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Non-Invasive Functional Optical Brain Imaging Methods: A Review

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ABSTRACT

Optical Brain Imaging is basically an imaging technique which uses light for understanding structures of our brain for various medical applications. Optical brain imaging methods within the last few years have showed tremendous revolutionary development. The current review is mainly focused on principles of novel brain imaging techniques. The methods included in this review are Intrinsic optical imaging, Diffuse Optical Tomography, Photoacoustic Microscopy, Diffuse Optical Tomography, Terahertz radiation, Near infrared microscopy, Voltage-sensitive dyes imaging, Ca^{2+} and other ion sensitive dye Imaging, Auto fluorescence and Metabolic related optical imaging and Optical coherence tomography. Some of these methods find their applications in clinical research and others in experimental neuroscience.

Keywords: Brain imaging, Intrinsic optical imaging, Diffuse optical tomography, Photoacoustic microscopy, Optical coherence tomography, Near infrared microscopy, Terahertz radiation, Voltage-sensitive dyes imaging, Ca^{2+} and other ion sensitive dye Imaging, Auto fluorescence, Metabolic related optical imaging

INTRODUCTION

In the history of neuroimaging or optical brain imaging, an Italian neuroscientist, Angelo Mosso is the pioneer who discovered the 'human circulation balance'. It is a non-invasive method which measures the circulation of blood during emotional state and intellectual activity of the brain. [1,2] Techniques in brain imaging have been flourishing over the many years. In the end of the last century, Camillo Golgi and Santiago Ramón y Cajal pioneered the work of neuronal tracing using light microscopy. [3,4] The brain consists of neurons, neuroglia, microglia and vascular tissues.[5] With Intensive development of optical imaging within last few decades, scientists were able to analyze the anatomical, physiological and pathological condition of brain more accurately. They discovered the processes of emotion, sleep, cognition, diseases of nervous system, such as autism, depression, Parkinson's disease, and Alzheimer's. The above conditions are analyzed using optical imaging method, i.e. by simulating the functional changes in neural tissue by light absorption and scattering. Different wavelengths are used to observe anatomical and physiological functional changes in the brain trans-cranially in closed and in the open brain. Therefore, Optical brain imaging has proven to be one of most powerful and efficient technique to carve a path for neuroscience.[6]

In the current review, the basic principles of each method are described. The novel approaches of brain optical imaging presented in this paper are Intrinsic optical imaging (IOS), Diffuse Optical Tomography (DOT), Photoacoustic Microscopy (fPAM), Optical coherence tomography (OCT), Near infrared microscopy (NIRS), Terahertz Radiation

Brain Imaging, Voltage-Sensitive Dyes (VSD) Imaging, Metabolic Related Optical Imaging, Ca^{2+} and other Ion Sensitive Dye Imaging and Auto fluorescence. These imaging methods are successfully used by various scientists for research and clinicians for disease diagnosis and treatment all around the world.

1. Intrinsic Optical Imaging (IOS) Method

The intrinsic optical (IOS) imaging technique is used to determine changes in blood flow, metabolism, and cellular swelling associated with the neuronal activity. It is an oldest and efficient optical Imaging (IOS) method for functional mapping of the brain.[7,8] The sources for IOS are based on the physical properties of the tissue which affect changes in light absorption and scattering as well as, to a lesser degree, auto fluorescence and its changes associated with neuronal activity of brain.[7] This method is based on the optical changes in the features of brain tissue, which permits visualization of activity patterns with a spatial resolution higher than ten microns. The Intrinsic Optical Imaging (IOS) depends on the illumination wavelength. The first component of the IOS depends on mainly local oxygen saturation levels, which is an activity-dependent biological process. However, this component consists of two stages. In the first stage: there is increase in deoxyhemoglobin concentration in the cerebral blood due to high metabolic activity in activated area in which the cells need high oxygen consumption.[7,9] In the second stage: As the vasodilatation of local capillaries increases cerebral blood-flow (CBF), there is an increase in local oxyhemoglobin concentration. The blood flow-related components are observed at all parts of light spectrum with different intensities.[10]

Another IOS component, which is weaker and less studied than the other, originates from the changes in light scattering accompanied by neural and astrocyte activity. These optical changes are probably caused by the movement of small molecules and ions (including protons and dissociated water molecules) through the cell membrane.[11]

One of the main advantages of IOS is that it can be realized without any extrinsic chemical probes. In human research, IOS can be applied only during neurosurgery relatively for a short period of time. During the surgery, surgeon can keep a verbal contact with the patient and apply IOS for speech and cognitive research. With regards to the practical aspects of IOS experiment, the animal is anesthetized, scalp is removed from the area of interest and the area above the skull is thinned and flattened. By this way, the scientists can record different cortical surface functional areas. This is a well-known fact from the Ramón y Cajal period.[12]

In sensory cortex areas of the brain, IOS technique is used to obtain information on visual cortex.[13] For functional brain mapping, intrinsic optical recording can be applied as efficient method of analysis.[14] The analysis of recorded optical signal data includes filtering of a particular range of spatial frequencies.[15] In the animal experimental studies conducted by Anita *et al*, 2017, they recorded the evoked optical and electrical responses of the visual cortex by combining the use of intrinsic optical signal imaging (IOS) with micro-electrocorticography (μECoG).[16]

2. Photoacoustic Imaging Method

Photoacoustic microscopy (PAM) is a popular microscopic imaging technique based on photoacoustic effect. It is used to obtain optical absorption information in biological samples. It includes photo acoustic microscopy (PAM) and photo acoustic tomography (PAT).[17] The principle of operation of this method is based on the conversion of photon's energy into acoustic waves due to light's absorption and thermal excitation.[18]

In Photoacoustic microscopy, due to rapid rise in temperature and thermo-elastic

expansion/relaxation process of the tissue, a broad range of ultrasonic wave is produced when the sample is illuminated by a pulsed laser of few nanoseconds of pulse width.[19] The photoacoustic (PA) waves are detected by an ultrasound transducer, and as a result, an optical absorption-based PA image is built.[20] The magnitude of the ultrasonic waves is proportional to the light absorption by the tissue due to which the local anatomical and physiological changes in the tissue can be observed.[21]

The photoacoustic imaging depth is limited by light penetration and scattering, while the spatial resolution might be determined by ether optical focusing depth into tissue. The spatial resolution strongly relies upon imaging depth (as high as 1µm), whereas temporal resolution entirely depends on the substrate volume, spatial resolution, and technical characteristics of the imaging system.[22] Optical Resolution Microscopy can be used to photograph the brain surface of the mouse by using a microelectrode and recording the sequence for electrical stimulation. Optical-resolution photoacoustic microscope and photoacoustic images of the mouse cortical microvasculature are acquired at the wavelength of 570 nm lasers when a tungsten microelectrode is introduced into the cortical tissue.[18] To analyze the cerebrovascular responses, electrical stimulations are applied to the brain and those responses are observed in the form of vasoconstriction and vasodilatation of blood vessels in imaging.[18]

In vivo, Photoacoustic brain imaging is based on the local oxygenation levels and cerebral blood flow of the particular area of the brain. The Endogenous pigments (oxy and de-oxyhemoglobin) have a high sensitivity to optical absorption.[21] Arash *et al*, (2019) integrated different contrast mechanisms such as photoacoustic microscopy (PAM), optical Doppler tomography (ODT), optical coherence tomography (OCT), and confocal fluorescence microscopy together to achieve a system that is capable of imaging structural, functional and molecular information of living tissues for experimental, preclinical, and clinical research purposes.[23]

3. Diffuse Optical Tomography (DOT) Method

Diffuse optical tomography (DOT) is a high contrast imaging technique where an infrared (NIR) light of range 650 - 930nm is injected into tissue boundaries at various locations. Then, the light leaving the tissue is measured by optical fibers which are in contact with the tissue. [24,25] It is a low cost, non-invasive and non-ionizing technology. This tomography method is useful to record neural activity, visualization and spatial resolution up to several millimeters. The principle of operation is based on the measurement of absorption photons and scattering, related to physiological function of the brain tissue. The DOT technique demonstrates rising hemodynamic response by recording blood-oxygen level dependent signals. To record these signals, infrared emitters and detectors are positioned on the head surface. They also depend upon the average path length of photons from emitter to detector. Each detector can receive light from several emitters.[26] This process enables the formation of 3D images of the brain, detected by fiber array geometry. The multispectral DOT imaging system, the non-contact scanning illumination and a clinical prototype system developed by Daniel L *et al*, (2018).[27]

A key feature of this method is that it can be performed on a freely moving object. Therefore, the optical data gives information about physiological activity of the brain tissue in a particular area. Both clinical and experimental use of DOT has increased in the last few years. Moreover, this method has important advantages over conventional fMRI notably in terms of cost and portability.[28]

4. Terahertz Radiation Brain Imaging (T-Ray) Method

Terahertz Radiation Brain Imaging (T-Ray) is a new generation brain tissue imaging technique. It uses wavelength range between the microwave and the far-infrared region (~10 μm to ~3000 μm). The non-ionizing, noninvasive nature of the radiation and its relative transparency to most of materials except metals is well suited to analyze biological structures naturally. Electromagnetic rays (terahertz radiation) of frequency around 0.3 to 3 THz which is in between infrared and microwave range in the electromagnetic spectrum are used for this type of brain imaging. This imaging provides spatial resolution of hundreds of micrometers and information about the molecular activity in living tissue. One of the best characteristic features of T-Ray is that the T-photons are nonionizing, interact with the molecules of the absorptive substance, the T-ray can penetrate into a living tissue up to few millimeters and can detect differences in water and ion concentration.[29, 30, 31] Imaging setup of a near field, single pixel Terahertz imaging. An 800nm pump pulse is shone to photoexcite a semiconductor wafer (Highly resistive silicon wafer). The next THz pulse is then allowed to pass through an object onto a single pixel detector.[32]

This type of imaging is well suited for brain imaging. Through this method, we can obtain clear images of anatomical brain structures. The high ionized water content and proteins in the brain are responsible for signal intensities in THz images. It is most accepted technique of the neuroscience.[33]

5. Near Infrared Spectroscopy (NIRS) Method

Near Infrared Spectroscopy (NIRS) Method is an alternative method to fMRI method. It is inexpensive, portable, fast and non-invasive method for assessment of brain function with few limitations.[34] The infrared light ranging from 800 nm to 2500 nm can penetrate the skin, muscle, and bone more effectively.[35] The Near Infrared Spectroscopy (NIRS) without sophisticated hardware, signal processing methods significantly offer low spatial resolution, because of the diffuse nature of light propagation in tissue. fNIRS devices detect changes in concentration in oxygenated and deoxygenated hemoglobin molecules in blood. The light absorptions by Endogenous pigments, oxy and de-oxy hemoglobin depends on hemoglobin levels of the blood. fNIRS is also an "indirect" neuroimaging process similar to fMRI, which can sense the hemodynamic responses to neural activations coupled to vascular processes which is popularly known as neurovascular coupling. Thus, NIRS can provide valuable information about local metabolic activity in the brain.[36] In neuronal oxygen metabolism, oxygen is used up to produce energy which reduces the concentration of oxyHb and increases the deoxyHb concentrations. Then, Neurovascular coupling is induced by changes in cerebral hemodynamics triggered by neural activity. Since oxygen supply is greater than its usage, there are higher concentrations of oxyHb and less concentration of deoxyHb in in activated brain regions.[37]

Currently, NIRS is currently the only method of portable neuroimaging, which is especially important for the neural study of higher cortical functions such as cognition and language.[38] Because of the above-mentioned properties, fNIRS has a numerous application including studies of pain,[39] emotion,[40] learning,[41] speech,[42] hearing,[43] and vision.[44]

It is very important to note that this method is also suitable for obtaining fast optical signals that are known as Event-Related Optical Signals (EROS). This signal is strong enough to optically measure vascular activity as well as neuronal activity noninvasively in animals and humans.[45] The fast light scattering changes are caused by cell swelling and conformational changes. There is a different hypothesis about the origins of these optical signals, thus some researchers were unable to detect fast optical signals transcranial in humans.[46] But technical progress in the

light delivery system and light detectors are aiming to improve the situation.

6. Voltage-Sensitive Dyes (VSD) Imaging Method

Optical imaging with the use of voltage-sensitive dyes (VSD) appears to be one of the best tools in neuro imaging. In vivo, Voltage-sensitive dye (VSD) imaging facilitates to measure cortical spatiotemporal dynamics with a temporal resolution of a millisecond and a spatial resolution nearly 100-μm. Thus, VSD imaging seems to be beneficial for neocortex imaging including the spatiotemporal dynamics and electrical activity. [47,48]

In this imaging technique, dye molecules bind to the membrane and changes in membrane potential is converted into the energy of the emitted photons. These signals are indications of both hyperpolarization and depolarization. Therefore, it allows to measure this potential without using any of the electrode techniques. The VSD works on the principle of electrochromism i.e. after photon's absorption, the molecule undergoes a charge change from the initial level to the excited level, and fluorescence occurs due the emission of a photon during the inverse process from the excited level back to the initial.[49]

In in vivo cerebral cortex imaging, the VSD signal is associated with the stained membrane area. Therefore, the optic signal originates from dendrites and axons. The neural body generates only a minor part of the signal. Dendrites of neurons in a certain cortical structure might cross relatively big cortical areas. So, the fact that VSD signal is mainly a dendritic signal definitely affects the spatial resolution. A minimal recording speed of hundreds of frames per second is required to resolve the time course of physiologically important voltage changes. Many modern CCD cameras or complementary metal-oxide-semiconductor (CMOS) detectors are acceptable for such recording. The detector must be able to not only allow for fast imaging, but it also must have low noise and be able to accept a large number of photons, because induced voltage amplitude variation is typically less than one percent. The combination of high sensitivity, high spatial and temporal resolution remains a critical task for creation of new photosensitive devices that are suitable for VSD imaging. VSD provides direct measurements of neuronal activity and is typically combined with a fluorescence microscope to record neuronal activity at the single cell.[50]

The dye optical images of somatosensory cortex showing single-whisker simulation fluorescence changes, the time after stimulus onset (ms) is shown at the left bottom of each image. RH1691. Is the voltage-sensitive dye molecule used and Excitation and emission spectrum of Channelrhodopsin-2 of the dye and optical control of excitable cells.[51]

Genetically encoded voltage-sensitive proteins can be used for in vivo epifluorescence experiments. Work over the last couple of decades has yielded an array of established voltage-sensitive imaging methods for optical recording of electrical activity by using voltage-sensitive dyes and genetically modified neurons.[51] The use of these methods provides answers for many fundamental questions that were previously intractable using other neuroscience methods. Many auditory research scientists used VSD in auditory functional topography to study the auditory cortex and thalamus.[52]

7. In Vivo Ca^{2+} and Ion Sensitive Dye Imaging Method

Ca^{2+}-sensitive dye is one of the most powerful imaging methods. The main principle of this method is based on the changes in intracellular calcium (Ca^{2+}) concentration and the ion optic signal detected by Ca^{2+}-sensitive probes. The Ca^{2+}-sensitive dye molecules penetrate through cell membrane into the cells. In contrast with VSD, the Ca^{2+} sensitive dye reflects changes in the calcium concentration in the

intracellular spaces. The signal reaches about half of its maximum strength at an intracellular calcium concentration of approximately 0.2 μM.[53]

The fluorescent Ion chloride-sensitive intracellular dye method reflects changes in intracellular Cl^- and recoded by epi fluorescence or ultraviolet laser scanning.[54] Finally, in vitro, this fluorescence indicator opens new ways for probing the neural network.[55] Figure 7 shows calcium signals from each neuron correlated with inspiration in an embryonic mouse brainstem spinal cord preparation.[56] Fluorescence obtained by Ca^{2+} sensitive probes is strong, but dye penetration into the cells is very problematic, therefore the application of this method for in vivo imaging is limited.

8. Autofluorescence Method

It is a powerful method for investigating the neural activity. the Flavoprotein autofluorescence imaging techniques are useful for *in vivo* and *in vitro* investigation of neuroenergetics and functional mapping patterns of neuronal activity. The potential for diagnosis of autofluorescence depends upon capability to probe alterations in tissue structure and metabolism.[57] When a tissue is irradiated by a specific wavelength of light foe excitation, fluorophore molecules absorb photons and emit lower energy photons in the tissue which are detected as fluorescence from the mucosal surface. The dominant fluorophores are responsible for autofluorescence signals. They consist of reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD) in the epithelium along with the collagen matrix and elastin in the stroma.[58]

The flavoproteins and peptides are a part of mitochondrial electron transport chain system. The endogenous signals from auto fluorescence flavoproteins are used to detect aerobic energy metabolism. This method is called flavoprotein autofluorescence method. Peptides, flavoproteins contain flavin adenine mononucleotide or dinucleotide which is involved in a many biological processes. The flavor proteins are commonly used to detect neuronal activity and mitochondrial metabolism coupling strategy. [57,59]

Latest, experiments with FAS optical imaging gave a strong support and evidence to the hypothesis of astrocyte–neuron lactate shuttle (ANLSH).[60] The FAS was successfully used for the monitoring direct cortical stimulation, brain metabolism during hypoxia and spreading depression. It is compelling method for neuroenergetics and functional mapping patterns of neuronal activity.[61]

9. Metabolic- Optical Imaging Method

Metabolic- Optical Imaging Method is the most advanced optical imaging methods for brain imaging. Metabolic optical imaging is a noninvasive method and is gaining increased importance in the research and clinical management of various diseases in oncology, cardiology, and neurology. Due to indication of metabolic changes in a large spectrum of tissue function, evaluation of metabolic process is vital in leading a healthy life.[62] In this process, imaging plays an important role in analyzing biochemical and physiological processes. Positron emission tomography, one of the well-known Nuclear imaging method is limited by the use of ionizing radiation and possibility of single parameter sensing at every scan. Despite these disadvantages, these nuclear imaging methods are widely applied for imaging metabolism. [63,64,65]

In this technique, biomolecules are labelled with positron-emitting isotope for imaging. In positron emission tomography (PET), the Fluorine-18 is widely used to radiolabel the biomolecule because of its property of emitting positrons and a suitable half-life (109.8 min). Further, Isotopic 2-Deooxyglucose (14C) and 2-deoxy-2-18F-fluoro-β-D-glucose (18F-FDG) are the most commonly used biologically active molecules for PET which are used to measure radioactive signals. The radiolabel

biomolecule concentration demonstrates the metabolism of tissues in terms of regional glucose metabolism.[66,67].

Fluorescent glucose analogs such as 2-Deooxyglucose (14C) or Fluorodeoxyglucose (18F) are injected into the blood stream that can be taken up by the cells. They cannot be further metabolized as 2′-hydroxyl group which is needed for glucose metabolism is absent. 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino)-2-deoxyglucose (2-NBDG), a fluorescent glucose substitute can be used in vitro as well as in vivo for visualization of neural activity.[64,65] In experimental and clinical practice, a radioactive beam confines the usage of the radioactive labeled 2-DG analog. However, Contrary to isotopic labeled glucose analog, 2-NBDG resolves the limitation by giving an optical fluorescence signal of the high metabolic activity in the cortical tissue of the brain.[66]

Better image results were observed when fluorescent glucose substitute methods are used in combination with diffuse optical tomography (DOT) and photo acoustic tomography (PAT). In vivo, recent scientific experiments revealed that the glucose intake can be observed by PAT using 2-NBDG brain imaging experiments. PAT can separate metabolic and local hemodynamic responses.[65]

10. Optical Coherence Tomography (OCT) Method

Optical coherence tomography (OCT) is a non-contact; noninvasive, higher resolution, a Michelson interferometer-based imaging method. It is an optical imaging method that measures scattering of light at different depths. The infrared laser is used as coherence light. The light is separated into two beams, first one towards the tissues and the second towards a moving mirror. The light that is reflected from the mirror and the beam from the tissue are directed to the detector (CCD-camera, charge-coupled devices), which measures the light intensity. Positive interference happens only when the photons path of the probe and reference beam are equal at different depths and generate a 3-D image of the sample.[68] The principle of optical coherence tomography.[69]

OCT allows light to penetrate the scattering medium, achieving, at least in some cases, sub-micrometer resolution. Recently, OCT has been used in animal experimental brain research and in diagnostic medicine (mainly in ophthalmology) to obtain detailed images of the human retina.[70] Impressive results based on the combination of OCT and IOS has been obtained recently on the rat somatosensory cortex.[68] They showed that OCT is capable of giving high-resolution, cross-sectional images of hemodynamic activity and show significant spatiotemporal correlations between OCT and IOS signals.[69]

SUMMARY

A wide range of approaches to Noninvasive optical brain imaging and insights into the fundamental basis of many optical imaging techniques are presented in this paper. The diffusive nature of biological tissues, spectral range makes non-invasive monitoring of brain function possible. Light can penetrate deeply and eventually be re-emitted on to the surface, carrying valuable information on the probed cortical area. The main differences between the non-invasive brain methods are highlighted below for better understanding of the review.

The Intrinsic optical imaging (IOS), Photoacoustic Microscopy (fPAM), Diffuse Optical Tomography (DOT), Optical coherence tomography (OCT) methods are based on the optical changes in the features of brain tissue. fPAM is conversion of photon's energy into acoustic waves whereas DOT is based on photon absorption and scattering in the brain tissue which can be performed on a freely moving object at reduced cost and high portability. OCT measures scattering of light at different depths up to sub micrometer resolution and is commonly used by ophthalmologists. NIRS uses light rays (800nm to 2500nm)

near to infrared where these rays penetrate deeper into cortical structures and are useful for noninvasive assessment of brain function in intact skull. It is most effective in cognitive psychology. Terahertz Radiation Brain Imaging uses electromagnetic rays in the terahertz (0.3 to 3 THz) range. They penetrate the tissue up to few millimeters. The spectrum of Voltage-Sensitive Dyes (VSD) Imaging applications is very broad and it differs from other methods by usage of voltage sensitive dyes. These voltage sensitive dyes are used to understand the neuronal networks. Metabolic Related Optical Imaging is an advanced imaging technique which uses radioactive glucose mainly isotopic 2-Deooxyglucose for visualization of neuronal and total brain metabolic activity. It also measures the oxygen consumption by neurons. Ca^{2+} and other Ion Sensitive Dye Imaging is based on detection of changes in the intra cellular calcium levels reflected by optic signals which are then detected by calcium sensitive chemical probes. Auto fluorescence method uses the flavoprotein autofluorescence signals for identification of brain metabolism during hypoxia, visualization of neural activity predominantly astrocytes of brain tissue. All these methods are useful for functional brain mapping and identification of neuronal activity.

The presented optical techniques target different physiological effects linked to brain function, therefore each of them can give only a partial picture of the overall phenomenon. Integration of techniques can potentially provide a more complete neurophysiological description.

CONCLUSION

Optical Imaging techniques which are applied in human and animal experimental research and clinical diagnosis are reviewed in this paper. The knowledge of optical imaging techniques is useful for scientists and clinical researchers for widespread applications in understanding various structures of the brain as well as for clinicians for diagnosis and treatment of diseases associated with brain. These methods emerged as an indispensable tool in the detection, staging and response assessment, treatment, monitoring, and identification of various stages of neurological diseases and detection of metastasis malignancies. In addition, this detailed review will aid researches to understand various imaging techniques that are commonly applied on brain and to determine which technique best suits their need. The development of such imaging techniques is rapidly flourishing, leading to the technological advancements for an efficient and powerful imaging of brain.

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