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Focus Diagnosis of Mesial Temporal Lobe Epilepsy by Using Functional Near-Infrared Spectroscopy

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Ryozo Nagai

RYOZO NAGAI, M.D., Ph.D.
President, Jichi Medical University

EPILEPTIC FOCUS DIAGNOSIS

BY USING fNIRS

By

Rizki Edmi Edison

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This Dissertation is dedicated

- *To my wife Rahimi Syahida, MD and my daughter Ranayuki Mikhalia Edmi for their support and understanding during my study in Japan*
- *To my Father Prof. Dr.Eng. Edison Munaf, my mother Prof. Rahmiana Zein, PhD, my younger brother Eijiro Sugiyama Edison, MD, PhD and Ebill Fuji Edison, MD, whose at great sacrifice made it possible for me to have the luxury of lengthy education*
- *To all those taught me and encouraged me.*

CONTENT

I. INTRODUCTION

1.1. Definition of Mesial Temporal Lobe Epilepsy

Epilepsy was defined by International League Against Epilepsy (ILAE) as a condition characterized by two or more unprovoked seizures over a period longer than 24 hours (ILAE, 1993). A decade later, the definition requires the occurrence of at least one seizure plus a clear predisposing factor (Fisher et al., 2005). Although the definition of epilepsy had been renewed, the tentative description should based on suggestive clinical features plus electroencephalogram (EEG) findings (Roger et al., 1989).

The classification released by ILAE in 2010 recognizes some diagnostically meaningful forms of epilepsy such as mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis that was not included in the previous classification (Berg et al., 2010). MTLE is described as a condition characterized by recurrent and unprovoked seizures that originate in limbic areas of the mesial temporal lobe, particularly in the hippocampus and amygdala. It is frequently resistant to anti-epileptic drugs (AEDs) treatment, and hippocampal sclerosis is considered its pathophysiological substrate (Engel, 2010).

1.2. Epidemiology of Mesial Temporal Lobe Epilepsy

The median incidence rate of epilepsy in the developed countries ranges from 25 to 50 per 100,000 person years while in the developing countries it ranges approximately 30 to 115 per 100,000 person years (Kotsopoulos et al., 2002). The prevalence of epilepsy in the developed countries ranges from 4 to 10 cases per 1,000 (Bell and Sander, 2001) while developing countries have reported a higher prevalence rates, ranging from 14 to 57 cases per 1,000 persons (Carpio and Hauser, 2009).

Unfortunately, although there are few epidemiological studies in temporal lobe epilepsy (TLE), there are no any studies in MTLE. Initial epidemiological study explored by Hauser and Kurland (Hauser and Kurland, 1975) in the community of Rochester Minnesota from 1935 to 1967. The incidence rate was 6.5 per 100,000 persons between 1935 and 1944. It had been increased between 1945 and 1964 where incidence rate was 10.4 per 100,000 persons. Other estimates regarding the prevalence of epilepsy have been obtained from tertiary referral centers (Semah et al., 1998) who studies 2,200 patients with epilepsy. In this study, 1,369 patients (62.2%) had localization-related epilepsy while 66% of them had TLE.

1.3. Current Status of Surgical Treatment on Mesial Temporal Lobe Epilepsy

Surgery has become the standard of care for patients with intractable temporal lobe epilepsy The basic surgical goal, removal of the amygdala, hippocampus, and parahippocampal gyrus, is based on the hypothesis that these structures represent a uniform and contiguous source of seizures in the mesial temporal lobe epilepsy syndrome (Thom et al., 2010). Early surgical treatment for pharmacoresistant epilepsy has proven to be helpful in achieving seizure control and is superior to pharmacotherapy for MTLE with respect to seizure outcome (Spencer, 2002). Results of meta-analyses surveying the literature from 1985 to 2003 indicate that about two-thirds of patients are seizure-free in the first two to three years after surgery for MTLE (Tellez-Zenteno et al., 2005). In comparison, best medical therapies over a similar period yield a 5% chance of becoming seizure free and a 0.5 to 1.0% chance of death per year from the epilepsy (Wiebe et al, 2001). Hence, surgery is a highly effective treatment for patients with medically refractory MTLE.

1.4. Problems of Current MTLE Tests

The localization and delineation of the epileptogenic zone is a fundamental step in the presurgical evaluation of patients with pharmacoresistant focal epilepsy (Berg et al., 2003). When magnetic resonance imaging (MRI) fails to detect a lesion or dysplasia, one must adopt invasive intracranial electrode examinations that may entail a risk of infection and hemorrhage (Gallagher et al., 2008). Such risks could be reduced if the diagnostic powers of non-invasive methods of presurgical evaluation are improved (Steinhoff et al., 1996).

There are several imaging modalities that can be used to observe cerebral activation changes involved in epileptic seizures.

A scalp EEG, which measures the voltage differences of electrophysiological activities of the brain, is a completely noninvasive method that is required essentially and critically for the clinical diagnosis of epilepsy (Smith, 2005). Although scalp EEG has stood as the gold standard for presurgical evaluation to determine epileptic focus side, it has some limitations (Smith, 2005). First, determination of the epileptic focus side is not efficient with scalp EEG, which fails to detect up to one third of patients with temporal lobe epilepsy (Spencer et al., 1985). Second, its distance to extracranial electrodes further complicates interpretation of the signal source. Consequently, there is still uncertainty in the role of ictal scalp recordings for presurgical assessment: laterality determination has been estimated to be 22% to 90% successful with scalp EEG recordings (Alarcon et al., 2001).

Ictal SPECT is the most commonly used imaging modality in current for functional seizure localization by observing ictal hemodynamic changes (Duncan., 1997; Cascino., 2001; Salek-Haddadi et al., 2002). It takes a single snapshot of regional

CBF changes reflected in the uptake by neurons of a radiotracer injected after seizure onset over a period of up to 30 seconds (Verma et al., 2013). However, since SPECT only allows detection of accumulated haemodynamic changes over a relatively long period of measurement, it may not always provide sufficient temporal resolution to distinguish ipsilateral haemodynamic changes reflecting epileptic seizure onset and contralateral changes representing patterns of seizure propagation (Kaiboriboon et al., 2005; Huberfeld et al., 2006; La Fougere et al., 2009). While ictal SPECT has been shown to be accurate for localizing temporal lobe seizures when the radiotracer is successfully injected immediately after the seizure onset (Van Paesschen, 2004), there tends to be a delay in tracer injection, which leads to difficulty in determining focus side. In the worst case, such a delay may lead to a "postictal switch" phenomenon, where false laterality determination is made based on falsely indicated seizure propagation to the opposite side (Newton et al., 1992).

In other hand, ictal PET measurement is also used for functional seizure localization, but it entails the same problem as ictal SPECT, and quantitative PET measurements of ictal rCBF associated with a seizure are no less difficult to achieve (Duncan, 1997).

Although complementary assessments such as video-electroencephalography (EEG) monitoring, single-photon emission computed tomography (SPECT), and positron-emission tomography (PET) are often practiced, the choice of noninvasive methods remains limited (Gallagher et al., 2008).

1.5. About functional near-infrared spectroscopy

Functional near-infrared spectroscopy (fNIRS) is a non-invasive method to measure cerebral hemodynamic changes by measuring the absorption of the near-infrared light between 650 and 950 nm through the intact skull (Villringer and Dirnfal, 1995). As the absorption spectra of oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) are distinct in this region, it is possible to determine the concentration changes of HbO and HbR from diffusely scattered light measurement (Jobsis, 1977).

fNIRS has several merits in regards to epileptic focus diagnosis: it is safe, compact and cost effective (Steinhoff et al., 1996). Its forgivingness of body movements allows continuous bedside monitoring of epileptic patients in a manner less restrictive than that of other modalities. It also has yielded a promising alternative: simultaneous fNIRS/EEG monitoring (Machado et al., 2011; Wallois et al., 2010). This is especially applicable for the presurgical diagnosis of mesial temporal lobe epilepsy (MTLE).

1.6. The Purpose of Study

Non-invasive localization of an epileptogenic zone is a fundamental step for presurgical evaluation of epileptic patients. Although pioneering studies suggested the potential of fNIRS/EEG measurements for epileptic focus diagnosis, several issues need to be clarified before it can be accepted for clinical routines.

Here, we introduce long-term simultaneous fNIRS/EEG monitoring for focus diagnosis in patients with MTLE. Thus, we developed a system to allow long-term, bedside fNIRS/EEG monitoring for 8-16 hours per day for four days. Such long-term

monitoring is virtually impossible in the restrictive environment of an fMRI, and can be best-realized using fNIRS.

II. METHODOLOGY

2.1. Subject Cases

This study included six MTLE (mesial temporal lobe epilepsy) patients (4 females; mean age 30; range, 20-54 years; all right-handed) who were candidates for epilepsy surgery and who underwent long-term (8-16 hours) video-fNIRS/EEG monitoring as part of their presurgical evaluation in the Neurosurgery Department of Jichi Medical University Hospital, Japan. In addition, 16 MTLE patients (12 females; mean age 33 years; range, 20-48 years, all right-handed) undergoing middle-term (up to two hours) video-fNIRS/EEG monitoring were included for comparison. Written consent was obtained from all patients.

2.2. Measurement

2.2.1. Measurement of EEG

The video-EEG was recorded with an EEG1000 system (Nihon Koden, Japan) via 18 electrodes according to the international 10-20 system excluding O1 and O2 (1000 Hz sampling rate; 60 Hz high-cut filter; 0.1-s time constant). Movement artifacts (head or body) were monitored using video recordings. Clinical seizure onset was identified by the epilepsy neurosurgeons.

2.2.2. Measurement of fNIRS

We used the multichannel fNIRS system ETG-4000 (Hitachi Medical Corporation, Kashiwa, Japan), using two wavelengths of near infrared light (695 and 830 nm). The sampling rate was set at 2 Hz.

2.2.3. Simultaneous video-fNIRS/EEG measurements

Simultaneous fNIRS/EEG measurement was accomplished using a head shell that can be comfortably secured to the head of the subject, and that keeps the source and detector optical fibers in contact with the skin. We fastened the probe holder tightly with a belt so as to minimize artifacts. Placement of fNIRS probes is depicted in Figure 1A. It took approximately 10 min. Additional fixation of EEG electrodes with a stapler took approximately one and a half hours for each patient. Spatial correspondence between fNIRS probes, channels and international 10-20 positions were assessed according to a virtual registration method (Tsuzuki and Dan, 2014).

Cautious tapering of antiepileptic drugs was used to increase the possibility of seizure occurrence. Simultaneous fNIRS/EEG monitoring was done in a quiet room for four days or until seizures occurred.

Middle-term monitoring monitored for spontaneous seizures for up to two hours per day for one or two days. For long-term monitoring, patients were recorded continuously for 8 – 16 hours per day for up to four days. During recording, patients did not perform any tasks. All recorded seizures were spontaneous (Figure 1A, 1B).

2.3. Data Analysis

2.3.1. EEG Seizure Onset

The EEG data was reviewed offline and manually marked by four epilepsy neurosurgeons. Seizure onset was defined by the unequivocal ictal EEG rhythm as compared to baseline (namely, regular 4-7 Hz rhythmic activities, known as theta bursts, that were found on temporal electrodes during the first 30-ictal s persisting for at least 5

s) or by the first ictal clinical symptom identified on the video recording (Williamson et al., 1993).

2.3.2. EEG Laterality Determination

Determination of the focus side of seizures in epileptic patients was based on the observation of electrographical changes during a seizure. Specifically, we looked at attenuation of background activity in the scalp EEG mainly consisting of alpha and beta waves (Sakai et al., 2002) , which was expected to be followed by the presence of rhythmic theta bursts (Risinger et al., 1989), and designated these events as the initial discharge. The side exhibiting these electrographical changes was determined as the ipsilateral focus side.

2.3.3. fNIRS

We analyzed the optical data based on the modified Beer-Lambert Law (Cope et al., 1988) as previously described (Maki et a., 1995). This method allowed us to calculate signals reflecting the oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) concentration changes, calculated in units of millimolar millimeter (mM·mm). Oxy-Hb signal was used for further analysis due to its higher signal amplitude than that of deoxy-Hb (Strangman et al., 2002).

2.3.4. fNIRS Seizure Onset

In order to eliminate subjective estimates of epileptic onset involved in visual inspection of fNIRS data, we adopted a numerical analysis based on timeline data.

First, the fNIRS-defined epileptic onset (hereafter, fNIRS onset) search was limited to within 30 s before and after the EEG-defined epileptic onset (hereafter, EEG onset) (i.e., total 60 seconds). For each fNIRS data point within the determined range, the average oxyHb value for the next 10-s period was calculated (mHb_{10}^{0}), and this average was subtracted from the oxyHb value for that time point (Hb_0). Then, the standard deviation of oxyHb was calculated for the timeline data of the preceding 60 to 0 seconds for each time point (sHb_0^{-60}). Finally, the subtracted value ($mHb_{10}^{0} - Hb_0$) was divided by SD. fNIRS-defined epileptic onset was defined as the first time point at which this value exceeded 6 ($\frac{mHb_{10}^{0} - Hb_0}{sHb_0^{-60}} > 6$).

2.3.2.2. fNIRS Laterality Index

We explored two hypotheses for cortical haemodynamics of the temporal region of epileptic and non-epileptic hemispheres: (1) fNIRS-defined epileptic onset precedes seizure on the epileptic side, and (2) oxy-Hb amplitude immediately after the ictal onset is higher on the epileptic side.

To determine immediate oxy-Hb amplitude, we calculated the average value of oxy-Hb over 20 s from the fNIRS-defined epileptic onset. This value was determined for four channels and averaged between the channels in the same hemisphere. Then, averages for left and right hemispheres were compared. We determined that the side with the higher value was the lateralized side.

2.4. Final Diagnosis of Focus Side

The final focus diagnosis of epilepsy in each patient was determined during an epilepsy surgery conference after all available data were reviewed. MRI examination

revealed all patients had unilateral hippocampal sclerosis. This served as the primary evidence for epileptic focus side.

III. RESULTS

In long-term monitoring (8-16 h/day for 1-4 days), four seizures were successfully recorded during fNIRS/EEG monitoring in four out of six patients with intractable MTLE. The other two patients had no seizures during simultaneous fNIRS/EEG sessions (monitoring time: 24 and 32 hours, respectively). The preliminary examination with middle-term monitoring (2 h) conducted prior to the current study produced seizures that were successfully recorded for four out of sixteen patients.

In the four patients with successful seizure detection, we detected a distinct haemodynamic response change as represented by a large increase of oxy-Hb signal around the onset of epileptic seizure, which entailed attenuation of background activity in the scalp EEG and/or rhythmic theta burst. Detailed diagnostic information (Figure. 2) and electrophysiological and haemodynamic responses (Figure. 3) for each patient are as described hereafter.

3.1. Cases

Case 1

Since the age of 7 years, this 24-year-old woman had suffered from weekly seizures. Her attacks usually began with a tingling sensation and flapping of her right arm followed by altered consciousness. No generalized tonic-clonic seizures were observed. Because treatment with antiepileptic drugs was ineffective, she was referred to Jichi Medical University Hospital for preoperative evaluation.

Magnetic resonance imaging studies yielded a high-density FLAIR (FLuid-Attenuated Inversion Recovery) signal in the right hippocampus. Administration of

iomazenil (IMZ) led to sings of reduced benzodiazepine receptor (BZR) density in the right hippocampal area.

During simultaneous video-EEG and fNIRS monitoring, one complex partial seizure was clearly captured. Paroxysmal rhythmic discharges were observed dominantly in the right hemisphere. The seizure's onset as defined by EEG was estimated as where diffuse desynchronization occurred 31 s prior to the obvious ictal rhythmic theta activity over the right temporal region. Discharges persisted dominantly on the right temporal region throughout the seizure. Right hand automatism was captured 20 s after desynchronization.

The initial fNIRS onset was determined in channels over T6 and T4 at 19.5 s before EEG onset. fNIRS onset could only be determined for the channels on the right hemisphere, and remained undermined for both channels on the left hemisphere. A steep increase of oxyHb beginning immediately after fNIRS onset was characteristic of both fNIRS channels on the right hemisphere. Increased oxyHb reached 2 mM·mm, which was approximately 20 times greater than activation induced by typical cognitive tasks (e.g., go/no-go, picture naming) (Monden et al., 2012a; Monden et al., 2012b; Moriai-Izawa et al., 2012)

Finally, the seizure focus was confirmed in the right medial temporal lobe during the right selective amygdalo-hippocampectomy, which relieved the patient of seizures.

Case 2

This 29-year-old right-handed man had suffered from refractory partial epilepsy since the age of 24 years. His seizures were characterized by an aura, usually began

with a sensation of fear followed by tonic-clonic seizures with loss of consciousness, and lasting about two minutes. His seizure condition progressively worsened over time with multiple daily seizures, and epilepsy surgery was considered after multiple antiepileptic drugs failed to control his seizures.

Left hippocampal sclerosis was identified on an anatomical MRI. We verified that there was no reduction of BZR density on the left and right temporal regions visible with IMZ SPECT.

One seizure was monitored during a simultaneous video-EEG and fNIRS session. The seizure was associated with a sensation of fear 15 s prior to the first obvious electrical evidence of seizure onset with high-frequency, rhythmic-spike activity appearing predominantly on the left temporal region.

Initial fNIRS onset was determined for a channel over T3 at 25 s before EEG onset. fNIRS onset for other channels spread sequentially through channels over T6, T4 and finally T5. Increase of oxyHb started immediately after fNIRS onset was marked for the T3 channel on the left hemisphere. The greatest increase of oxyHb among the four channels reached 3 mM·mm in the T3 channel.

The patient was finally diagnosed as having left medial temporal lobe epilepsy with successive video/depth-EEG monitoring. A left selective amygdalo-hippocampectomy relieved the patient of seizures.

Case 3

This 55-year-old woman suffered from intractable epilepsy associated with right mesial temporal cavernosus angioma. She started having seizures at the age of 53 years. Since then, she had periodically experienced seizures characterized by oroalimentary

automatisms, lip smacking, and hand rubbing, with loss of consciousness. Sometimes she would suddenly stand up and walk to a place that she could not recognize. Cavernosus angioma was detected with MRI on the right uncus.

With simultaneous video-EEG and fNIRS monitoring, one seizure was successfully captured. Electrographically, diffuse desynchronization was observed 20 s prior to a rhythmic theta wave, which appeared dominantly in the right hemisphere and was assumed as EEG onset. During the seizure, lip smacking and right hand automatisms were captured 13 s after desynchronization and throughout the seizure.

Initial fNIRS onset was determined for a channel over T4 at 1 s before the EEG seizure onset. fNIRS onset for channels over T5 and T3 were determined at time points close to the theta onset. An increase of oxyHb was marked for the T4 channel on the right hemisphere, with the largest increase exceeding 2 mM·mm.

The patient underwent a right selective amygdalo-hippocampectomy, and has since remained seizure free.

Case 4

This 21-year-old woman had suffered from seizures since the age of 12 years. After her first episode, she had periodically had seizures characterized by an aura of a foul odor and a sensation of fear, followed by a generalized convulsive seizure lasting less than two minutes, with or without altered consciousness. In addition, she would continuously pinch her nose during seizures. She underwent a comprehensive presurgical evaluation after multiple anti-epileptic drugs failed to control her seizures.

MRI studies, including detailed hippocampal images, displayed right hippocampal atrophy. IMZ SPECT studies demonstrated no decrease in BZR density on the left or right temporal lobes.

One complex partial seizure was successfully captured during simultaneous video-EEG and fNIRS monitoring. Extracranial ictal EEG examination first revealed obvious electrical changes identifiable on scalp electrodes followed by rhythmic theta activity over the right temporal region evolving in amplitude and frequency 12 s later. In the homologus contralateral temporal region, the EEG revealed similar wave patterns with lower amplitudes throughout the seizure. Pinching of her nose was observed in this seizure 5 s prior to electrical changes occurring on the EEG.

fNIRS onset was determined for the channels over T3 and T4 almost simultaneously at about 5 s after EEG onset. fNIRS onset remained undetermined for other channels. The increase of oxyHb was greater for the right T4 channel than for the left T5 channel. The greatest oxyHb increase among the four channels was about 3 mM·mm in the T4 channel on the right hemisphere.

The patient underwent a right selective amygdalo-hippocampectomy, since which she has been seizure free.

3.2. Determination of fNIRS laterality

We examined two hypotheses for cortical haemodynamics of the temporal region of epileptic and non-epileptic hemispheres: (1) fNIRS Hb onset precedes seizure on the epileptic side, and (2) immediate fNIRS Hb amplitude after ictal onset is higher on the epileptic side.

fNIRS onset on the epileptic side preceded that on the contralateral side in three out of four cases. Therefore, fNIRS onset precedence did not fully correspond to the epileptic side.

fNIRS amplitude was calculated as averaged Hb increase during the first 20 s after fNIRS onset. Averaged Hb values were larger for the epileptic side than the contralateral side for all four cases. Thus, fNIRS amplitude immediately after ictal onset could be a reliable laterality index for the epileptic side.

IV. DISCUSSION

4.1. fNIRS for Clinical Diagnosis of Epilepsy

fNIRS is more robust to body motion than other imaging modalities. Albeit that it is not completely resistant to every motion that is experienced in everyday life, it is reasonably tolerant of body motions associated with walking and talking, which are necessarily involved in long-term bedside monitoring. Such resistance to body motion necessitates a higher tolerance to motions often involved in ictal epileptic seizures. However, even for fNIRS, less body motion is preferred for stable data analyses. In practice, time periods with intolerable motion artifacts should be carefully avoided in order to achieve robust data interpretation.

Epileptic seizures result in an increase of oxyHb signals both on the ipsi- and contralateral sides. OxyHb increase is observed 2-8 s after the onset of a seizure and lasts for 20-50 s, returning to the resting level later (Watanabe et al., 2002). Similarly, a recent study also reported that seizures in MTLE patients were associated with significant increases in oxyHb signal of up to 13% compared to baseline periods (Nguyen et al., 2012). These increases are several times more than expected for experimental paradigms under usual physiological conditions (Gallagher et al., 2007). Such a large oxyHb increase is relevant to haemodynamic changes that were observed in a previous fMRI study on epileptic seizures with a BOLD signal change of 6%, which is larger than those for interictal spikes and cognitive tasks (0.5 - 1.0%) (Kobayashi et al., 2006).

The onset of haemodynamic changes reflecting epileptic seizures occurred at nearly the same time as seizure detection using EEG. However, haemodynamic changes

were also detected in the contralateral temporal lobe in a temporally similar manner as for the ipsilateral temporal lobe, but with a lower amplitude. In order to determine the epileptic focus side, fNIRS must detect haemodynamic changes in the ictal onset zone but not propagated signals.

Assuming that the epileptic focus of MTLE is in the hippocampus, we can logically expect scalp EEG and fNIRS signals in the lateral temporal lobe around T3/4 and T5/6 to have the following characteristics. First, the EEG signal is expected to reflect direct hippocampal neural activity as well as that propagated to neighboring regions in the lateral temporal lobes including T3/4 and T5/6. Second, albeit unlikely that fNIRS would detect the haemodynamic changes that are evoked by neural activity in the hippocampus, we expect that fNIRS can detect haemodynamic responses that reflect the early propagation of neural activity in the ipsilateral temporal lobe. In addition, fNIRS is also expected to detect haemodynamic responses that are evoked by neural activity propagated to the contralateral temporal lobes. In this case, laterality determination is only possible when neural activation is dominant in the ipsilateral temporal lobe temporally or spatially.

However, such expectations may not always be met for scalp EEG measurements. In cases of MTLE with severe hippocampal sclerosis, signs of seizure onset may not always be propagated to the ipsilateral scalp, rather they may be propagated to the contralateral scalp a few seconds later, resulting in false lateralization in up to 10% of cases (Chung et al., 1991). Thus, it would be preferable to assume that spatially and temporally propagated signals over the scalp are inevitable and we should extract meaningful parameters from such signals.

Hence, in this study, in order to extract the signals that are expected to reflect the early period of seizure onset, we focused our analyses on 0 to 20 s from the beginning of oxy-Hb increase. In so doing, we are likely to avoid the influence of propagated signals that spread bilaterally as a seizure progresses.

Although haemodynamic signals may not reach their maximum during this time range, there is a higher likelihood that the early phase haemodynamic signal changes are more closely related to neural activation in the ictal onset zone. On the other hand, haemodynamic signal at the seizure's peak (usually occurs at approximately 1 min from onset) is likely to be contaminated due to seizure propagation. Indeed, when comparing oxyHb increase for 0-20 s after the fNIRS onset in both hemispheres, we detected higher values on the ipsilateral side than on the contralateral side in all cases.

Interestingly, when we revisited data by Nguyen et al. (2012), there were conversions of laterality indices between 0-20 s and after 20s in one out of three cases. In all cases, the laterality indices in the earlier periods were consistent to the epileptic focus sides. This observation further validates the relevance of focusing on the early phase hemodynamic changes.

Based on these findings, we propose that the oxyHb signal average 0-20 s after fNIRS-defined seizure onset is an appropriate parameter for determining epileptic focus side, and would serve as a valuable parameter for presurgical determination of resection side.

4.2. Video-EEG/fNIRS Measurement Technique

Technical prerequisites for long-term monitoring were a short set-up time for the measurement system especially for probe setting, comfortableness during measurement,

forgivingness of movement involved in minimum everyday life operations that are still involved in bedside monitoring, and storage and processing of large-scale data. The ictal fNIRS/EEG simultaneous measurement system in the current experiment solved these technical issues and enabled successful simultaneous monitoring of epileptic patients from morning till night for up to four days, while keeping the mental and physical burdens of patients to a minimum and thus maintaining their quality of life. Moreover, the current system enables simultaneous acquisition of electrophysiological and haemodynamic signals to provide a wider perspective of the symptoms associated with spontaneous seizure.

4.3. Relationship Between EEG and fNIRS Onsets

In the present study, simultaneous long-term ictal fNIRS/EEG monitoring for 8-16 hours per day led to the successful detection of spontaneous seizures in four out of six cases. The earliest detection of spontaneous seizure was at 2 h from the beginning of ictal fNIRS/EEG monitoring, which would have been difficult to detect using conventional simultaneous fNIRS/EEG monitoring that allows continuous use for only 2 h (Nguyen et al., 2012).

The present simultaneous ictal fNIRS/EEG system revealed the relationship between electrophysiological and haemodynamic responses associated with epileptic seizures, which could contribute to the enablement of estimating the epileptic focus side. In time frames adjacent to EEG epileptic onset, we observed substantial oxy-Hb signal increases, which were considered to be evoked by increased neuronal activity at the epileptic focus. Analyses of fNIRS-based ictal oxy-Hb signals 30 s before and after EEG onset enabled detection of haemodynamic response as increased oxy-Hb signal

reflecting neuronal activity on the epileptic focus side, but not on the contralateral side, with spread neural activity.

In the present study, we detected fNIRS-defined onset earlier than EEG-defined onset, detected as theta bursts, in three out of four cases. A similar tendency was observed in a previous fNIRS/EEG study (Nguyen et al., 2012)

In the three cases where laterality was determined with EEG measurements, fNIRS analyses successfully determined the epileptic focus on the same side. In the fourth case, where EEG measurement failed to determine laterality, fNIRS analyses enabled an accurate estimate of the focus side, which was eventually confirmed during the amygdalo-hippocampectomy. Taken together, the current findings suggest that haemodynamic response as measured using fNIRS can well estimate the epileptic focus side in cases of mesial temporal lobe epilepsy.

In the fourth case, although visual inspection allowed the detection of fNIRS onset prior to the theta burst, our algorithm based on baseline SD failed to detect the putative fNIRS onset due to noise in baseline periods.

In this case, the baseline period included a large noise spike, immediately after which oxyHb started to increase. Nevertheless, the spike noise contributed to an increased SD, and thus also to an increased threshold for fNIRS onset. This resulted in a delay of fNIRS onset detection. Based on such observations, we estimate that the true fNIRS onset in this case was prior to the EEG onset. Although the current method using baseline SD provides an objective measure for determining seizure onset using fNIRS, it is not quite sufficiently robust against noisy data, which can occur in actual clinical situations.

The physiological mechanism underlying observed behaviors of fNIRS and EEG signals is an important topic to explore; the limited resources available to the current study did not allow further examination. Deeper studies with more extensive cases are necessary to elucidate the relationship between electrophysiological and haemodynamic signals evoked by neural activity associated with MTLE.

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ENCLOSURE

FIGURE 1.

FIGURE 2

FIGURE 3

CURRICULUM VITAE

PERSONAL DATA

N a m e	:	Rizki Edmi Edison
Place and Date of Birth	:	Padang, December 7, 1984
Marital Status	:	Married

EDUCATION

1. BS in Medicine	:	Faculty of Medice, Andalas University, August 2003 - March 2008
2. Medical Doctor	:	Faculty of Medicine, Andalas University, March 2008 - March 2010
3. PhD	:	Department of Neuro Surgery, Graduate School of Medicine, Jichi Medical University, Japan, April 2010 – March 2014.

WORKING EXPERIENCES

1. Head of Laboratory , Laboratory of Neuroscience, Center for Medical Physics and Research Cancer, CTech Lab Edwar Technology, May 2014 – present.
2. Consultant of Biophysiciologi, Faculty of Physiology Hamka University, May 2014 – present
3. Research Assitant, Department of Neuro Surgery , Jichi Medical University, Japan, 2011 – 2013.
4. News Prsenter, Padang TV, 2008

ORGANIZATIONS

1. Members of Board of Neuroscience Research, Muhammadiyah, 2013 – present

2. Chairman of Indonesian Student Association, Tochigi Prefecture, Japan, 2012-2013.
3. Board of Education, Indonesian Student Association of Japan, Kanto Area, 2011 – 2012.
4. Vice Chairman, Young Doctor Communication, Andalas University, 2009-2010.
5. Chairman od Board of Internal, BEM Faculty of Medicine, 2005-2006.

ACADEMIC EXPERIENCES

1. Keynote Speaker, Seminar Nasional Engineering Islamic Fair Fakultas Teknik Universitas Andalas, Indonesia, September 2014 (Keynote Speaker)
2. Keynote Speaker, Medical Talk Show Fakultas Kedokteran dan Kesehatan Universitas Muhammadiyah Jakarta, Indonesia, September 2014 (Keynote Speaker)
3. Keynote Speaker, 2nd International Young Scientist Conference on Analytical Sciences, Indonesia, September 2013 (Keynote Speaker)

   Title: Investigation of Epileptic Focus by Near-Infrared Spectroscopy
4. Presenter, 1st National Conference of Neuroscience Indonesia, Indonesia, September 2013

   Title: Application of Near-Infrared Spectroscopy for Presurgical Evaluation of Epilepsy
5. Presenter, 30th International Congress of Epilepsy, Canada, June 2013

   Title: Focus Diagnosis of Mesial Temporal Lobe Epilepsy on Spontaneous Seizure by Optical Topography
6. Presenter, 36th Annual Meeting of Epilepsy Surgery Society of Japan, Japan, January 2013

   Title: Differential Diagnosis of Epilepsy by Using Optical Topography

7. Keynote Speaker, 33rd Tochigi Epilepsy Research Society, Japan, July 2012

   Title: Musicogenic Epilepsy as Differential Diagnosis of Syncope

8. Presenter, 14th Japan Human Brain Mapping Association Japan, Japan, July 2012

   Title: Application of OT and DDOT for Epileptic Focus Diagnosis

9. Presenter, 35th Annual Meeting of Epilepsy Surgery Society, Japan, January 2012

   Title: Usefulness of DDOT to Find the Focus of Epilepsy

10. Presenter, 5th Annual Meeting of Epilepsy Japan Society, Japan, June 2012

    Title: Neurally Mediated Syncope as Differential Diagnosis of Epilepsy

INTERNATIONAL PUBLICATION

1. Determining of Epileptic Focus Side in Mesial Temporal Lobe Epilepsy using Long-Term Non-Invasive fNIRS/EEG Monitoring for Presurgical Evaluation Neurophotonics, 2014
2. Direct Cortical Hemodynamic Mapping of Somatotopy of Pig Nostril Sensation by Functional Near-Infrared Cortical Imaging (fNCI) , Neuroimage, 2013