute analysis, i.e., for absorption of solutes dissolved in water [20,21]. For example, time resolved fourier transform, infrared spectroscopy has been used to obtain structural information about the dynamics of chemical reactions occurring in water, including information about reaction kinetics, ligand interactions and protein conformational changes [22]. By monitoring the spectral region at the intersection of

the near and mid infrared at 6300 nm for instance is capable of monitoring aldehydic and sulfoxyl groups undergoing chemical rebonding. Moreover, measurements of body fluids in this spectral region have identified unique vibrational fingerprints of protein profiles [23] without use of subtractive filters that could improve resolution by diminishing spectral contributions from water.

Significantly, NIRS has also been successfully used for examination of prepared and living tissue - that is, speciments comparable in complexity to brain tissue and containing water and hemoglobin chromophores. In their study, two dimensional arrays have been used for biological samples of frozen, prepared tissue specimens as well as of neuronal cultures. For example, Lasch and Naumann notably employed NIRS to examine frozen colon mucosa and achieved identification of unique proteins and microscopic scale spatial resolution [24] at a spatial resolution of about 8 microns. Examination of colonocytes within the mucosa revealed the presence and characteristic IR signature of mucin glycoprotein. Examination of a frozen neurological sample of dorsal root ganglia infected with scrapie virus, detected misaggregates of the prion protein. In this instance spatial resolution approximated 10um and the spectral signature of the amide I/II band - a distinctive marker for proteins with abundant beta sheet structure - could be detected at 0.1% background protein levels. Finally, in a technically comparable study, the progression of amyloid genesis could also be monitored with NIRS [25], with the specific identification of plaque presence. Together these studies indicate that IR specific information of relatively low quantities of specific components is obtainable when steps are taken to reduce the total tissue analyzed, through the use of spectral confinement, and employed in conjunction with data treatment.

Array configurations and data treatment

Besides the use of fourier transform data treatments of tissue specimens has drawn from procedures used for probing solid mixtures, like pharmaceutical compounds, where its ability to detect spectral absorption features of compounds in either transmittance or scattering modes enables the discrimination, localization, and identification of compounds in complex samples. Because the samples are typically prepared by surface irradiation with probe stimuli analyses are generally tailored to surface characterization or slice preparations. Such preparations have been modified to detect minute sample quantities with high spatial resolution by capturing the reflectance spectra with microscopic optics and focusing these on two-dimensional detection arrays [26]. Data collection is comprised of spectral imagery taken from individual point sources with near and mid infrared spectra. Compiled data can then be used to generate three-dimensional data sets, termed hypercubes, that include x and y coordinates of the surface points. These may then be correlated with a z coordinate constructed from the specific spectral information of component composition. NIRS imaging thus enables direct quantitative information to be taken from heterogeneous samples. Using this approach, moreover, it is possible to detect and quantify the spatial distribution of unique compounds across the surface of an analyzed sample; hence, the format is capable of detecting as well as locating compounds that would otherwise be hidden in transmission modalities directed through whole samples.

Due to spectral overlap and the relatively lower absorptivity in the near infrared region, the analysis of physical matrices with NIRS has frequently resorted to mathematical processing of accumulated data to isolate and quantify signal contribution, a pretreatment that is available for *in vivo* and *in vitro* uses [12]. Mathematical pretreatment functions in several capacities including the reduction of physical scatter effects on baseline modulation, a reduction of component number, and the learning and calibrating of signals associated with unique components. For example, mathematical treatments used to correct for baseline variation that are associated with reflectance scattering include Taylor smoothing algorithms [12] that can eliminate much of the variation in light intensity and baseline variability preventing the isolation of components of interest. Mathematically, variable reduction is usually approached by orthogonal characterization, which functions to identify principal mixture components. Additionally using principal components it is then possible to perform multivariate calibration and classification to identify and quantify components [27].

Overcoming limitations in spatial resolution

Light obstruction and thick tissue specimens

The successful use of NIRS in arrays and thin tissue specimens are positive indicators that analogous approaches to spatial confinement could be profitably used for component reduction and spatial discrimination. Such analogous approaches, however, will need to overcome difficulties currently associated with light obstruction and travel in existing fNIRS configurations. Specifically, there is general consensus that the path of light travel through the cranium and brain tissue assumes a complex profile [6,16]. Ferrari points out that the current technical configuration generates a curved parabolic shape, with the sensitivity of the source detector pair defining the profile. Boas and Franceschini additionally point out that its penetration is relatively shallow, limited primarily to the superficial cortex and involves light scattering mathematically described by radiative transport. Shallow depth penetration and light dispersion thus account for current limitations to fNIRS analysis associated with radiative travel effects. Among other consequences, spatial resolution and localization are severely restricted, resulting in its roughly 10-fold lower resolution than the current capability of fMRI. Although this resolution permits the assessment of regional activity variation, the considerable overlap of functionally linked activity levels within a domain of such size limits neurological interpretation. Hence, the ability to suitably apply confined imaging is greatly restricted in current modes, and will likely require wholesale modification of light delivery, focus, and detection methodologies to enhance analysis.

In this regard, several promising technical developments that have emerged from imaging techniques in thick tissue specimens hold promise for improving light travel and diminishing light scattering effects. Accordingly, these methods promise to greatly improve spatial resolution and component identification and quantification within *in vivo* contexts; hence they can be expected to extend the scope of neurological diagnosis. Such methods collimate and narrow tissue illumination profiles and include, among the chief methods, optical sectioning of thick tissues with laser imaging microscopy, whole body photoacoustic tomography, and multi photon laser scanning of thick tissue slices. Strengths and shortcomings as these may apply to fNIRS use will be briefly considered here.

Thin sheet laser imaging [18]. Thin sheet laser imaging is an optical sectioning procedure that projects a thin light sheet through a sample to illuminate a plane of tissue. Observation is orthogonal to the plane and to date has been configured with a system of lenses typically used for microscopy. Originally conceived as early as 1903 [28] the technique now relies exclusively on synchronized radiation of laser light sources that are selected from the visible wavelength range. With clarification of tissue preparations image quality approaches the diffraction limit below 10 um. The quality of light depends, however, on the geometry of the light sheet, which outside of the lens focal plane is gaussian in shape; accordingly, for large sections the focal plane is the only region that can be observed without image distortion. The technique has been used for small animal tissue such as brain tissue from rat and zebrafish. For example, stacks of 100, 20 um serial sections of zebrafish brain have been compiled with spatial resolution approaching the diffraction limit.

Photoacoustic computed tomography with ring shaped configurations [29,30]. In whole mount preparations including crania limitations to non-invasive NIRS use relate to lens configurations that are optimized for planar samples rather than thick samples. These limitations have been overcome somewhat in whole body, ring shaped configurations that employ confocal photoacoustic computed tomography. Photoacoustic tomography utilizes laser illumination to generate localized small temperature rises in tissue, following on absorption of IR by compound in the light path. The resulting pressure wave, due to thermoelastic expansion, can be detected by ultrasonic transducers that then reconstruct the tissue image using the temporally displaced signals. In the ring configuration, light delivery occurs across a 360 degree profile that is focused through a conical lens and optically condensed to project a probing band around the sampling region. Photoacoustic signals can then be detected with a full ring transducer array. With this system reported values for spatial resolution approach 100 um. This system offers a depth of penetration that significantly exceeds current fNIRS use with single light sourcing and multichannel detection and also offers advantages of an established detection technology. By substituting detectors or narrowing tuning illumination, moreover, the technique offers the prospect of directly monitoring specific spectral features within deep brain regions.

Conclusion

Clear differences between the specialized technique of fNIRS for detecting functional, brain activity and that of its parent method of NIRS raise the obvious question of whether such theoretical capability is exploitable, that is, whether the greater analytical capability of the latter can be appropriated to improve functional interpretation and provide an IR specific reservoir of information. Despite significant impediments encountered in current formats of continuous wave, and frequency and time domain fNIRS, the development of applications involving complex tissue preparations and the use of new configurations coupling light confinement with highly transmissible sonic media hold promise for significantly improved spatial resolution and compositional determinations.

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