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Methodologies on the Enhanced Spatial Resolution of Non-Invasive Optical Brain Imaging: A Review

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ABSTRACT Optical brain imaging (OBI) has the potential for a bright future thanks to its low cost and portability relative to other biomedical imaging modalities. Temporal and spatial resolutions are considered to be the discriminatory features for selection of biomedical imaging equipment. OBI systems, however, still face the bottleneck of limited spatial resolution. In this study, existing methodologies and designs for enhancement of spatial resolution of OBI are comprehensively summarized. This is the first study reviewing all such techniques, therefore, is beneficial for researchers working in this field. The study presents general overview of principle of OBI followed by pros and cons specifically the challenges in enhancement of spatial resolution. Later, different novel existing methodologies, algorithms design and configurations, phantom related studies presenting spatial resolution enhancement have been discussed. Finally, conclusion and future directions are presented with an idea to enhance the spatial resolution of OBI up to nanoscale.

INDEX TERMS Optical brain imaging, spatial resolution, optical nano-antenna, fNIRS, fMRI, fast optical imaging.

I. INTRODUCTION

Imaging has attained an enormous attention in different fields of science, since Galileo's era [1]. It has extensively been used for the measurement of physical properties like size [2], surface area [3] and tissue characteristics [4] and also to gather temporal insights of the biological functionality [5]. Neuroimaging has been a technological breakthrough for cognitive brain science based upon the development of psychophysics [6], behavioral conditioning [7], cognitive psychology [8] and neuroscience [9]. Brain imaging technologies can generally be classified by type of energy source utilized and resultant/observed data/principle [10] as shown in figure 1. In addition, with the ubiquity of molecular probes, brain imaging can be carried out not only to visualize neurological structures [10], [11] but also to perceive functionality of cells and surveilling of molecule dynamics [12], [13]. Different combinations of the key words related to the focused research topic were used in Web of Knowledge (WOK) search engine to statistically analyze the number of publications/year in the field of brain imaging and the bar chart of number of publications per year from 2000 to 2018 is shown in figure 2.

Well in the United Kingdom, every three minutes a patient is admitted to the hospital due to a traumatic (e.g. fall, attack, motor vehicle accident) or semi-traumatic brain injury (e.g. stroke, brain hemorrhage, anoxia), approximately equal to 300 thousand admissions per year [14], [15]. Several of these patients recovered with short-term treatment, but most of them will develop a prolonged consciousness disorder [16]. Vegetative patients (also referred to as non-responsive wakefulness syndrome [17]) are neurologically awake, have open eyes and preserved reflexes but seem to be unsuspecting of their environments or themselves. Full or partial recuperation from serious brain injury can often involve progression between all of these states [18]. The progression is

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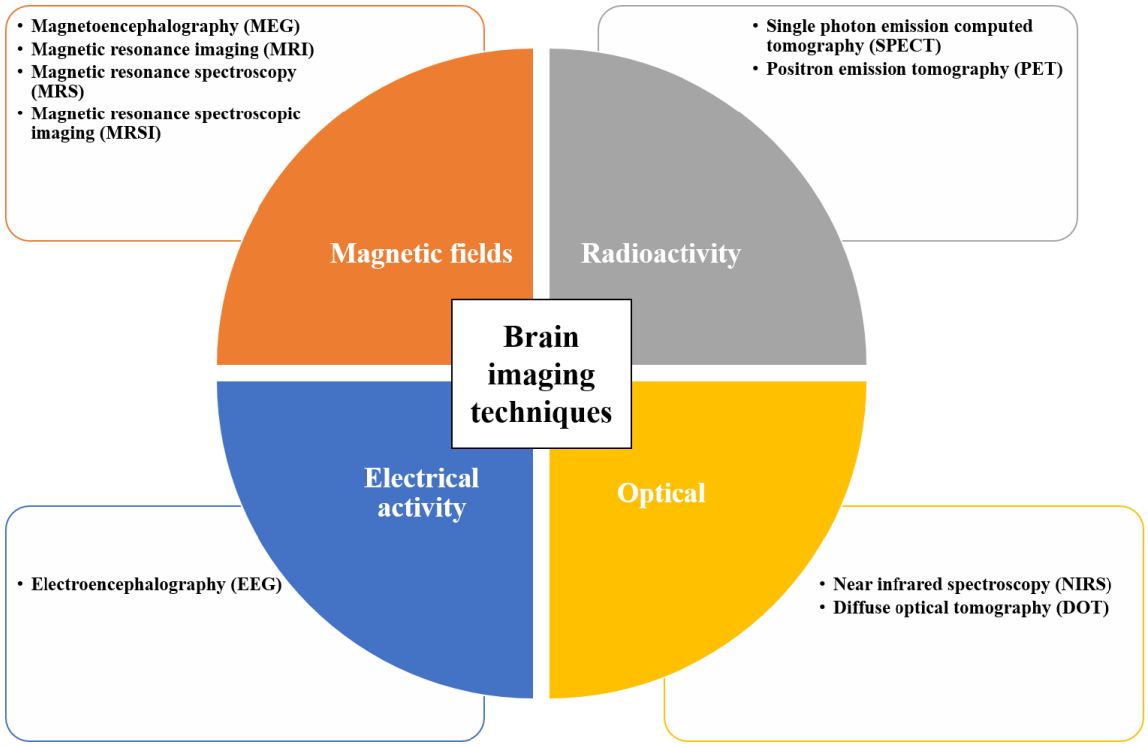

FIGURE 1. Classification of different brain imaging technologies in reference to the type of energy source utilized for the measurement.

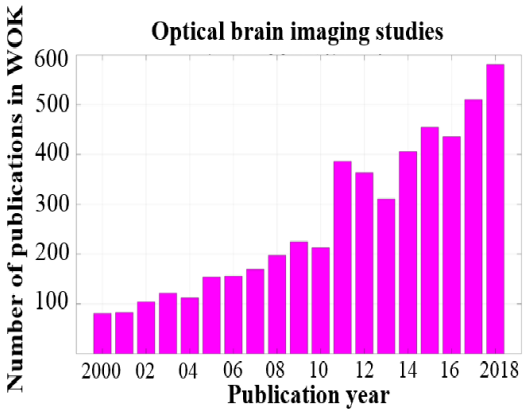

FIGURE 2. Number of articles (according to Web of Knowledge database) on OBI published annually since 2000. Database survey conducted on April, 2019.

usually smooth, therefore the real challenge lies in order to determine and prescribing a patient in one condition using accurate diagnostic methods [19]. Thus, accurate detection of the actual condition and state of consciousness continues to remain a comprehensive area of study, because misdiagnoses can cause to unacceptable healthcare decisions [20]. The recent ''gold standard'' for identifying awareness indications of patient are standardized behavioral assessments [21], [22]. However, as physicians mostly depend on empirical behavior and attitude to assess a patient's awareness level, it could happen that a substantial proportion of patients might be misdiagnosed, if they do not build up intentional behaviors due to equipment deficiency [23]. Moreover, it has also been calculated that 15 percent of patients [24] who satisfy the cognitive ''gold standard'' for coma have a behavioral-motor disassociation [25] or secretive awareness, whose brain conditions can only be estimated through neuroimaging.

Amyotrophic lateral sclerosis (ALS), Alzheimer's disease, brain tumor, epilepsy, HIV dementia, Huntington's disease, multiple sclerosis, Parkinson's disease, stroke, and traumatic brain injury (TBI) are among the most ideal age-related neurological disorders throughout the world. Disability-adjusted life years (DALYs) [26] published an estimate of the coming years stream of healthier life (years anticipated to really be lived in decent health) harmed as a result of both the occurrence of brain disorders and injuries as shown in figure 3. Rehabilitation is a biological process in which injured or diseased individuals acquire a full rejuvenation or recognize their optimal mental, physical and social potential, either when a complete recovery is not conceivable and are embedded to their most ideal environment [27]. Rehabilitation entails a planned and iterative problem-solving mechanism along the spectrum of severe hospital-to-community care. By learning the structure and the function of the brain, scientists can better understand emotional [28], sleep-and cognitive mechanisms [29] but can also give relief to nervous-system patients [30] including depression [31], autism [32], Alzheimer's disease [33] and

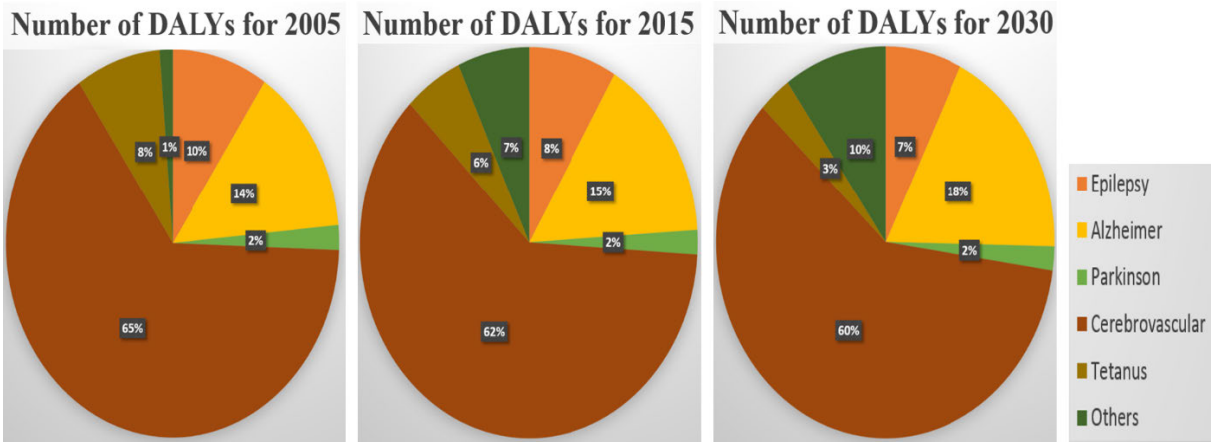

FIGURE 3. The total number of DALYs associated with neurological disorders and as percentage of global DALYs projected for 2005, 2015 and 2030.

Parkinson's disease [34]. Techniques for investigating the structure and functionality of the brain can be categorized as invasive and non-invasive [35], [36]. Optical brain imaging (OBI) methodologies enable doctors and scientists to perceive activity or problems inside the nervous system non-invasively [37].

II. OPTICAL BRAIN IMAGING

A. HISTORICAL BACKGROUND

There are several categories of OBI systems, although these techniques are based upon a certain basic principle, the technical details affect the data resolution and often influence the terminology [38]. Jobsis [39] first explained the in vivo utilization of near infrared spectroscopy (NIRS), and this instrument was originally intended for the medical surveillance of tissue oxygenation, as described in existing literature [40]–[44]. The advancement in this field shows the development of an instrument "functional near-infrared spectroscopy (fNIRS)" that enables humans to investigate functional insights of cortical activities [45]–[47]. The technique has been progressing for about 30 years and a wide variety of NIRS devices have been manufactured [45], [48], [49]. These devices enable us to monitor dynamic fluctuations in regional cerebral blood flow (CBF) in real-time by evaluating concentration changes in cerebral hemoglobin [50]–[52]. Different types of cognitive tasks such as motor [53]–[55] and social activity [56]–[58], have been evaluated using NIRS. Currently, fNIRS devices are flourishing and have been noted as being useful in psychiatry [59], [60] and psychology [61]–[64] development.

B. PRINCIPLES AND INSTRUMENTATIONS

Fundamentally, OBI involves the light shining onto the surface of skull through one or multiple sources placed in close proximity or apart depending upon the nature of study and configuration [45], [49]. Similarly, single or multiple detectors are placed at specific locations nearby sources (0.7 to 4 cm) to estimate the absorption and scattering coefficients of NIR light (almost 650–1000 nm) emitted through sources and received by particular detector [65], [66]. The physical insights of NIR light emitted through source and received by detector/detectors, facing the phenomena of absorption, scattering and detection after spreading at particular path (banana shaped) is shown in figure 4 with explained optical measurement principle [67], [68]. Usually two or sometimes more wavelengths are used, that have different tissue-dependent absorption constants [45], [49]. In order to differentiate light from different sources, source encoding (i.e. lighting sources at distinct moments and frequencies) can also be used [69], [70]. Detectors measure attenuated light that passed through a specific path (banana shaped) inside the brain after emitting from source [49]. Aptly, the NIR light absorbed by hemoglobin relies on whether or not the hemoglobin is oxygenated. It is therefore possible to determine both oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) signals as well as total hemoglobin (HbT), incorporating light configurations that distinguish how light is absorbed by blood with HbO and HbR [71]–[73]. Three different kinds of devices those are mainly used for fNIRS are continuous wave, frequency domain and time domain [74], [75]. The types of fNIRS instruments, their probe arrangements with existing methodologies and pre/post observed data challenges and processing are summarized in pictorial form, displayed in figure 5.

C. CONTINUOUS WAVE INSTRUMENTS

The first and most pervasive instruments to evaluate the fNIRS signals are continuous wave devices (Table 1). All such instruments emit light intensity constantly and measure the changes in the intensity of the attenuated light, which has crossed through the tissues. To determine the chromophore concentration from the collected light intensities, the modelling of the physical insight through which light gets scattered [45], [49], [75] is required. The best historical model

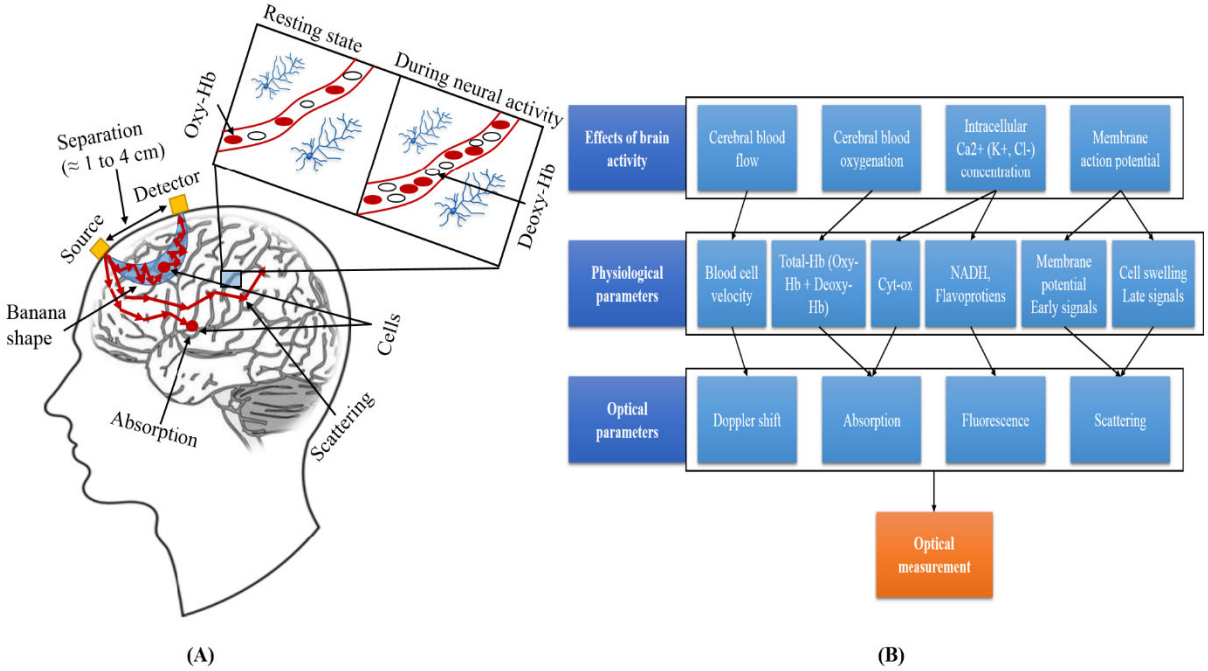

FIGURE 4. **(A) The concept of fNIRS measurement and related absorption and scattering properties of NIR light in relation with consumption of oxy-hemoglobin. (B) Steps involved in brain activity as basis of optical measurements and corresponding physiological parameters.**

for this is the Beer-Lambert law [75], [76], introduced following the initial work of the French mathematician Bouguer in the 1700s [77]. This kind of spectroscopy describes a linear correlation between absorption and concentration of an absorbing species, and therefore has been extensively used in mass spectroscopy analysis with analogous biological tissue principles [78]. The biological tissue, including the brain, has a highly scattered environment [75]. To address such kind of light scattering, Delpy et al. evolved the modified Beer-Lambert law [79]. It has been commonly used in continuous wave instruments as a means of deriving concentration changes of each chromophore (HbO, HbR, and HbT) [75].

D. TIME DOMAIN INSTRUMENTS

Ultra-short (picosecond-order) laser pulses are attributed to the tissue in time domain devices and the evolving intensity is accessed as a time function (temporal point spread function [TPSF]) with picosecond resolution [80], [81]. There have been two detection strategies in TRS: the streak camera system and a time correlated single photon counting system [81]. The aforementioned has the disadvantage of poor temporal resolution, even though it is large, pricey and dynamically limited [81]. The time-correlated single-photon counting system also has several advantages including low cost components and wide dynamic spectrum, though it has also some disadvantages like the low speed [80]. Since, time domain devices have been introduced as laboratory-based research devices, they are challenging to be used in the medical environment [80]. However, in 90s technological advances have allowed the expansion of a compact time domain optical imaging system of 64 channels [82]. A single-channel and multi-channel time domain instrument that will broaden fNIRS clinical implementations has just been formed and is available commercially [82]–[84].

E. FREQUENCY DOMAIN INSTRUMENTS

The data contained in the temporal profile of the detected light intensity by time domain devices also can be acquired by frequency domain devices by using Fourier transformation [85]–[87]. The light source in frequency-domain instruments transmit radio frequencies, and readings/measured-optical-density depending upon detected light intensity, its phase-shift and modulation depth of the input (Table 2) [45], [88]. It has been shown that phase shift is linearly attributed to the mean total path length for typical tissues at frequencies lower than 200 MHz [45], [89]. Frequency domain devices are low-cost substitutes to time-resolved pulse-based methods. Several multi-channel frequency domain instruments are also now in commonly use [90]–[93].

F. BENEFITS AND LIMITATIONS

OBI is a cheaper and more effective method for all applications, provided that the position of the specified tissues is technically amenable [45], [94]. In contrast to SPECT or PET imaging, the initial measured data attained from OBI do not need auxiliary processing and can just be easily analyzed by users [95], [96]. Another significant benefit of OBI

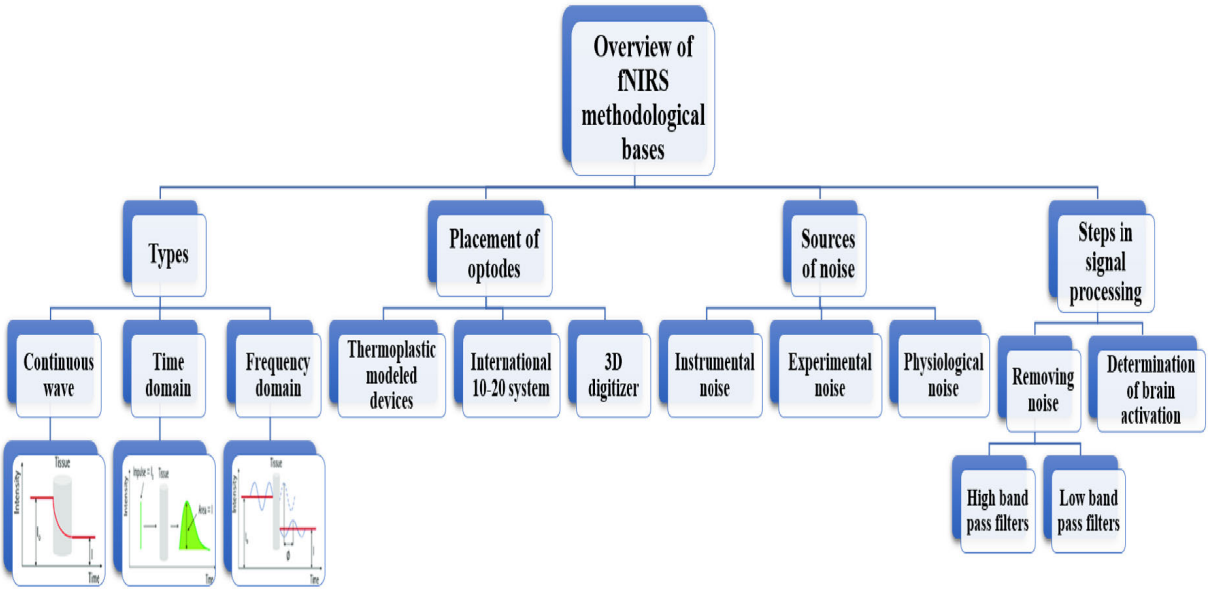

FIGURE 5. Brief overview of fNIRS methodological bases.

TABLE 1. Commercially available CW fNIRS instruments.

Device name	Company/Country	Wavelengths	Number of channels	High-density optode configuration	Website	Portable/Wireless
fNIRS Imager 1200S	fNIRS device LLC/USA	730 nm and 850 nm	48	NO	www.fnirdevices.com	No/No
Genie	MRRA Inc/USA	700 nm and 830 nm	496	Yes	www.mrrainc.com	Yes/Yes
NTS optical imaging system	Gowerlabs/UK	780 nm and 850 nm	256	Yes	www.gowerlabs.co.uk	No/No
NIRS Scout	NIRx medical technologies, LLC/UK	760 nm and 850 nm	384	Yes	www.nirx.net	No/No
HOT-1000	Hitachi/Japan	705 nm and 830 nm	2	No	www.hitachihightech.com	Yes/Yes
OEG-17APD	Spechtratech Inc./Japan	770 nm and 840 nm	16 to 57	No	www.spectratech.co.jp/En	Yes/Yes
fNIRS-FLEX	MRRA Inc/USA	700 nm and 830 nm	512	Yes	www.mrrainc.com	No/No
OctaMon	Artinis/The Netherland	760 nm and 850 nm	8	No	www.artinis.com	Yes/Yes

methodologies is the higher data acquisition speed [49], [97]. Furthermore advantages of OBI are its use of non-ionizing radiation [98] and are generally cheaper instruments than other clinical imaging methodologies. For medical applications, non-invasive OBI also can provide detailed information to other methodologies such as fMRI and in certain cases provide us a low-cost immediate solution [99]. Clinical OBI is usually non-invasive and utilizes near infrared (NIR) light to attain enhanced penetration (but limited in comparison with PET and fMRI) through the scalp, skull and brain [100], [101].

But at the other side, particularly in comparison with PET and fMRI, fNIRS has also few limitations. These deficiencies concern the following: the limited examined cerebral regions [102], since the fNIRS-light penetration depth is limited; the low spatial resolution [103] particularly in comparison to fMRI due to the restriction of physical properties of light propagation, dispersion and the consequent sparseness of coverage [94], [104]. While, in some circumstances, the structural scan that obtained additionally, provides the anatomical details for the interpretation of fMRI data, it really is to be stressed that the positioning of the NIRS probe strongly relies on additional cerebral marks which prevent the certainty of anatomical interpretation [105]. The summary of advantages and limitations of OBI has been shown in figure 6.

III. SPATIAL RESOLUTION

Technically speaking, spatial resolution is determined as the shortest separation between two activation points [106] as shown in figure 7. The efficiency of any imaging instrument

TABLE 2. Commercially available frequency domain fNIRS instruments.

Institute	Country	Wavelengths	Number of source/detectors	Type of light source	Reference
University college London	UK	780 nm and 815 nm	32/32	Fiber laser	Gibson et al. [85]
Hamamatsu Photonics (TRS-20)	Japan	760 nm, 800 nm and 830 nm	2/2	Laser diode	Oda et al. [158]
Physikalisch-Technische Bundesanstalt Berlin	Germany	689 nm, 797 nm and 828 nm	9/4	Laser diode	Wabnitz et al [159]
Politecnico di Milano Milan	Italy	690 nm and 830 nm	2/2	Laser diode	Re et al. [160]
University college London (MONSTIR2)	UK	8 selected from the range of 650-825 nm	32/32	SC fiber laser	Hebden et al. [161]
Politecnico di Milano Milan (fOXY2)	Italy	690 nm and 830 nm	16/8	Laser diode	Contini et al [162]
Physikalisch-Technische Bundesanstalt Berlin	Germany	690 nm	1/1	SC fiber laser	Mazurenka et al [163]

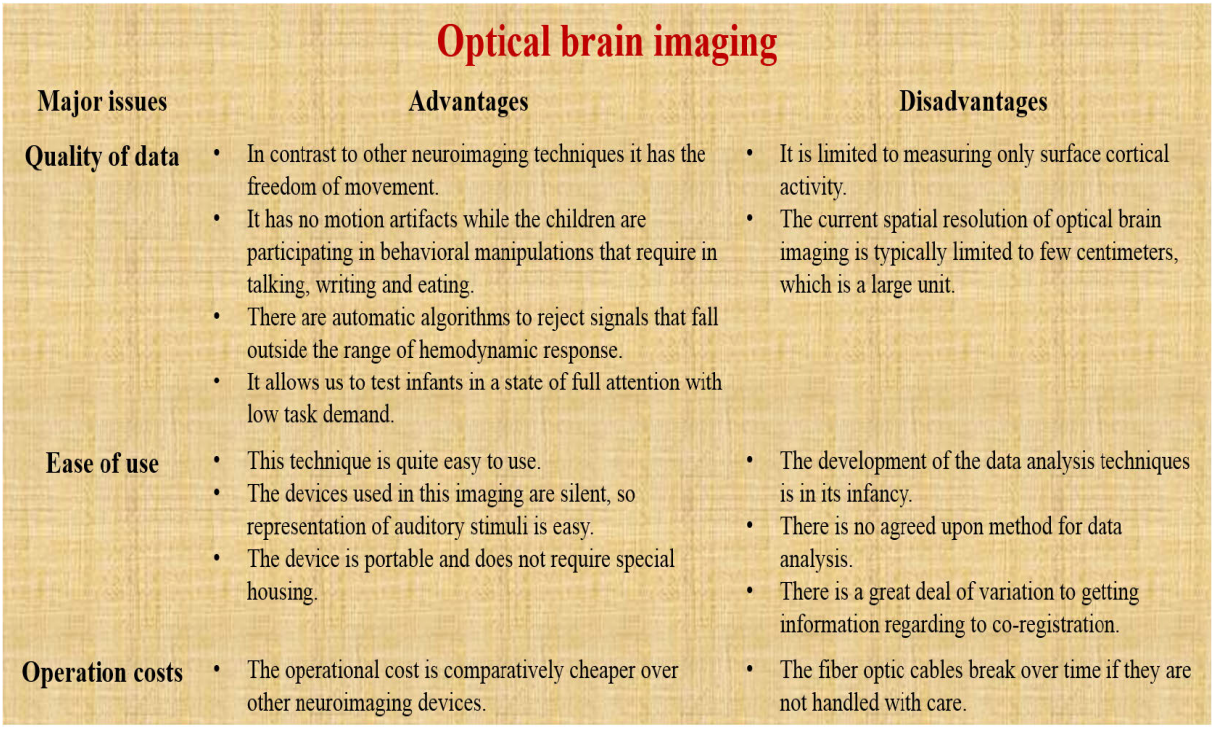

FIGURE 6. An overview of advantages and disadvantages of OBI.

to provide high quality images of the anatomy of activation, in order to reliably and separately locate these activities, is defined as its spatial resolution. The enhancement of methodological spatial resolution and development in data acquisition of imaging technology shall enable us the monitoring of hidden facts related to functionality and dynamics of brain in real time [107]. Several researchers are working on the enhancement of spatial resolution now a days, therefore, it could be predicted that in coming years such efforts shall result in improvement of spatial resolution. The significant challenge of OBI is to remedying the effects of light scattering [108], that not only restricts penetration depth but also a bottleneck to achieve high spatial resolution. ''OBI'', therefore, comprises a very wide variety of estimation methodologies, each of which has different techniques to eliminate scattering effects and improve the spatial resolution. Across the past 30 years, methodological and theoretical developments have involved to OBI systems in such a way that it can provide image of whole brain at a time with better spatial resolution and accurate localization.

The depth sensitivity of fNIRS is limited, which typically reaches up to 1-2 cm in adults brain, inside the inner walls of the skull for estimation of brain activity [66]. It can be enhanced with time-domain techniques where depth efficiency increases with deferred detection of propagating light pulse [109]. The ill conditioned inverse tomography problem limits spatial resolution in DOT. Most of the studies do not use overlapping interventions and therefore the lateral resolution

is approximately equal to the separation of source and detector. Lateral spatial resolution can be enhanced by embedding overlapping interventions [110]. However, the improvement in limited depth resolution is a challenging task because of the constraint of NIR light transmission through the head [66]. The limited lateral and depth spatial resolution triggers a partial volume problem that results in exaggerating changes in the concentrations of hemoglobin [66], [110].

A. SPATIAL RESOLUTION LIMITATIONS RELATED TO IMAGING MODALITIES

There is a mathematical bond between the obtained image and point spread function (PSF) [111]. The association between image spatial resolution and PSF is illustrated in Figure 8. It demonstrates that two activity points can be easily resolved, if they are disconnected with a gap greater than from the full width at half maximum (FWHM) of PSF [111]. Three factors mainly affect the PSF: digital resolution, relaxation during acquisition and data truncation [112]:

- ➢ Digital resolution is attained by separating the field of view (FOV) by the number of possible data points developed across each dimension.
- ➢ Data truncation usually occurs because it's possible to acquire only a finite number of digital data points. In this case, the wideness of the PSF is inversely proportional to the sample size acquired in the proportionate dimensions.
- ➢ The last factor is the relaxation degree during data collection. The slimmer the PSF will occur by greater the degree of relaxation.

A 3-D Dirac delta PSF is required to assure an optimal depiction of a 3-D volume [113], but in practical terms this mathematical limit is unachievable. It would also necessitate the implementation of an unlimited NIR light pulse to acquire an infinite number of independent data points. This would lead to a dramatically increased in overall data acquisition time that would violate the laws of a real-time practical application. Another major factor that restricts the spatial resolution throughout the data acquisition is the existence of motion artifacts related to subject as well as instrument [114]. Ultimately, images with better spatial resolution can rarely be achieved in the existence of motion artifacts [115], condoning the considerable interest for enhancing the spatial resolution by post-acquisition methodologies.

It is important to mention that in fNIRS data acquisition, if a source throw NIR light onto scalp, this light will be travelled inside thrown point in different directions [116]. We are just concerned to the light that received at detector say at time instant k and its next sample $k + 1$ which shall provide the relative concentration change of absorption. It is assumed in fNIRS community that light travels in banana shaped path [80] while traveling from source to detector (as shown in figure 7). It is worthy to mention, only a part of NIR light will be in banana shaped path [117] due to scattering. In figure 7, the upper point is considered to be the measuring point in this case, whose depth is known to the half

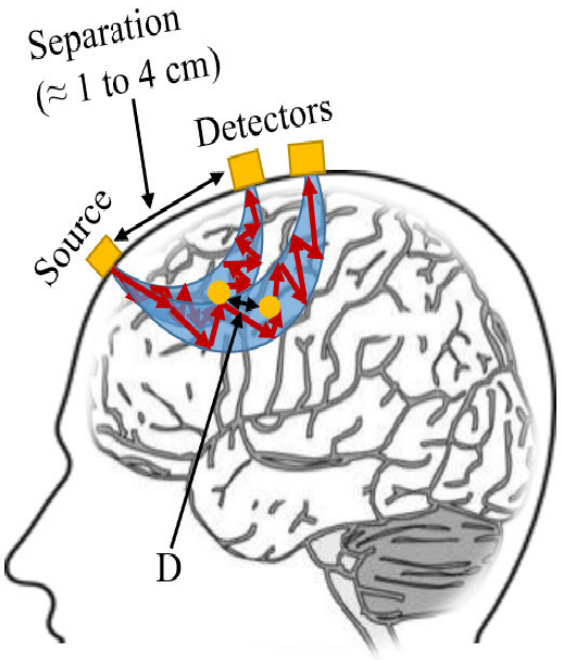

FIGURE 7. The concept of measuring two distinct specific brain areas D distance apart with one source and two detectors.

of distance between source and detector [118]. Now consider two detectors as described in figure 7. Second detector is at a larger distance from source. The lower point is considered to be the measuring point in the case of second detector (little bit deeper). The spatial resolution of results would be the distance between these two activity points as displayed in figure 7. Thus we can differentiate two different brain locations that defines spatial resolution in measurement units.

B. COMPARISON OF fMRI AND fNIRS SPATIAL RESOLUTION

Functional neuroimaging is performing a leading role in recent neurological research [119]. But anyway, the use of such a neurological research has been constrained in clinical desk as well as certain neuroscience studies because the existing tools have limited spatial resolution and localization accuracy, even being the combination of portable, non-ionizing and non-invasive [94]. OBI confronts most of these requirements, but has been hindered by limited resolution [49]. fMRI is typically considered as the ''benchmark'' for envisioning regional deviations in oxygen concentration changes and CBF [120]. Although, preliminary results of OBI have been promising, but it has been lacking the comparative and substantial quantitative results against the ''benchmark'' of fMRI. In fMRI, blood oxygen level dependent (BOLD) imaging is centered on basic differences in the para-magnetic characteristics of oxy-and deoxy-hemoglobin [121]. Local carbon dioxide and oxygen concentration changes control the CBF in neural tissues [122]. When a particular brain region increases the activity in reference to sensory, cognitive or motor task, of the specific brain area increases in reference to

a motor, sensory or cognitive work, the consumption of oxygen leads to a substantial initial decline of oxy-hemoglobin and an actual increase in deoxy-hemoglobin [123], [124]. Which means that CBF tends to increase after a few seconds that will bring more oxy-hemoglobin and reduce the supply of deoxy-hemoglobin. This process is comprehended by fMRI and can be used to image the brain functionality. fMRI uses the BOLD contrast to acquire premised spatial functional maps of neural activity with the fine resolution of few millimeters [125]. Since, Seiji Ogawa [123] discovered the BOLD-contrast in the 90s, the fMRI has begun to be the most widely used instrument for functional brain mapping studies.

Blood oxygenation and CBF can also be assessed by using fNIRS [126] which utilizes the distinct absorption spectra of NIR light in reference to HbO and HbR. Unlike fMRI, fNIRS seems to be more portable that can be used in newborns as well [127], [128]. However, fNIRS is one that is confined to scan cortical tissues only [105], while on the other hand, fMRI can measure activity throughout the brain [129]. In fNIRS, Laser Doppler flowmetry (LDF) also entails the propagation and detection of NIR light to/from neural tissue [130]. The frequency of NIR light transited in reference to the Doppler principle when it scattered towards the detector by passing through moving blood cells. This enables us to monitor the concentration changes in CBF. However, as a downside, as mentioned in Vongsavan and Matthews [131], LDF cannot measure concentration changes in absolute units.

The performance reliability of the recently reported HD-DOT systems allow the researchers to image the distributed functional responses based upon the task and resting state networks [132]. Multiple-order mapping of distributed brain functioning has been studied by emulating a landmark PET single word processing study [133]. Imaging of spontaneous brain functional activity has been measured by mapping numerous cognitive and sensory resting state networks utilizing a resting state model [134]. Multiple metrics of optical image quality have been investigated in task as well as rest patterns against the metrics acquired from fMRI over the same subjects [132], [135]. The data of both fMRI and HD-DOT has also been presented online through XNAT.org to encourage even more comparative research. To experience OBI in individuals at which fMRI is restricted, multiple research groups illustrated functional responses and resting state networks in populations having Parkinson's disease [136], [137]. Collectively, these research groups mention that recent advances in OBI provide a robust and practical approach for mapping brain functionality in comparison with fMRI.

In comparison, the spatial resolution of these two neuroimaging modalities play a substantial role for their effectiveness and use. fMRI having much better spatial resolution as compare to fNIRS is at favorable position but huge size, high cost and extra preparation before experiment are the hindrances for its use. On the other hand fNIRS being portable, safe and easy to use with low cost is more favorable. However, the source localization of fNIRS data is still a controversial issue. It is generally supposed the light travel through banana shape path from source to detector and the center point of this banana shape path is supposed to be the activation location [138]. But still, one can argue why not to consider so many points in a banana shape volume as activation points and how to eliminate the effects of all existing activation points on banana shape volume depending upon mesh size? Similarly, how close two sources/detectors are placed that can produce two distinct paths observable through fNIRS data? Additionally, another important point is that how the configuration of source and detector (separation between source and detector) is selected in such a way that light could travel up to maximum depth? So that, one can get the real hemoglobin concentration changes in proximity to specific neurons. Because low depth could result in limited measurement of concentration changes of blood hemoglobin through arteries close to skull.

C. WHY ARE THE ENHANCED SPATIAL RESOLUTION METHODOLOGIES REQUIRED?

Enhancing diagnostic efficacy and developing methods of communication between patients and clinicians has been a significant concern of the OBI studies. Recent available non-invasive OBI methodologies can provide only up to centimeters resolution [139]. However, it is still difficult to visualize correctly or characterize small but medically substantial lesions in brain or pelvis. Some brain tumors demonstrate an elevated perineural invasion rate that can occur insignificant even for MRI [140]. Cranial nerve activity detected by MRI has been demonstrated to be a negative diagnostic factor in nasopharyngeal carcinoma, and the enhancement of imaging resolution could enhance the detection sensitivity of such a significant factor and can lead appropriate radiation delivery for diagnosis [141]. The growing usage of functional imaging to apprehend intratumorally diverseness has led towards a clinical demand for enhanced spatial resolution for relatively lower-resolution sequences. The expansion of the whole brain vision also has strengthened the demand for elevated temporal and spatial resolution imaging.

Empirical medical investigations of the rehabilitation of awareness after serious brain injury entail an investigator to identify conscious behavior from spontaneous behavior. Because, many of these behaviors are limited and incompatible, behavioral evaluations are not accurate source of diagnostics [15]. Advanced brain imaging instruments can circumvent behavioral sensitivity and recognize secret consciousness and awareness inside the brains of patients, thereby facilitating precise diagnosis, more precise forecasting and communication in some cases. The most of the recent reports have used employed OBI techniques, such as studies of vision [142], hearing [143], speech [54], learning emotions and pain [144]. It has currently commenced also to be used for prolonged disorder of consciousness (PDOC) [145] instead of the intense brain stimulation in which an electrode is inserted straight inside the brain. So that, for the following

reasons, an enhanced spatial resolution OBI system should be designed:

- ➢ For the visual representation of several different stimulation outcomes from same cortical region.
- ➢ To evaluate action potentials explicitly from neuronal cells to observe real time changes in brain activity through any part along the whole brain volume.
- ➢ To map effectively a wide cortical region with smaller mesh.
- ➢ To illustrate correctly the organization of various functional cell properties.
- ➢ To map the difference between two overlapping targeted regions.
- ➢ To evaluate chronic recordings contribution in the advancement of brain machine interface.

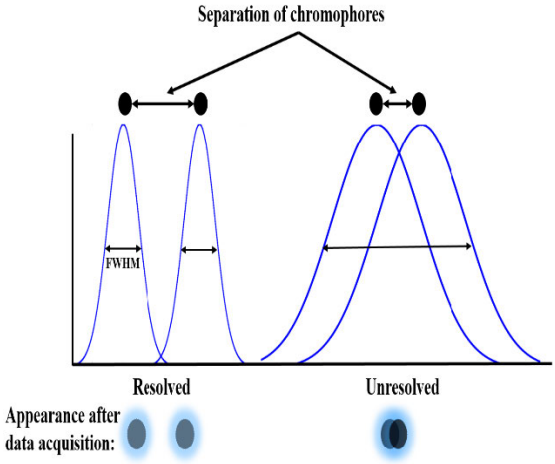

FIGURE 8. The concept of localizing two distinct points in brain with corresponding relation to FWHM.

IV. METHODOLOGIES TO ENHANCE THE SPATIAL RESOLUTION

The improvement (i.e. enhancement of spatial resolution) is a demanding aspect of OBI. Spatial resolution is limited to an extent of a source-detector separation for many OBI devices. As mentioned above, particularly that the spatial resolution is the area in which OBI has generally been lagged fMRI. This section reviews the methodologies that have been presented to enhance the spatial resolution of OBI.

A. HIGH-DENSITY DIFFUSE OPTICAL TOMOGRAPHY

Since, the commencement of the development of OBI, many endeavors have been presented to enhance the spatial resolution and image quality. In this section, we shall provide a comprehensive review about a direction to develop functional brain imaging originating from NIRS measurements. This imaging methodology is generally called diffuse optical imaging (DOI) and by introducing depth sensitivity is renowned as diffuse optical tomography (DOT) [49]. This medical imaging methodology can generally be segmented into two sub-parts: the forward problem and the inverse problem. The forward problem deals with theoretical and physical models of this imaging system while the inverse problem converts the observations into an illustration that shows objects of interest or intrinsic information.

In early days, the limited number of channels only one or two were used, distantly placed, to preclude light interventions [146]. Multichannel fNIRS devices were then evolved with a multiple arrays of source-detector combinations allowing simultaneous scanning through brain regions [147]. Multichannel fNIRS measurements are often processed discreetly and channel wise statistically analyzed within an individual [148] or in a group of individuals [149]. By using spatial interpolation, these fNIRS multi-channel measurements have been incorporated into two dimensional topographical images of brain, spatially presenting functional activation [108], [150]. In addition, NIR light transmission from a source towards a detector can be demonstrated when skull and brain tissues are segmented [118]. Consequently, a definite image is developed to provide precise estimation of depth resolution with the use of short and long source-detector separations measurements [103].

The average scalp and skull total thickness in an adult (man or woman) is generally 10 to 18 mm (approximately 7 mm is for scalp [151] and 6 mm is for skull [152], [153] has been reported). Delpy and Okada demonstrated an attenuation of eighty percent signal strength of NIR light intensity by increasing the width of skull from 4 to 10 mm [72]. Strangman et al., in contrast, concluded that the scalp consistently had more significant influence on fNIRS brain sensitivity than skull [153]. Moreover, they also investigated that how the separation of sources and detectors could resolve this problem and discovered that the increment of the separation above 20 mm can decrease the superficial layers influence and maximal sensitivity of brain activation can be achieved by using approximately 45 mm separation [153]. Hence, the spatial resolution of OBI can be determined to some extent by the sources-detectors density. Recently, technological developments have been enabling optical instruments with widening fields of view (FOVs) and higher sources and detectors densities [132]. These high-density instruments are often referred as high-density diffuse optical tomography (HD-DOT), although they are based on the same fundamental principles of fNIRS. These high-density probe arrangements use overlapping measurements of source-detector grids and enable us to demonstrate multiple informative measurements in each voxel of focused brain volume [110]. This method provides us an improved spatial sampling and a robust strategy of image reconstruction, in result we imaged the brain activation with enhanced spatial resolution and better localization. Some important HD-DOT studies have been summarized in Table 3 by presenting their major contributions and other significant information.

HD-DOT can measure tissue oxygenation at different depths throughout the FOV of the particular imaging array, enabling for superficial signal correlation processes that help

TABLE 3. Studies related to high-density probe configuration.

Reference	Findings	Population	Brain region	Task	Number of sources/detectors	Separation	Number of subjects	Filter used for noise removal	Wavelength
Brian et al. [178]	Demonstrated the high spatial resolution by using HD-DOT.	Healthy	Visual cortex	Phase-encoded paradigm	24/28	13 mm to 30 mm	14 (3 male, 11 female)	Band pass filter (0.02 to 0.5 Hz)	750 nm and 850 nm
Brian et al. [106]	Presented the better spatial resolution and lower positional errors by using HD-DOT.		Visual cortex	Black and white reversing logarithmic checkboard on gray background	24/28	1.3 cm to 3 cm		Band pass filter (0.02 to 0.5 Hz)	750 nm and 850 nm
Christina et al. [179]	Showed that activation for different fingers is projected to different tissue depths.	healthy	Primary somatosensory	Thumb and little finger tapping task of right hand	30/30	3 cm	8 (6 male, 2 female)	Band pass filter (0.016 to 0.4 Hz)	760 nm and 830 nm
Steve et al. [180]	Showed a high contrast-to-noise ratio in neonates by using HD-DOT.	Healthy infants	Visual cortex	Visual counter phase checkboard patterns	18/16		11 (4 male, 7 female)	Band pass filter (0.02 to 0.5 Hz)	750 nm and 850 nm
Adam et al. [132]	Showed higher order distribution brain function maps and compare their results with fMRI.	8 healthy and 3 Parkinson's disease patients	Sensory motor and sematic cortices	Hearing words, covert reading, imagined speaking and covert verb generation	96/92	1.3 cm, 3 cm, 3.9 cm and 4.7 cm	11		750 nm and 850 nm
Bandara et al. [181]	Classify and distinguish between the effectiveness of valence and arousal states and also develop models to predict emotional states across subjects.	Healthy	Valence and arousal states	Listening music videos	17/16	3 cm	20 (13 male, 7 female)	Band pass filter (0.01 to 0.5 Hz)	
Sun et al. [157]	Detected four different regions in mirror neuron system with better spatial resolution.	Healthy	Left hemisphere	Table setting task	20/20	3 cm	30 (15 male, 15 female)	Discrete cosine transform based high pass filter (0.0078 Hz) and low pass filter	780 nm, 805 nm and 830 nm
Jacob et al. [182]	Correctly predict driving difficulty separately for each visuospatial load.	Healthy	Whole head	Car driving	78 channels	3.5 cm	17 male	Low pass filter with cut-off frequency 0.1 Hz	760 nm and 850 nm
Hong et al. [183]	Proposed bundled-optod method and claimed that by using this method one can detect brain activity with better spatial resolution	Healthy	Prefrontal cortex	Mental computation task	256 channels	2 to 5.5 cm	5 male	Low pass filter with cut-off frequency 0.15 Hz	760 nm and 830 nm

to limit the effect of physiological noise [103], [154], [155] (i.e. it has improved the perspective of OBI by achieving dramatically enhanced spatial resolution and limiting the dynamic superficial tissue impact). By combining these developments of HD-DOT with current techniques to data registration [103], [156], [157], could impart an opportunity to effectively enhance actual image quality. However, increasing the FOV of high-density devices to comprise a substantial portion of the brain, faces significant problems in high channel count measurements like fiber-optic-scalp coupling, separate signal detection from multiple sources, imaging array ergonomics, anatomical light modelling algorithms and data quality management. As well as, it has not been cleared yet whether a reconstruction of image by using the spatial sensitivity profile is beneficial in lower density arrangements or not, and whether the arrangements for higher density probes will effectively enhance the spatial resolution if the image is acquired by mapping method. But it is important to note that the optimization of the probe density is a key factor between the image enhancement and instrumentation cost. It should also be noted that having a high-density configuration is a necessary condition for enhanced three dimensional image reconstruction, but not sufficient, because sophisticated reconstruction algorithms are required as well to obtain three dimensional images successfully.

B. IMAGE RECONSTRUCTION ALGORITHMS

The image quality in OBI is affected by the sparse probe arrangement and broadened spatial sensitivity due to scattering of the tissue, and the size and intensity of the activated region in the image depend on the relative position between the activated region and neighboring source-detector pairs. The influence of tissue scattering on the broadening of the image is not considered in the simple mapping algorithm for topographic imaging, whereas the spatial sensitivity profiles for source-detector pairs are used to solve the inverse problem of image reconstruction in DOT. This section reviews the algorithms that have been used to enhance the spatial resolution of OBI.

The forward problem in NIRS is formulated in the form of diffusion equation that is derived/extracted from radiative transport equation [49]. Therefore, this formulation is nonlinear and complex in nature to determine the scattering and absorption coefficients. Several reconstruction methodologies such as numerical methods and back projection algorithms have been presented to solve this problem with a better spatial resolution. These methodologies differ with their nature of complexity, imposed constraints and by computational efficiency. Jacob *et al.* [164] presented a reconstruction algorithm (level-set algorithm [165]) to improve the spatial resolution and imposed an assumption that the

cortical activation areas are concentrated/sparse. Therefore, they formulated this problem mathematically in the form of sparse-inverse problem [166]. Since, the independent activation locations measured through NIRS are lesser than the activated voxels, therefore, the authors imposed certain constraints for example, the activation is smooth over a particular region. Thus, the degree of freedom of the problem is reduced and a two-step iterative scheme is utilized to solve the problem. Their results have been concluded that a significant improvement in the resolution is achieved as compare to existing methodologies such as truncated conjugate gradient and iterative reconstruction methodologies.

Yao *et al.* [167] presented a new quantification method for reduction of noise variance based upon a linear Rytov approximation [168] related to transport of light photons. The results suggest that it is an effective reconstruction approach to improve the spatial resolution with acceptable noise variance. The mathematical derivation indicates that noise variance could be estimated with lesser number of sources in case a small period is provided for the acquisition of base line datasets. Similarly, Lu *et al.* [169] have recently reported a complex but effective L1 norm based nonlinear reconstruction algorithm to improve the spatial resolution of specific type of images imposing the sparse condition, as the proposed method is robust and edges of images are also preserved. They implemented three well established L0, L1, L2 regularization algorithms [166], [170], [171] by mathematically formulating the forward and inverse model. The main advantage of this method is that it automatically selects the required regularization parameters with the expense of increase computational requirements. Some of the studies in past have utilized high-density probe arrangements in addition with reconstruction algorithms that increases the number of sources by reducing imposed constraints for example, White and Culver [106] have utilized high-density probe arrangements in two different scenarios by formulating inverse problem through finite element method [172] and later its solution was obtained through Moore-Penrose inverse [173]. Their results concluded that optimal value of parameter is depending upon a proposed new parameter whose value is constrained with maximal singular value of designed matrix. This work is extension of Boas *et al.* [174] in which they analyze the improvement of spatial resolution with smaller localization error in the case of square and hexagonal high-density probe arrangements.

Another possible aspect to improve the spatial resolution is the estimation of depth localization. Niu *et al.* [175] have presented depth compensation algorithm and showed results that it can effectively improve the depth localization in optical imaging. The authors provided results that such algorithms improve the lateral resolution as well as better depth localization. They imposed a constraint through equilibrium point that equity the depth dependent sensitivity decay. Thus, it is concluded that iterative reconstruction algorithms are very important aspect that could be utilized to improve the spatial resolution, but it is required to reduce the complexity of such algorithms that results in an efficient methodology for such challenging requirements.

C. SPATIAL REGISTRATION

To analyze the brain imaging measurements, generally the procedure is to spatially register subject's brains to a typical co-ordinate system to reduce inter-subject fluctuations, facilitate inter-subject illustration averaging, and enable investigation of limited results well into the form of three dimensional (x, y, z) coordinates [105]. There exist numerous techniques of registering data, like manual versus automated and linear versus nonlinear methodologies. Moreover, various brain spaces or templates are also used for spatial normalization tasks [176], [177]. fNIRS data has so far been acquired from the surface of head without brain structural information. fNIRS, therefore, measures only the activation of the brain, but cannot classify the source of the cortical structural activation [49]. The association between certain scalp location at which fNIRS data is being measured and the underlying cortical surface of the fNIRS signal must be determined to assess fNIRS data spatially. In this section, we will present a methodological overview of spatial registration of fNIRS data.

The International 10/20 system (ITTS) is a significant head surface based registering system for the stereotactic brain mapping methods, such as fNIRS and Transcranial magnetic stimulation (TMS) [184]. As probe placement guidance, the ITTS allows for appropriate region of interest (ROI) coverage as well as spatial accuracy among various subjects and experiments in an MRI-free environment. This procedure is currently supported by two categories of methods. One class is dependent upon MRI techniques, which guides positioning with the subject's own magnetic resonance images [185], [186]. Such techniques provide significant accuracy up to few millimeters resolution [187]. However, MRI instrument is costly and complicated, and not often available in many institutions. Even if available, MRI instrument would deny subject's access with inadequate cardiac pacemakers, and the limited and noisy scanning room may face additional stress on subjects. Ultimately, most fNIRS and many TMS studies are carried out without MRI measurements in experiment. Therefore in this situation, optode placement is generally adopted as an MRI-free probe positioning method based on the ITTS [105], [187].

The ITTS is a corresponding landmark scheme for head surface, consists of four particular reference points at the top of the head and the landmark points identified at certain comparative distances from these reference points [188]. Cadaver [188], CT [189], and MRI [190] studies have discovered that each ITTS landmark on the head surface associates to a particular cortical area and can be generalized among different subjects by using cranio-cerebral correlation [190]. Accordingly, after exactly identifying the ITTS landmarks on the head surface, expected cortical locations can be accessed by means of optodes that are accurately set to the ITTS landmarks [191], [192]. The ITTS comprises of 21 points

(including the Fpz and Oz) to cover whole head surface. This ITTS defines scalp positions which have corresponding distances among cranial landmarks with nasion (Nz), inion (Iz), left pre-auricular and right pre-auricular points (RA, LA) being primary landmarks (figure 9). Also, the ITTS then registers landmarks along the head surface systematically at 10 percent and 20 percent pitches. This system assumes that scalp positions and their corresponding internal cerebral structures have a consistent association. Multiple studies have identified this structural association using fNIRS [184], [191], [193]–[195].

Moreover, this extensively used technique also faces some issues in terms of reliability and initial time cost, largely due to the manual landmark evaluation procedure on the surface of head [196]. So that, kind of a laborious and error-susceptible procedure (making manual landmark measurements on the subject's head), makes it very difficult for the researcher to maintain a high accuracy. However, a semi-automatic method to deal with these problems has also been reported recently in order to place optodes quickly and reliably on the head surface of the subject [184]. They have been validated their proposed scheme by simulation experiments and then also by a real experiment to access the reliability and time cost of their methodology. In order to monitor the focused cortical volume, Machado *et al.* [197] introduced an alternative technique for determining the proper set of optodes locations by an EEG-fNIRS cap. They evolved this so-called proper setup methodology to ensure the highest sensitivity to certain targeted cortical volumes of interest in kind of clinical fNIRS experiments to target patients' particular area of interest. Yücel et al. argued that an enhanced quality of optical signal measurements and minimization of motion artifacts can be attained by the use of a water resistant glue (e.g. collodion) to register optodes on the head surface [198]. Such methodologies are particularly helpful when extended multi-hours acquisitions for clinical applications are required. Many other research groups have also been working to enhance the spatial resolution by registering the optodes on the head surface with the help of ITTS. Their studies validate that to achieve accurate measurements with high spatial resolution usually requires the use of high-density probe arrangements, allowing overlapping measurements and uniform spatial registration [105], [106], [199]–[201].

D. FAST OPTICAL IMAGING

Recent theory about brain functioning emphasized the significance of fast (within approximately 100 ms) interactions among multiple components of diverse neuronal networks. Fast optical imaging (FOI), and especially the event-related optical signal (EROS), an innovation that has been appeared within the last fifteen years, may provide interpretations of localized (up to sub-cm resolution) brain activity with high temporal resolution of approximately 100 ms [202]–[204]. Fast optical signals pertain to fluctuations in optical scattering that happen in brain tissue by comparing the conditions that tissue is active or not. Firstly, they were identified in isolated nerves in the 1940s [205] and subsequently presented in hippocampal [206]–[208] and brainstem slices [209], as well as important brain processes in both invertebrates [210],[211] and vertebrates [212]. Because, the entrance is blocked by tetrodotoxin, it indicates that closing and opening of ion channels are important for its appearance [213]. The study [214] indicates that the physiological principle of the phenomenon is shrinking [209] or swelling [213] of dendrites due to the flow of water through the membrane associated with transport of ions [213].

Though, the measurement of optical fluctuations in the invasive cortex have been recorded from several decades with high spatial resolution [215], [216], but measurements for non-invasive cortex faces so many other challenges that obviously limit the feasible spatial resolution. The scattering and absorption of NIR light incident on scalp through source, is due to the biological properties of scalp and other brain tissues. Light absorption has been occurred mostly because of the hemoglobin flowing in the blood and it can be reduced by using far-red or near-infrared (NIR) light spectrum [217]–[219]. In both ranges of these wavelengths, the main limitation to specific brain imaging is because of scattering, which mostly happens due to membranes, mitochondria, and other vesicles observed in the tissue [218], [220]. Accordingly, the research reported in the last few years provides a solid support for the concept that fast optical signals can be measured from surface detection, allowing a method for investigating swift changes in normal brain activity [221]. The spatial and temporal resolutions of FOI are partially dependent on the techniques employed in the study. However, in the most published fMRI research in behavioral neuroscience, it has been reported that when phase and high spatial measurements are employed, spatial resolution can be obtained up to 1–5 mm [222]–[224]. As well as, the temporal resolution happens approximately comparable to that acquired from EEG, but again depends upon the sampling rate.

As compared to other methodologies of brain imaging, FOI has several merits and some demerits as well. The major constraints include the limited penetration depth (a few centimeters through the head surface) and low signal to noise ratio (SNR) that makes it more essential to accrue measurements through the number of trials [225]. The main advantages include low costs and comparative portability (in comparison to MRI, PET and MEG) and efficiency of simultaneous scanning with other modalities. In addition, FOI has been reported simultaneously with fMRI [226] and in TMS [227] with no evidence of errors in either area. This is probably a major advantage as FOI may render an ideal foundation technology for brain imaging data fusion [228]. With the help of this methodology, multiple researchers [204], [225], [229]–[231] have shown that fast optical signals can be measured consistently with combined high spatial and temporal resolution. However, some research groups have also been questioned these possibilities [232], [233].

E. MULTI DIRECTIONAL SOURCE AND DETECTORS

In traditional diffuse optical method, multiple source and detector probes are positioned on the head surface as discussed in the previous sections, and then from the measured light values functional image is reconstructed by using an optimal image reconstruction algorithm. However, high-density probe arrangements increase the experimental workload as compared to conventional fNIRS studies as well as the cost of experimental setup. To address these issues, Shimokawa et al. presented a multi directional monitoring system by using multi-directional sources and detectors [116]. This methodology increased the amount of measured data drastically without increasing the number of optodes by using different optical pathways generated in multi-directional measurements [234]. Moreover, it does not increase the experimental workload and the effective cost of the instrument. They utilized hierarchal Bayesian algorithm [235] to evaluate the system which is based on inverse problem mechanism by a phantom experiment. They used a light source with only single wavelength. They displayed the results from the fNIRS measurements and exhibited their comparison with t_{value} maps acquired from fMRI. Compared to the generally used minimum-norm depth compensation and repeating the iterations 10,000 times, the algorithm attained smaller false positives and enhanced spatial resolution.

Recently, they extended their work and developed a two-wavelength system, applied at humans and evaluated it as a human field study [236]. They received the NIR light from all four directions of the source which increased the amount of observed data 16 times in comparison with a conventional single-directional fNIRS system. In order to test the system, the left somatomotor brain region of a subject has been measured throughout a right-hand gripping task, and the detected multi-directional fNIRS measurements have been compared to fMRI measurements of the same subject and task. However, they only evaluated one subject with shaved head to initially test the efficiency of the multi-directional fNIRS system. Therefore, in order to assess its efficiency in human brain imaging, some more experiments with multiple subjects are necessary to check, that up to a certain extent the multidirectional fNIRS data is advantageous in functional image reconstruction. In addition, their presented optode size is big enough to be radiation hardened for practical use, particularly for hairy subjects. However in future, if the size of these multi-directional fNIRS optodes will resemble the conventional fNIRS optodes, it will be able to experiment with hairy subjects as well.

V. PHANTOM STUDIES

The spatial resolution of biomedical image is one that is comparable with a reference-image that defines and targets the detail inside what is required? Since, there is absolutely no reference-image available that defines the stage of spatial resolution, so therefore, it is a bottleneck and challenging task

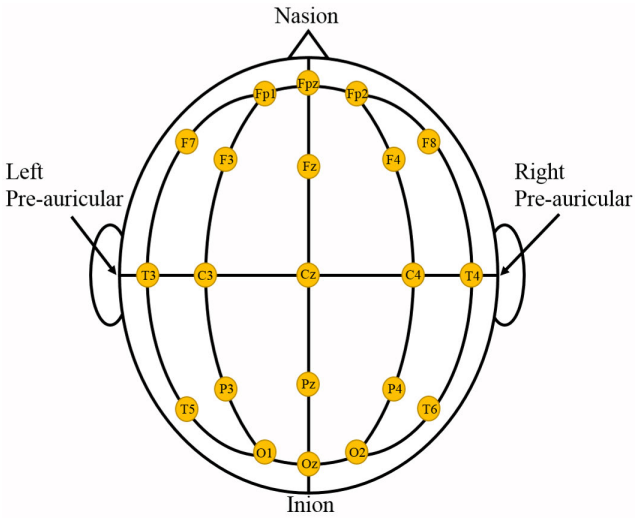

FIGURE 9. International 10-20 system configuration for cortical imaging.

to determine the quality of resolution in an image obtained from processing of optical data. Usually, the quality of resolution is assessed by visual inspection. In some cases, medical doctor's advice regarding quality of image obtained through specific methodology is consider to be beneficial. However, such evaluation of resolution performance cannot be a standard to support or reject specific method. On the same time, researchers still have not developed a standard procedure that evaluates the resolution level of a biomedical image. One solution to this problem is to validate and compare results based upon predesigned phantom. This section presents the review of some existing studies from literature that shows the advantage of using different phantoms to measure the spatial resolution enhancement of reconstructed image.

Phantoms are normally used for two major reasons, one is the scientific proof of presented method and second is to validate experimental results. But on the same time, this proof and validity cannot be used for a claim of enhanced spatial resolution when specific methodology applied on real subject. Yamamoto *et al.* [244] revealed that the arrangement of optical fiber is not a source that enhance the spatial resolution of resultant image. Additionally, numerical/iterative mapping algorithms are not the effective solutions those enhance the spatial resolution of topographic image because they do not utilize the whole volume that has been covered through a source-detector pair. Several studies in past have presented certain results regarding the sensitivity profile for source-detector configuration to determine the solution of inverse problem in DOT [245], [246]. Kawaguchi *et al.* [246], [247] determine a unidimensional statistical profile of variation of absorption in a predesign head model that determine the errors of estimation in localization and the dimensions of topographic images obtained through reconstruction algorithms and mapping methodologies. Their results revealed that the sensitivity profile has a strong relation to enhance the spatial resolution of multi-dimensional topographic image.

TABLE 4. Findings of simultaneous fNIRS-fMRI studies.

Reference	Findings	Population	Task	Brain region	Number of subjects	Wavelengths used in fNIRS
Bainbridge et al. [237]	Spatial correlation between P_{ratios} and [O_xCCO].	Diseased	Anesthetized	Whole brain	24 Piglets	650 nm and 780 nm
Benaron et al. [238]	Determination of spatial agreement to activation maps.	Healthy	Finger tapping	Motor cortex	3 male	780 nm
Cannestra et al. [239]	Spatial co-localization results from similar physiological events.	Patients	Awaked	Sensorimotor cortex	8	610 nm
Murata et al. [240]	Comparison of de-oxy hemoglobin concentration changes.	6 healthy and 6 Patients	Hand grasping	Motor cortex	12	NA
Yamamoto et al. [241]	Precise theoretical insight of hemodynamic activation.	Healthy	Multiple word repetition task	Left inferior frontal and left superior temporal gyrus	1 female	780 nm and 840 nm
Deng et al. [242]	Compared results of measured activity and achieved accuracy of 0.9.	Healthy	NA	Whole head	1 mouse	650 nm and 950 nm
Hyun et al.	Compared individual brain activity and acquired clear lateralization.	Healthy	Hand grasping	Motor cortex	2	NA
Tronov et al.	Comparison of BOLD and deoxy hemoglobin concentration changes.	Healthy	Block-designed visual task	Visual cortex	9 (7 male and 2 female)	690 nm and 830 nm
Bulgarelli et al. [156]	Showed high reliability by applying to infant.	Healthy	Sleep	right hemisphere	1	770 nm and 850 nm
Yuan et al. [243]	Generate full spatio-temporal snapshots and movies.	NA	Finger tapping	Whole brain	NA	781 nm and 856 nm

In another study, Cao *et al.* [248] proposed the constraining of sparseness of the light abnormality using L1-norm-regularization and an iterative solution is found through expectation maximization. Actually, the main purpose of expectation maximization algorithm was to estimate the unknown data inside the mesh of a volume whose some locations are known. They validate their results on 3-D simulated phantom by constraining the scattering coefficient to be known and constant. Thus, the only thing required is the estimation of absorption parameter. The authors showed that this methodology results with enhanced spatial resolution as compare to existing regularization methodologies. Kavuri *et al.* [170] analyze the multidimensional approach that is a combination of depth-compensation-algorithm [249] and regularization methodology based upon L1-norm [248]. The authors validated their results through a fiber based multi-channel phantom. Additionally, they also presented results of human subjects related to motor task. Shimokawa *et al.* [250] proposed a tri-dimensional reconstruction methodology with defining the spatial variant regularization and sparsity. They utilized a phantom with fNIRS system to present their results. They design their phantom by putting single or multi absorbers to evaluate the depth accuracy and spatial resolution in case of their presented methodology. They presented results that the depth of absorber could be determined accurately by their method and specific high-density configuration. It is also revealed that two distinct absorbers could be accurately localized if their distance is smaller than the distance between the probes.

Baikejiang *et al.* [251] evaluated the reconstruction algorithm based upon kernel approach. A very attractive property of such approaches, as compare to conventional methodologies, is that these algorithms are not based upon region segmentation. Instead of using single pixel intensities as done in regularization methods they utilized neighboring voxel values those enhance the 3-D information for resultant image. The authors validated their results based upon Agar-phantom. Their results revealed that spatial resolution significantly improved by using kernel methodology. Similarly, several other researchers are frequently using predesigned phantoms to validate their results, for example [252]–[255].

VI. SIMULTANEOUS fNIRS- fMRI STUDIES

The development in biomedical imaging modalities have shown that different modalities have different pros and cons. The fusion of two or more imaging modalities is very interesting, so that, the positive aspects of each modality utilized to receive an enhanced and more informative image. Therefore, several research groups in past have used the concept of multi-modality imaging [256]–[258]. In the context of this article, the first study [259] discussing the enhancement of spatial resolution based upon two imaging modalities which were different in technology but measuring hemodynamic response. It is well known fact that fMRI instrument have come up at a favorable position with much more spatial resolution [260]. On the same time, significant progress have been made in the domain of OBI during past decade. If we generally overview fNIRS, the major limitation is the low

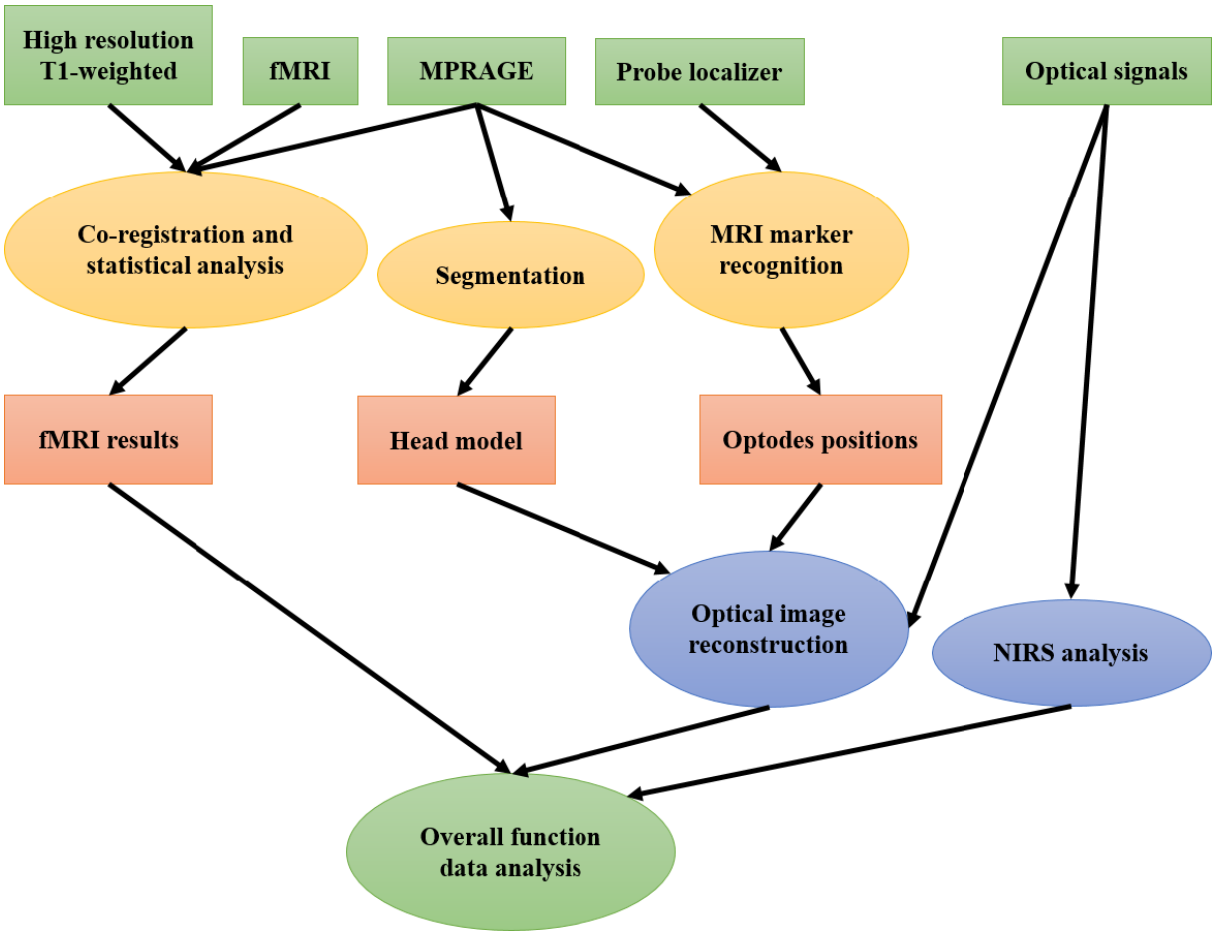

FIGURE 10. A flow chart of the data acquisition and processing procedures used for simultaneous fNIRS-fMRI.

penetration depth, that is assume to be two to three centimeters [49]. In addition, the poor spatial resolution of hemodynamic variation due to longer photon travelling path in highly scattering medium [45]. Therefore, some of researchers concluded that concurrent studies of fMRI and fNIRS could resolve this problem. In past, several research groups have published their work by examining animals under concurrent fNIRS-fMRI data measurements [243], [261], [262]. And in recent past, some research groups have developed the simultaneous fNIRS-fMRI setup [242], [263], [264] and shown their results. An important aspect of such studies is that the integrated instrument design imposes certain constraints for optical probes [265]. In addition, the accuracy of placement of optical sources/detectors and RF pulse results the reproducibility of measured data. In the light of the issues discussed above this section is added to present a general overview of simultaneous fNIRS-fMRI studies. Some of fNIRS-fMRI studies have been summarized in Table 4 by presenting their major contributions and other significant information. The overall data acquisition and processing structure used in human studies are also summarized in figure 10.

VII. CONCLUSION AND DIRECTIONS FOR FUTURE RESEARCH

This paper is novel in the sense that it addresses first time, different issues related to spatial resolution of OBI and its existing proposed solutions and their limitations and shortcomings. For the said reasons, basic principle and instrumentations and their different types with benefits and limitations have been summarized (probably for new researchers). Later, the actual problem of spatial resolution is formulated and comprehensively summarized followed by its comparison with a better spatial resolution instrument (fMRI). The major contribution of this article is the summarization of different existing methodologies to improve the spatial resolution of OBI with scientific data available at WOK.

Noninvasive OBI has positioned itself at a favorable position among other biomedical imaging instruments due to its low cost, portability and ease of use. But on the same time, it encounters some limitations and unresolved issues that need to be addressed to extract useful information from OBI data with more detail. One such limitation is low spatial resolution of optical imaging devices specifically designed for brain images. To achieve this, the fundamental bottleneck is low

penetration of NIR light through deep tissues. Another such bottleneck is the unknown path of NIR light photon travelling between source and detector. These two major issues need to be addressed and resolved for better spatial resolution and detailed informative images.

The authors believe that a possible solution for this challenging task is to position sources/detectors with high-density probe arrangements to get overlapping measurements. Thus, if a configuration is designed in such a way that multiple sources are placed at a particular area then multiple channels produce datasets from each of these sources and detectors. However, the minimum possible distance between two sources has been limited by the mechanical limitations of optodes. In author's opinion, nanoantennas can play a very important role to solve this problem. Because, nanoantennas has played a very important role in different fields of science and engineering with current advancements and availability of nanoscale designs. So that, optical nanoantennas composed of certain metamaterials could be a possible solution to arrange and guide NIR light at different places less than millimeter distance apart (up to nanoscale distance). At nanoscale level there is still a limitation of the availability of CCD array that can detect NIR light photon having resolution of nanoscale distance (up to micrometer resolution are available). But authors believe that utilization of the array of optical antennas to through NIR light at submillimeter scale would be advantageous for better spatial resolution and enhanced images of cortical functionalities by getting overlapping NIR light paths in brain. In addition, these arrangements would result in increased FOV as well at the cost of high computational requirement and hardware. But the future of nanotechnology would solve this problem as well.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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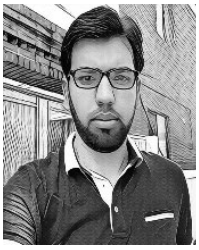

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