The Use of Functional Near Infrared Spectroscopy Technique in Neurology

Ali Rıza Sonkaya

ABSTRACT

In recent days functional near-infrared spectroscopy (fNIRS), which is non-invasive, portable, affordable, safe, easy-to-use device that does not expose people to radiation, has become popular as an emerging optical imaging technique for studying human brain function. It has significantly contributed to the understanding of neural correlates. These advantages make it especially useful in the investigation of neurological disorders. However, fNIRS has still not become prevalent compared to other neuroimaging techniques in the field of Neurology. For this reason, the purpose of this review article is to introduce fNIRS techniques and report fNIRS studies in the field of Neurology. In addition, the basic principles of fNIRS, including the features, advantages, and limitations are summarized in the review.

Key Words: fNIRS Technique, Neurology, Neurosurgery, Neurophysiology

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Introduction

fNIRS is a device designed to detect changes in the concentration of oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin molecules in the blood, a method commonly used to assess cerebral activity (León-Carrión and León-Domínguez, 2012). In recent years fNIRS, which is a non-invasive, portable, affordable, safe, easy-to-use device that does not expose people to radiation, has become popular as an emerging optical imaging technique for studying the human brain's functions. These advantages make it useful in the field of neurology. Although the possible contributions of fNIRS and its usability for many years, it has not achieved substantial clinical use (Irani *et al*., 2007), and also it is still largely unknown to clinical neurologists.

For clinical use in neurology, fNIRS is conceivable as an option to provide a bedside oximeter for the brain, broadly available at comparatively low costs (Obrig, 2014). Despite this, its potential has been limited to routine brain monitoring during cardiac and vascular surgery and in neonatology has been established (Obrig, 2014). It is therefore of key interest to introduce fNIRS techniques for examining neurological diseases, which fNIRS may be useful in, and to develop new fNIRS methods to be applied in neurology.

To sum up, due to the no comprehensive investigation of the appeals of fNIRS to brain disorders, the present study aims to give an information about fNIRS technique and examine the researches which was used fNIRS in major neurologic diseases.

Principles of fNIRS

In 1977, Frans F. Jöbsis indicated that it was possible to measure changes in near infrared light attenuation from temple to temple in anesthetized cats during normoxia, anoxia and asphyxia (Jobsis, 1977), which thereby initiated the field of fNIRS brain imaging (Schytz, 2012). 8 years after Jöbsis (1977), the first human brain clinical studies were published by Brazy *et al*., (1985) and Ferrari *et al*.

Corresponding author: Ali Rıza Sonkaya
Address: Neurologist, Okmeydani Training and Research Hospital, Department of Neurology, 34384 Okmeydani-Sisli/İstanbul/TURKEY
e-mail ✉ drsonkay@gmail.com
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(1985), (Brazy *et al*., 1985b; Brazy *et al*., 1985a; Ferrari *et al*., 1985). Since the development of multichannel apparatuses in the late 1980s and early 1990s, fNIRS has been increasingly used to study human brain function in adults (Hoshi and Tamura, 1993; Villringer *et al*., 1993) and infants (Chance *et al*., 1988).

fNIRS is designed to employ near-infrared light to non-invasively measure changes in the concentration of oxygenated (oxy-Hb), deoxygenated (deoxy-Hb) and total (tHb) hemoglobin in the brain, readily penetrating the skull and reaching cortical tissue (Dieler *et al*., 2012, Wolf *et al*., 2007). The measurement of changes in the ratio of oxy-Hb to deoxy-Hb is the most commonly used method of fNIRS (Irani *et al*., 2007). By far the most biological tissues are relatively transparent to light in the near infrared range between 700–1000 nm, largely because hemoglobin absorption and water absorption are relatively small at these wavelengths (Irani *et al*., 2007). However, the chromophores oxy-Hb and deoxy-Hb reflect specific wavelengths in this range. As such, this spectral band is often referred to as the ‘‘optical window’’ for the non-invasive assessment of brain activation (Irani *et al*., 2007; Jobsis, 1977). Each wavelength of light is differentially absorbed by the oxy-Hb and deoxy-Hb species of hemoglobin, allowing concentration changes of each to be estimated. In a similar manner with fMRI, cerebral blood flow is used as a proxy for neuronal activity (Fishburn, 2017).

The fNIRS system consists of two main components: a light source and photodetector. A light source known as a light-emitting diode (LED), emits a ray of quasi-infrared light at the scalp, half of the wave is absorbed by the chromophores (oxy-Hb, deoxy-Hb and cytochrome c-oxidase) found in the nervous tissue (León-Carrión and León-Domínguez, 2012). A photodetector captures the light wave, resulting from the interaction with the chromophores, which typically follows a banana-shaped path back to the surface of the skin (Figure 1) (León-Carrión and León-Domínguez, 2012, Fishburn, 2017). The characteristics of this light wave have changed with respect to the original light emitted by the LED due to the absorption and dispersion capacity of the nervous tissue and chromophores (León-Carrión and León-Domínguez, 2012).

Characteristically, a functional near infrared equipment is included a light source and a light detector. A light source is tied to the participant’s head with either LEDs or though fiber-optical bundles (the optode, or source). Also a light detector receives the light after it has been reflected from the tissue. Since light is dispersed after getting into the tissue, a photodetector embed in 2–7 cm away from the optode can gather light after it has passed through the tissue. When the distance between the source and photodetector is set at 4 cm, the fNIRS signal becomes susceptible to hemodynamic changes within the top 2–3 mm of the cortex and expands laterally 1 cm either side, vertical to the axis of source–detector spacing(Dieler *et al*., 2012).

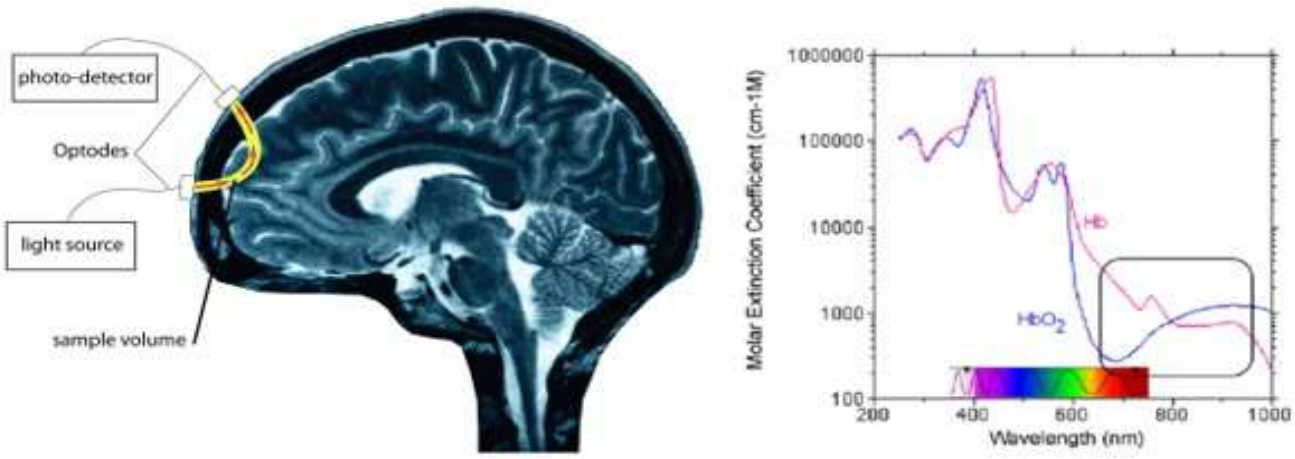

Figure 1. The surface of the head is irradiated with a combination of near-infrared wavelengths of light generated by the light source. A photo-detector will collect the light. The photons follow a banana-shaped path from light source to detector (León-Carrión and León-Domínguez, 2012)

Different fNIRS systems have evolved over the years. The most widely used method measures the intensity of the near infrared light reflected via continuously-emitting sources (Dieler *et al*., 2012). By measuring light scattering between a light emitter and a detector, which are sufficiently separated, the proportion of reflected light can be traced back to cortical tissue surrounding the emitter-detector pair (Dieler *et al*., 2012). Intensity changes in two or even more wavelengths are then converted into concentration changes of oxy-Hb and deoxy-Hb by using a modified version of the Beer-Lambert law, which is substantially an experiential description of optical attenuation in a highly sprinkling medium. Because fNIRS light does not pass through tissue unscattered, and therefore the exact volume of tissue pervaded by detected light is not known, continuous wave systems are unable to derive absolute values of oxy-Hb and deoxy-Hb concentrations (Dieler *et al*., 2012; Irani *et al*., 2007).

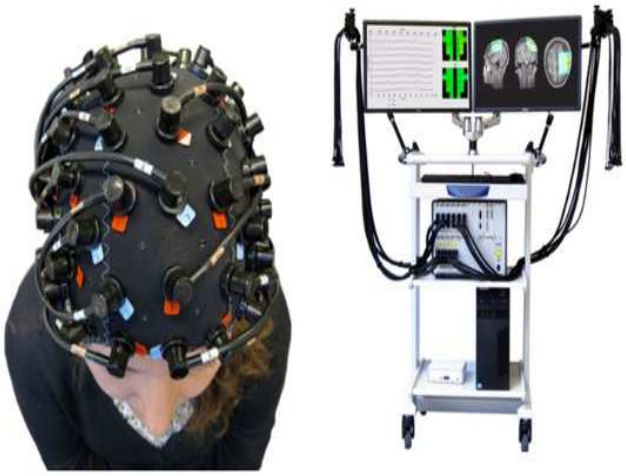

Figure 2. Sample of fNIRS-EEG compatible cap and fNIRS device

fNIRS Data Recording

The data collection equipment includes fiber optics which are attached to the head via optodes. Optodes are generally placed on the regions of the brain using a NIRS-EEG compatible cap. The fNIRS data are recorded with light emitters and detectors. When the data is recording from the fNIRS, optodes are attached to the subject's head and can be monitored either connected directly to a computer, or a portable computing device that records the subject's data as he or she engages in specific tasks. The data is recorded and then analyzed for changes in the blood flow or oxygenation levels of the brain before, during, and after the task. Therefore, hypotheses can then be tested about how brain activity is being affected by certain tasks or behaviors (Figure 2).

Advantages of fNIRS in the study of Neurology

Several advantages as compared to other imaging methods make fNIRS an attractive tool for researching human brain function in various domains, from basic sensorimotor mapping (Dieler *et al*., 2012) to the study of major neurologic disorders. Unlike fMRI, fNIRS is very silent and ensures a great setting for pre and post treatment. Besides silent operation, an unconfined scanning environment make fNIRS more suitable to subjects that have sensory hypersensitivity or claustrophobia (Fishburn, 2017). Also, it is safe, portable, affordable, easy-to-use and it does not expose people to radiation. These qualities make fNIRS suitable not only for adults, but also pediatric populations. To sum up, these advantages make it useful in the field of neurology. Treatment consequences for fNIRS can also be expanded to modulating neural reflects during neurorehabilitation. In one study carried out by Chute (2002) has emphasized the continuous assessment and transposability of fNIRS (consists of wireless capabilities) can serve to help in functional brain rehabilitation by ensuring fittest neurometabolic timing for rehabilitation, and immediate feedback during neurometabolic training of the brain for everyday tasks (Chute, 2002).

Limitations of fNIRS

Although fNIRS was developed as a tool for clinical monitoring of tissue oxygenation, it also has some limitations for neuroimaging. fNIRS is not useful for deep brain tissue studies because the spatial resolution of fNIRS is on the order of 2.5-3 cm and is capable of imaging depths of 1-2 cm (Villringer *et al*., 1993).

It has some limitations including the use of cranial reference points, the attenuation of the light signal by extracerebral matter, comparisons of fNIRS data between subjects, the impact of skin pigmentation on signal detection, and difficulties obtaining absolute baseline concentrations of oxy-Hb and deoxy-Hb.

The Use of fNIRS in the field of Neurology

This review will present a comprehensive survey of the various studies which were carried out using by fNIRS technique in the field of neurology. Here, research using fNIRS in major neurological

disorders such as Alzheimer's, Parkinson's, headaches, cerebrovascular diseases and others are reviewed.

A large proportion of fNIRS work in the neurology has focused on Alzheimer's disease (Fallgatter *et al*., 1997; Hock *et al*., 1996; Fladby *et al*., 2004). One of the studies about Alzheimer's disease in adults using fNIRS was carried out by Fallgatter *et al*. (1997). Authors aimed to measure the changes of concentrations of oxy-Hb and deoxy-Hb in left and right hemispheric prefrontal brain tissue areas during performance of the Verbal Fluency Test in patients with Alzheimer's disease. The study was conducted on 10 patients with Alzheimer's disease and 10 healthy controls. Their findings showed a significant interplay between hemispheric affects and diagnosis of participant. They demonstrated the good performance by controls on the Verbal Fluency Test was related with a predominance of left hemispheric activation, whereas in patients with Alzheimer disease a low number of correct responses were related with the loss of this asymmetric activation pattern. At the end of the study, authors discussed the results compared to the previous literature and they deduced the loss of asymmetry during Verbal Fluency Test is possibly characteristic for Alzheimer disease (Fallgatter *et al*., 1997). Another study by Hock *et al*. (1996) investigated the contribution of fNIRS in the diagnosis of Alzheimer's disease. Authors monitored changes in oxy-Hb in the frontal cortex using fNIRS while patients with probable Alzheimer's disease performed a verbal fluency task. According to the results of study, healthy individuals demonstrated raises in the local concentrations of oxyHb and tHb, patients with Alzheimer's disease indicated significant decreases in oxyHb and tHb shortly after get started the task. This effect was more explicit in the parietal cortex than in the frontal cortex. Authors recommended that their results of a regional reduced oxygen provide during activation of brain function might be of relevance to the development and the time course of neurodegeneration (Hock *et al*., 1996). In addition to these studies, the pathway for the olfactory response in early stage of Alzheimer's Disease was also explored with fNIRS by Fladby *et al*. (Fladby *et al*., 2004). Authors measured the olfactory response in 21 patients aged 56 to 79 years using by fNIRS. The response was measured as the sum of the deviation of oxygenated and deoxygenated hemoglobin from baseline mean. At the results of the study, authors emphasized that control subjects show a clearly definable response with increased oxy-Hb and decreased deoxy-Hb bilaterally to smell of vanilla. By contrast, response amplitudes to vanilla in patients with Alzheimer's disease were found to be in the range of sham stimuli. Therefore, early deterioration of olfactory responses in Alzheimer's disease was stated (Fladby *et al*., 2004).

fNIRS has become a useful tool for investigating conditions such as stroke and Parkinson's disease. It has been shown that a significant increase in asymmetrical hemodynamic response occurs in a number of regions mediating motor functions, including the sensorimotor cortex, prefrontal cortex, premotor cortex and supplementary motor area when patients who had suffered from strokes or were suffering from Parkinson's Disease perform motor-related tasks, consisting of treadmill walking and postural perturbation tasks (Kim *et al*., 2017). Maidan *et al*. (2015) evaluated a more direct link between freezing of gait (FOG) and frontal lobe dysfunction in patients with Parkinson's disease (Maidan *et al*., 2015). fNIRS was used to measure frontal activation, i.e. oxy-Hb levels in Broadmann area 10 before and during FOG. The study was carried out with 11 patients with Parkinson's disease and 11 healthy older adults. Changes in frontal lobe activation before and during FOG that occurred during turns were determined. As a result of this study, an association between FOG episodes and changes in frontal lobe oxy-Hb was found. Increased activation in Broadmann area 10 before FOG, specifically during anticipated turns, highlighted the connections between motor planning, information processing, and FOG. According to the authors, these results support the idea that alterations in executive control play a role in this debilitating motor disturbance (Maidan *et al*., 2015). Nieuwhof *et al*. (2016) also found increased oxy-Hb levels in the prefrontal cortex during walking which is in line with the findings of Maidan *et al*. (2015), (Nieuwhof *et al*., 2016). fNIRS also holds meaningful covenant for neurobehavioral researches of Parkinson's disease by the reason of the protection that this technology can afford against motion artifacts (Irani *et al*., 2007). In one study conducted by Murata *et al*. (2000), fNIRS was used to explore cerebral blood oxygenation changes in the frontal lobe induced by direct stimulation of the thalamus or globus pallidus in patients with Parkinson's disease or essential tremor (Murata *et al*., 2000).

Under conditions of neural activation of the frontal lobe, oxy-Hb and tHb increased, while deoxy-Hb decreased in two cases during globus pallidus stimulation, and increased in four cases during low-frequency stimulation of the thalamus. The results demonstrated that fNIRS detected neural activation-induced patterns of cerebral blood oxygenation, particularly in oxy-Hb. The authors suggested that fMRI based on the BOLD contrast might not consistently detect the area of neural activation, highlighting a potential advantage (Irani *et al*., 2007).

In addition to Alzheimer's and Parkinson's diseases, a number of fNIRS researches were conducted on epilepsy in the field of Neurology (Villringer *et al*., 1993; Sokol *et al*., 2000; Watanabe *et al*., 2002; Vannasing *et al*., 2016; Adelson *et al*., 1998). Sokol *et al*. (2000) investigated the differences in cerebral oxygenation for complex partial seizures and rapidly secondarily generalized complex partial seizures. The study was carried on 8 adults with medically refractory epilepsy undergoing evaluation for temporal lobectomy. 17 seizures were recorded in eight patients using by fNIRS. Authors found cerebral oxygenation increased for complex partial seizures and decreased for rapidly secondarily generalized complex partial seizures. At the end of the study, it was stated that fNIRS distinguishes cerebral oxygenation patterns between complex partial seizures and secondarily generalized complex partial seizures (Sokol *et al*., 2000). Another study was conducted by Watanable *et al*. (2002) which sought to establish a noninvasive method for focus diagnosis of epilepsy. Authors examined the use of fNIRS and monitored cerebral blood volume change with fNIRS during long-term EEG monitoring of epilepsy in 32 cases with intractable epilepsies to diagnose the epileptogenic focus. According to the results, in 96% of cases, fNIRS showed significant hyperperfusion in the side of seizure foci, whereas ictal SPECT showed hyperperfusion in 69% of cases. It was suggested that ictal fNIRS was a reliable method to evaluate the focus side in epilepsy, especially when it is coupled with ictal SPECT (Watanabe *et al*., 2002). Because it is safe and flexibility, fNIRS has also been studied on children with epilepsy. Vannasing *et al*. (2016) evaluated pre- and postsurgical language localization in a right-handed boy with refractory epilepsy. In this case study, authors compared fNIRS results obtained while the participant performed expressive and receptive language tasks with those obtained using fMRI. At the result of the study, authors illustrated the potential for fNIRS to contribute favorably to the localization of language functions in children with epilepsy and cognitive or behavioral problems and its potential advantages over fMRI in presurgical assessment (Vannasing *et al*., 2016). Another fNIRS study was conducted by Adelson *et al*. (1999). In the study ictal events were recorded and compared with the pre-, intra-, and post-ictal periods for cerebral oxygen availability children in a pediatric intensive care and epilepsy-monitoring units. At the end of the study authors showed that fNIRS admitted of the continuous and non-invasive monitoring of changes in cerebral oxygenation peri-ictally, therefore allowing investigations into the pathophysiology of seizures and the examination of the potential of cerebral oximetry as a tool for seizure localization (Adelson *et al*., 1998).

fNIRS has been widely used to investigate headache disorders (León-Carrión and León-Domínguez, 2012; Pourshoghi *et al*., 2015; Schytz, 2015). One study, carried out by Pourshoghi *et al*. (2015), focused the migraine which is one of the common headache disorders. In the study, fNIRS device was used to explore the cortical vascular reactivity of migraine patients in response to drug infusions and its possible correlation with changes in pain experienced. Authors used the fNIRS on 41 chronic migraine patients receiving three medications: magnesium sulfate, valproate sodium, and dihydroergotamine. Patients rated their pain on a 1–10 numerical scale before and after the infusion. They found significant differences in cortical vascular activity both oxy-Hb and tHb between medications. According to the authors, fNIRS showed the potential to be a useful tool in the clinical setting for monitoring the vascular reactivity of individual patients to various migraine and headache medications (Pourshoghi *et al*., 2015). Also, fNIRS has used to detect pharmacological changes and evaluate the effectiveness of migraine treatment (Schytz, 2015). Watanabe *et al*. (2011) investigated the effective tools for monitoring hemodynamic changes in the cortical and scalp surface during migraine attack and treatment. Using fNIRS system and laser Doppler skin blood flow (SkBF) devices in combination, authors monitored changes in extra- and intra-cranial vasculature states upon sumatriptan injection during spontaneous migraine attack. 4 migraines without aura patients during attacks following

subcutaneous sumatriptan injection in comparison to 4 healthy subjects receiving sham injections. The authors showed following sumatriptan injection a simultaneous decrease in oxyHb measured by fNIRS, which was correlated to changes in skin blood flow measured by laser Doppler flowmetry. Sumatriptan induces blood vessel contraction at both cortical and scalp surfaces was found. At the end of the study authors suggested that simultaneous oxy-Hb/SkBF recording enables real-time continuous monitoring of the effects of sumatriptan treatment in clinical situations (Schytz, 2015; Watanabe *et al*., 2011).

fNIRS has closely reflected the etiological factors in ischemic or other neuroinjuries (Andrews, 2001). Andrews (2001) highlighted that a major application for fNIRS is neuromonitoring in operating rooms or in intensive care units for patients who are undergoing operations with significant risk of reversible cerebral ischemia (e.g., carotid endarterectomy) or in patients who have suffered severe head injuries or strokes, and/or who may be at risk for intracranial hemorrhages (Andrews, 2001; Irani *et al*., 2007). It has been demonstrated in a study carried out by Gopinth *et al* (1993) which utilized fNIRS for the early detection of intracranial hematomas, including epidural hematomas, subdural hematomas, and intracerebral hematomas. Authors conducted serial examinations using fNIRS to detect the development of delayed hematomas in a large sample of patients. They showed that 16% of the patients developed a type of late hematoma: intracerebral hematoma in 8 patients, extracerebral hematoma in 6, and postoperative hematoma in 13. Of the delayed hematomas, 18 seemed between 2 and 72 hours after admission and caused significant mass effects necessitating surgical evacuations. Many of the patients had a significant increase in the absorption of light prior to increases in intracranial pressure, changes on neurological examination, or changes on CT scans. A favorable outcome occurred in 67% of the patients with delayed hematomas. At the results of the study, the authors emphasized the utility of fNIRS in early diagnosis permitting early treatment and the reduction of secondary injury caused by delayed hematomas (Gopinath *et al*., 1993). Additionally, Kampfl *et al* (1997) evaluated the fNIRS to measure changes in regional cerebral oxygen saturation in eight head-injured patients with an intracranial pressure higher or lower than 25mmH. According to their findings, they were able to conclude that fNIRS might be an additional diagnostic tool in the non-invasive evaluation of impaired cerebral microcirculation in patients with increased intracranial pressure (Kampfl *et al*., 1997).

Conclusions

In conclusion, since there is no comprehensive investigation of the appeals of fNIRS in the neurology, this paper aimed to focus on fNIRS techniques and reported fNIRS studies in the field of Neurology. In addition, the basic principles of fNIRS including the features, advantages and limitations were summarized in the review.

In the future, fNIRS can be an important alternate or supplementary neuroimaging technique in the diagnosis and follow-up of specific patients with neurological disorders.

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