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# Review Article

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## Multimodal Functional Near-Infrared Spectroscopy in Monitoring Cerebral Haemodynamic: A Review Article

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### Abstract

Functional near-infrared spectroscopy (fNIRS) is an optical imaging tool to study brain activities. Moreover, many researchers combined fNIRS with other modalities to gain a better understanding of the brain. This paper provides an overview of the combination of fNIRS with other imaging modalities in the detection and measurement of the cerebral hemodynamic. Cerebral haemodynamic such as the cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral blood oxygenation (CBO) are the important parameters in many neuroimaging studies. Cerebral hemodynamic had been studied by various medical imaging modalities. Initially, Xenon enhanced Computed Tomography (Xenon CT), Computed Tomography (CT) perfusion; Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) are used to measure the cerebral hemodynamic. Recently, fNIRS is used to optically observe the changes in cerebral haemodynamic during brain activities and the combination of fNIRS with other modalities also become an interest to study the relations within brain activities and the cerebral hemodynamic. Therefore, this paper provides an overview of existing multimodal fNIRS in detection of cerebral haemodynamic changes and provides an important insight on how multimodal fNIRS aid in advancing modern investigations of human brain function.

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## Introduction

The cerebral haemodynamic could be categorised as cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral blood oxygen (CBO). CBF is the blood supply to brain in a given period of time such in adult, CBF is typically 750 ml per minute. CBV is define as the volume of blood in a given amount of brain tissue, most commonly millilitres of blood per 100 g of brain tissue. CBV is one of the parameters generated by perfusion techniques whereas CBO is the oxygenation of the cerebral blood. These parameters are important to study the brain activities since the blood deliver glucose and other nutrition to the brain. Nowadays, many imaging modalities used to measure these cerebral hemodynamic parameters to understand the physiology of human brain activities [1]. Brain activities always relate with increase blood supply to the brain. For example thinking consumed cortical metabolic energy, reflected in multifield increases of regional CBF and the estimated cortical energy consumption during thinking was equivalent to or larger than the estimated cortical energy consumption during intense voluntary movements[2]. Initially, CBF is measured using xenon computed tomography (xenon CT), CT perfusion and single photon emission tomography (SPECT) whereas positron emission tomography (PET) and magnetic resonance imaging used to study the cerebral blood perfusion and metabolism [1,2]. Coles JP. Has reviewed the differences of each type imaging modalities used to monitor the CBF in 2006 whereas Rostami E., 2014 reviewed the different modalities to image the CBF in patient with severe traumatic brain injury [1,3].

Recently, functional near-infrared spectroscopy (fNIRS) is getting attention to study the cerebral hemodynamic during brain activities. fNIRS is the optical imaging that used near-infrared for measuring the changes of oxyhaemoglobin (oxy-Hb), deoxyhaemoglobin (deoxy-Hb) and total haemoglobin (t-Hb) in response to the brain activation or certain clinical condition. The fNIRS system emits infrared light and this infrared light passes through the cortex and cerebral, which some of the light is either absorbed, scattered, or reflected from oxy-Hb and deoxy-Hb. The wavelength of the infrared light use is within 650 nm – 850 nm which is low absorption in biological tissue and allows the light to penetrate deep enough to the head through skin and skull and reach the outer layer, 5 mm - 10 mm of brain tissue[4]. By measuring the absorbance reflectance changes at two (or more) wavelengths, one of which is more sensitive to oxy-Hb, the other to deoxy-Hb, changes in the relative concentration of these chromophores can be calculated [5]. Since fNIRS is non-invasive technique, it has been widely used to monitor the cerebral hemodynamic as the changes of t-Hb is use as an indicator of alteration in CBV within the optical field and the alteration in CBV is nearly related to those in CBF[6].

More recently, fNIRS are combined with other modalities to study CBF, CBV and CBO to increase the diagnosis of understanding. This current review is to provide an overview of the combination of fNIRS with other imaging modalities in the detection and measurement of the cerebral hemodynamic. This review is structure as 1) an overview of the previous study on monitoring cerebral hemodynamic using fNIRS; 2) an overview of the combination fNIRS with other modalities in monitoring cerebral hemodynamic and 3) discussion on how the multimodal of fNIRS and other modalities could be used in future research. The multimodal fNIRS that discussed in this review are fNIRS-MRI, fNIRS-fMRI, fNIRS-PET, and fNIRS- electroencephalography (EEG). It should be stressed that, the goal of this review is to report the overview of where and for what purposes the multimodal procedure was applied, and it is not intended to report meta-analysis or to perform a deep critical evaluation of the specific findings within each application. These analyses would be not suited for a single, broad topic review of the technology and the applications and should be reported in more focused reviews.

## Overview of fNIRS in monitoring cerebral hemodynamic

fNIRS first discovered by Jöbsis was in 1977, demonstrate the possibility of fNIRS to detect changes of adult cortical oxygenation during hyperventilation [7]. Since the discovered of fNIRS, it has been widely used to study brain activities. fNIRS measurement shows the oxygenation state of haemoglobin in cerebral blood. Increase in oxy-Hb is line with an increase in t-Hb means that increases in cerebral blood supply is more than neuronal demand whenever there are mental activities in brain[6]. Therefore, the continuous measurement of changes of t-HB concentration generally reflects changes in CBF. Absolute quantification of CBV is also possible using fNIRS where oxy-Hb is directly proportional to CBV [8]. This measurement can be used to provide a baseline value for CBV. However, the use of fNIRS method may underestimate CBF and this is likely to relate to the contribution of non-cerebral in the field of view since only 30% of tissue interrogated by fNIRS is cerebral brain tissue[8]. However, fNIRS is advantageous compared to other modalities to measure CBF therefore, fNIRS may offer a great variability of a single measurement.

Hoshi Y. and Tamura M., 1993 performed some of the early studies to image the CBF and CBO using fNIRS. They had demonstrated the use of tissue transparent near-infrared light to detect the specific region changes in haemoglobin oxygenation state and blood volume during mental task[9]. fNIRS involves non-invasive technique, non-radiation and task dependent, therefore, it has been used widely to monitor oxygen changes during brain activities. fNIRS also used to monitor brain oxygen in neonate as in review article; there are four group of neonates subject being monitor the CBF and cerebral autoregulation; preterm infants during the transitional period, neonates receiving specific medication/treatment, neonates with congenital heart disease and neonates with hypoxic-ischemic encephalopathy (HIE) treated with therapeutic hypothermia[10]. Some other studies show CBF, CBV and CBO increases with cortical activities during motor and cognitive task[8,11]. Meanwhile in certain cases of the disease, there are variety of blood hemodynamic. The oxy-Hb and t-Hb is decreases during electrical stimulation of the thalamic nucleus ventralis intermedius (VIM) among Parkinson disease patient [12]. fNIRS signal is lower in the frontal and parietal areas in the Alzheimer disease (AD) patient and whereas in the mild cognitive impairment (MCI) group patient is significantly lower only in the parietal area[13].

fNIRS is safe, portable which can be bedside monitoring, radiation safe, non-invasive method and inexpensive compare to other brain imaging modalities.The most special about fNIRS is task related, where it can be done while subject is doing specific task such as cycling or motor sensory task. fNIRS is completely silent, providing a nonintrusive environment and allowing for an easy presentation of auditory stimuli [14]. Even though fNIRS has many advantages as stated, still, fNIRS also has some limitations. The penetration of light in fNIRS is only at the cortex region thus fNIRS only measures haemoglobin concentration on the cortex region rather than in deeper brain structures [14]. Other than limited to frontal regions and surface analysis, fNIRS also lack of anatomical information and it introduce challenges in interpretation of the signal from multiple source of vascular. fNIRS also has low spatial resolution and low signal to noise ratio (SNR). Therefore, in order to compensate the strength and limitation of fNIRS, many studies combined fNIRS with other modalities such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and positron emission tomography (PET).

**Overview of multimodal fNIRS in monitoring cerebral hemodynamic**

**1. fNIRS-fMRI**

fMRI is the most common modalities combined with fNIRS. In brain imaging, fMRI is used to visualise the active brain region. It is based on blood oxygen level dependent (BOLD) effect where it detects the blood oxygen level changes due to the changes in neuronal activities. Whenever there is a high demand for oxygen to an area, so the concentration of deoxy-Hb within tissue decreases. This decrease has a direct effect on the signals used to produce magnetic resonance images since blood that contains oxy-Hb is not very different, in terms of its magnetic susceptibility while deoxy-Hb is significantly paramagnetic[15]. Thus, the fMRI only related to the changes in concentration of deoxygenated haemoglobin only [14]. While fMRI signal is high due to the decrease of deoxy Hb and provides information on oxygen in the blood, as deoxy-Hb reduction is associated with the increase of oxy-Hb. Therefore, fMRI detects the BOLD changes in MRI signal, which is high when the brain is activated by stimulus or task because there are regional increases in CBF, and CBV occur to deliver oxygenated blood to the active neurons. The BOLD fMRI is non-invasive technique and produce high-resolution activation maps, make it as a preferable choice to be used in brain study. However, fMRI also has a limitation, in term of practical constraint and cost effectiveness. Due to the requirement of compatible equipment and the restriction on movement in a typical supine position, limit the task to be performed in MRI scanner. The BOLD effect in fMRI is basically similar as in fNIRS that measures the changes of oxy-Hb, deoxy-Hb and total Haemoglobin (total-Hb) in blood. In comparison to fNIRS, fMRI would have lower temporal resolution, and related in produce a large noise, which make it uncomfortable to the patient doing the task. Therefore, due to this limitation, many studies that combined fMRI with fNIRS to improve the finding and get a better understanding of brain studies. The fNIRS signal is said to be compatible with fMRI measurement parameter to study the CBF though lack of deoxy-Hb response by fNIRS, still the signal physiology for functional brain could be mapping by fMRI and allow assessment of both constraints and practicability of functional studies by fNIRS[16]. Other visual stimulation in healthy subject study by fNIRS, the haemodynamic respond measured by fNIRS were consistent with fMRI[17]. Other combination of fNIRS and fMRI studies has been reviewed in Scarapicchia et al., 2017 and there are over 100 published articles using combined fMRI-fNIRS in brain function studies [18].

**2. fNIRS and PET**

In addition to fMRI, the combination of fNIRS-PET also used to get a better understanding of cerebral hemodynamic. PET is based on injected radioactive tracer to image the physiological function of the human body. The radiotracer is normally a biological compound of interest labelled with a positron emitter such as $^{11}C$, $^{18}F$ and $^{15}O$, while each compound used to investigate different biological function. For example 18F-2-deoxyglucose (18-FDG) is used to investigate cerebral glucose metabolism, whereas $H_2{}^{15}O$ is used to examine cerebral blood flow[19]. fNIRS has high temporal resolution while PET has good spatial resolution compare to fNIRS. In neuroimaging brain imaging, fNIRS and PET both are the promising tool to study the oxygenation in the blood. Mintun et al., performed $O^{15}$-PET study during visual activation and hypoxia to examine the relationship of CBF and oxygen delivery and the finding shows that increase in CBF associated with physiological activation is regulated by factors other than local requirements in oxygen[20].

fNIRS and PET is a good possibility to localise and quantitation of brain activities based on changes of cerebral hemodynamic. Rostrup et al., performed fNIRS study to quantify CBV changes measured by PET where the CBV was measured simultaneously fNIRS-PET during the respiratory condition in hypercapnia and hyperventilation and found the difference between CBV obtained by PET and fNIRS where PET CBV-changes was 3.5 larger than calculated by fNIRS data. There is also a low correlation of the changes in CBV-PET and CBV-fNIRS. However, a combination of these two techniques in the neurophysiological events can provide alternate for the technique that suffers from specific limitation. For example, fNIRS technique measuring CBV reported to showing lowered value than PET measurement. Since the CBV is used in BOLD determination, there is caution in using fNIRS values for its quantitative analysis across different modalities [21].

Cerebral hemodynamic measured by fNIRS-PET also become a parameter to study other clinical condition. As in H. Polinder-Bos et al., fNIRS is used to monitor cerebral tissue oxygenation and compare to CBF measured by $^{15}O$-$H_2O$ PET changes during haemodialysis among patient age more than 65 years old, evaluate whether changes in frontal cerebral oxygenation can identify changes in frontal CBF during haemodialysis. fNIRS could be another option other than PET to detect intradialytic CBF changes, but a correction factor may be needed to correct for the underestimation of CBF changes by fNIRS[22]. fNIRS and PET, both are promising imaging tools for studying Alzheimer's disease. The earliest study on the combination of fNIRS and PET was to study the cerebral haemoglobin and rCBF in AD patient. Hock et

al., demonstrated the used of simultaneous fNIRS-PET to study the parietal cerebral haemoglobin oxygenation and regional cerebral blood flow (rCBF) in AD patients and the result shows that AD marked a reduction of regional cerebral blood flow and cerebral haemoglobin oxygenation during activation of brain function [23].

### 3. fNIRS-EEG

Another multimodal technique combined with fNIRS is electroencephalography (EEG). fNIRS and EEG both are optical imaging technique based on scalp measurement procedure. fNIRS measure hemodynamic changes during brain activation while EEG reads scalp electrical activity generated by brain structures [24]. This multimodal approach has already being used to observe brain physiology during language development, behaviour interaction, stimulus and auditory sensory studies[25–29]. In EEG, an electrical readout during neuron activation through voltage potential can be measured on the scalp[26]. Since activation of neuron networks are well defined and can be traced to specific stimuli, it give rise to event related potential (ERP) technique, where specific events are related to brain EEG and used in studying brain activity phenomenon [25]. A multimodal approach using fNIRS and EEG allows the high spatial resolution of fNIRS to be combined with good EEG temporal resolution while covering for EEG low spatial resolution.

Although EEG is detecting the electrical signal from the neuron activation, the slow voltage shifts recorded in the brain is said to correlate strikingly well with changes in cerebral CBF [30]. In the study done to proove this statement, the direct current (DC) EEG was recorded from 12 subjects during 5 non-invasive manipulations that affect intracranial hemodynamic and the DC shifted were compare to changes in the CBV measured by fNIRS [30]. The result shows that the hemodynamic changes in the human brain are associated with marked DC shifts that cannot be accounted by intracortical neuronal or glial currents. Therefore, there are some combine fNIRS-EEG studies are to compare the electrical response from EEG and oxygenation in blood from fNIRS. A study done by Lin C. et al., they explore multimodal physiological phenomena in response to driving fatigue through simultaneous fNIRS and EEG recordings and the result reveal relationships between the EEG power spectrum and the concentration levels of oxy-HB in the occipital region of the brain with respect to reaction times of the stimulation [31]. Clinical application of fNIRS-EEG already been seen in the area assessing of performance level of the brain during a task with high working memory load and increasing being studied for the usage of neurohabilation and proper pharmacointervention plans during brain injury rehabilitation[26,28,29].

The future direction of multimodal fNIRS in monitoring cerebral haemodynamic

Study on cerebral haemodynamic correlate to brain activity could be very beneficial to understand the working brain in term of energy consumption to the brain in relation to oxygen supply to the brain through cerebral blood flow. Collecting fNIRS signal along with other modalities may require additional time and effort to ensure fNIRS device is compatible to the combination devices, such as with fMRI, fNIRS should be non-magnetic material to compatible with the magnetic resonance environment and is also able to accommodate a variety of head sizes in the limited space allotted in the scanner [18]. For combination with PET, fNIRS is relatively high temporal resolution but measure only in the cortex region, however comparing with deep brain oxygen or blood flow given by PET, this will give a correlation of the whole brain blood flow during brain activities. Even though combination with fMRI and PET is costly, but it depends on the availability of the modalities. Both could be a better choice to combine study with fNIRS. Meanwhile combination with EEG, even though the equipment is also mobile as it only requires a multisensory helmet and it detectors for setup which allows for bed-side application and does not require for patient immobilisation [26,29]. However, there are a few difficulties in this multimodal. Since signal acquisition need to be collected simultaneously, electrical noise artefact and movement from both sensors may pollute the measurement readings [26]. There is also no standard helmet mounted to accommodate two different types of sensors, it resulted in different research groups employing their head mounted model [27]. This cause reading to varies between each studies group.

### Conclusion

The current review provided an overview of imaging physiology of cerebral haemodynamic bases on multimodal fNIRS technique. fNIRS is advantageous alone in monitoring blood haemodynamic but it would be beneficial with the combination with other modalities. Such a combined fNIRS modalities would help a better understanding on how the haemodynamic may differ among population variables.

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