Functional Brain Signals: A photon counting system for brain activity monitoring

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Abstract – **A simplified *in vivo* near infrared spectroscopy (NIRS) system for functional brain analysis and a protocol for the study of visual evoked potentials in the human brain is presented. A novel NIRS system bases on a simple photon counting technique using a CW light source (laser diode at 780 nm), fibre optodes delivering light to the subject and from the subject to detector, a photomultiplier tube (PMT) for high infra-red (IR) response and the 800 MHz Gated Photon Counter/multichannel scaler (MCS) for data acquisition. A chequerboard stimulus was used to elicit a response signal from the visual cortex. This photon signal arising from the cortical systems of the brain was processed to detect features indicative of the neural processing systems involved.**

Keywords – **NIR spectroscopy, brain signals, visual evoked potentials, photon counting, biomedical signal processing.**

I INTRODUCTION

NIRS systems have been applied in human brain mapping in an attempt to find a cost-effective, compact alternative with better resolution parameters to existing instruments such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), optical imaging (OI), magnetoencephalography and electro-encephalography. Each technique offers information about functional brain activity but with various tradeoffs with respect to size, spatial and temporal resolution, signal etiology, practicality and cost. There is currently no system that meets all these requirements, however out of all the above mentioned methods, optical imaging demonstrates the most dramatic advances in brain mapping. From a non-invasive perspective it is near infrared imaging in particular that holds greatest promise [1] although many problems still remain with this technique. For example, there is no standard optode positioning scheme as there is in electroencephalography [2-3]. Also an incomplete knowledge on how such photons propagate through the human head makes it difficult to calibrate the system and to make a quantitative measurement. On the other hand in addition to the previously mentioned advantages, it is an optical system, which offers the possibility of simultaneous and non-invasive *safe* measurement of neuronal and vascular signals in the brain with temporal resolution up to 1ms [4, 5, 8, 9].

In this paper we discus the design and testing of a system for acquiring such signals from the adult brain. Whereby most NIRS systems use conventional light detection techniques based on lock-in detection and other analog processing techniques, the technique here is based on a photon-counting paradigm. Photon-counting systems have the advantage of allowing a very detailed analysis of the optical signals emanating from the tissue under inspection. They also have the advantage of offering the highest possible detection sensitivity to ultra low light levels. Section II of this paper discusses the current state of the area while Section III describes the design of our system. Sections IV and V discuss and present some of the physiological signals we have been able to extract based on evoked potentials as commonly studied in electroencephalography.

II EXISTING OPTICAL IMAGING SYSTEMS

Optical imaging of the human brain measures intrinsic activity-related changes in tissue reflectance. These arise due to functional physiological changes, such as blood volume, haemoglobin oxymetry and light scattering properties. They offer a distinct advantage over extrinsic signal imaging such as dye imaging which may cause photo-toxicity. In particular at longer wavelengths optical techniques become non-invasive. Optical techniques are also particularly suited to chronic studies and recently ambulatory monitoring has been reported. In particular the interrogation of biological tissue with near-infrared light (700-1300nm) allows non-invasive measurement of biochemical processes. Specifically the absorption of compounds such as oxy- and deoxyhaemoglobin and cytochrome oxidase allow measures of metabolic activity to be made. This is the basis of in vivo near-infrared spectroscopy (ivNIRS) [2].

Interest in this technique has rapidly expanded over the last decade as increasingly non-invasive, non-ionising, safe techniques have been sought for clinical applications. Currently the main clinical applications include monitoring brain oxygenation changes in neonates [6] and during surgery in adults. It has also been realised by researchers in the neurosciences that this technique can be expanded to provide functional analysis of brain function to a remarkable degree. For example, through the use of multiple source-detector sets, images of cortical brain activity can be acquired through tomographic methods (termed *diffuse optical tomography*). This method produces information closely related to those acquired by the more expensive and involved functional magnetic resonance imaging (fMRI) method.

This technology has huge potential for in-depth noninvasive functional brain analysis particularly outside the clinical medicine environment where electromagnetic-based techniques (such as EEG) are the only techniques generally available. This is due to the fact that such techniques are non-invasive and relatively inexpensive. In order to realise the potential of optical techniques there are several advances that must be made. One of the most significant is the acquisition and investigation of the fast optical evoked response. Current *iv*NIRS systems are developed with the aim of measuring slow biochemical changes such as those associated with vascular dynamics. Such signals have a time course of anything from 10s to 60s and usually represent changes in biochemical processes indirectly associated with neuronal firing. It is now thought that on shorter time scales (ms) optical signals associated directly with neural activity could be acquired with appropriately designed *iv*NIRS systems. The terms *optical evoked responses* (OER) or more accurately the *fast optical evoked response* have been used to refer to these signals. Current systems have been unable to accurately and robustly detect this signal. This is because *iv*NIR data are noisy, and the OERs generate only a tiny fraction of the signal (I/I_0 = 0.05 %, [8]), with the remainder generated by noise processes of various sorts (muscular activation, heartbeat, shot noise, neuronal activity not of interest). We feel therefore that a photon counting technique can potentially recover all the signal information necessary to recover OERs reliably as well as more conventional haemodynamic responses. In the next section we describe our photon counting system before presenting the results of some preliminary experiments.

III PHOTON COUNTING TECHNIQUE

Previous work done in the area of NIRS systems has concentrated on using frequency domain techniques to obtain information on absorption and scattering of light. We describe here single photon detection techniques, which maximise the sensitivity of scattered light measurement and probe directly the time variation of extremely weak scattered light signals. A similar strategy is being investigated by the Biophysics research group at LANL, USA [9]. This involves tomographic reconstruction using first light, or more generally using the impulse-response measured with a temporal precision of 10^{-11} s, this is a promising technique although signal-to-noise levels are an issue and the technique is expensive.

A CW excitation photon-counting apparatus for measurement of ms-scale variation in optical scattering in response to vascular and neural activity related to visual function is reported here based on fast timing techniques [10]. A CW laser diode with wavelength 780nm and optical power 5mW is used as a light source. An 800 MHz Gated Photon Counter / Multiscaler is used for data acquisition (see Figure 1). It contains ultra fast discriminators for the counting and gating inputs, two fast 32 bit counters, memory for storing the results, the timing and control logic and the PC bus interface (see Figure 2).

Figure 1: Gated Photon Counter / Multiscaler, PMS400 [*After*: Becker&Hickl GmbH].

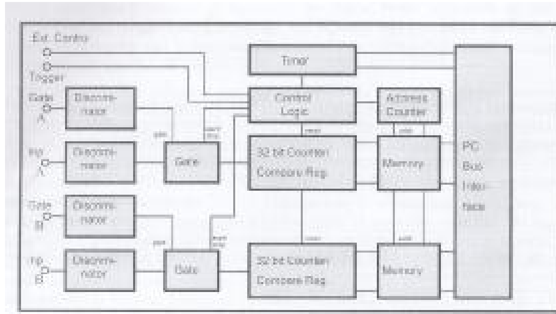

Figure 2: Architecture of the PMS400 [*After*: Becker&Hickl GmbH].

The most common detectors for photon counting are photomultiplier tubes. A photodetector comprising photomultiplier tube with S20 photocathode for high IR responsivity and a high speed amplifier-discriminator of Electron Tubes Ltd. was chosen. A spectral response of photocathode is shown in Figure 3.

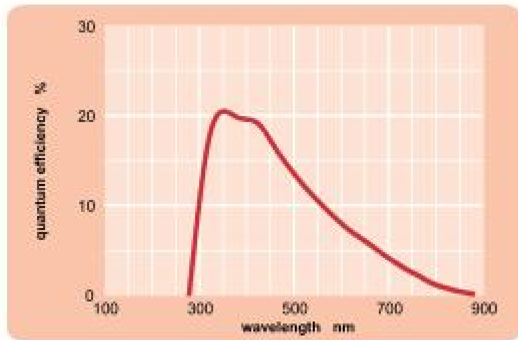

Figure 3: Photocathode spectral response [After: Electron Tubes Ltd.].

Photon counting is done by counting the detector pulses produced by the PMT within consecutive time intervals by a counter/timer combination using the MCS. It has the advantage that it is insensitive to low frequency noise and there is also no baseline drift due to spurious currents in the PMT or in the PMT voltage divider [10]. In addition to these advantages, time-resolved technique improves localisation and characterisation of inhomogenities of the living tissue, which allows better spatial resolution.

Two commercial multimode silica optical fibre (core diameter 0.6 mm) patch cords are used as optodes for light delivery from the laser diode to the subject and for light delivery from the subject to the photodetector. Optodes are positioned in the area of the visual cortex using an elastic headband allowing flexibility in changing the fibre position. The distance between the source and detector optodes is 30mm as is conventional for these studies[4].

Currently one of the few disadvantages of our described system is the requirement of a fairly dark environment because of the extreme sensitivity of the detector system. In the next section we describe the results of utilising this device for measuring evoked responses as commonly conducted in electroencephalography studies.

IV PROTOCOL FOR MEASUREMENT OF VISUAL EVOKED RESPONSES

In this study an experiment to measure the optical intensity changes associated with activation of the visual cortex is described. Such signals are referred to as visual evoked responses. In clinical electroencephalography there are several standard paradigms for such studies. The protocol used here is termed the *binocular full-field pattern shift reversal visual evoked response* [12].
The visual stimulus used here consists of a 6x6 black and white checkerboard with a red fixation-point in the centre of the pattern displayed on a flat-panel monitor at a distance of ~ 0.5 m from the subject. Reversal of this pattern on the screen elicits a transient neuronal signal at the visual cortex, which is usually picked up electrically. Here we look for such a signal optically as has been done recently by other researchers using analog optical techniques [5].

To monitor the associated slow haemodynamic changes in the brain, the following protocol was applied: flashing of the checkerboard with reversion rate 3Hz during 1min was interlaced with a 60s rest period. There were 6 flashing and 6 rest periods within a total time of 12 minutes.

The checkerboard protocol was synchronised with the MSC. Acquisition with the MSC was performed only on one channel. In this case of slow haemodynamic changes, triggering was used only once, to start acquisition.

An attempt to record fast brain responses was based on the known 'fast' response duration [4, 5]. From previous studies it is known that it occurs 100-300ms after the stimulus. Therefore, for that experiment the checkerboard is flashed at a frequency of 1Hz according to the timing diagram in Figure 4.

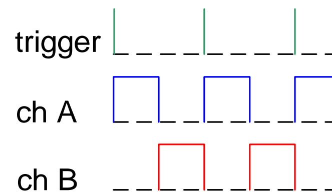

Figure 4: Protocol for data acquisition with MSC: trigger pulse from checkerboard during the fast optical response experiment.

This allows the recording of data after stimulus (with information) on the channel A during 500ms and during the next 500ms the signal without

stimulus (without information) was recorded onto channel B with the same duration. The checkerboard pattern is then reversed and the signal acquisition cycle repeats. This protocol allows subtraction of the signal with information of interest from the signal without any interesting information. In the next section we present some typical signals acquired using the above protocols.

V EXPERIMENTS

In this section some of the signals acquired using the protocols of Section IV are shown. Part (a) demonstrates the use of the system to measure blood flow changes induced by the cardiac cycle in the head. This signal is a photoplethysmograph (PPG) on cardiac time-scales akin to those used in clinical medicine for pulse wave velocity experiments [13]. In part (b) blood flow changes on long time scales in response to the checkerboard pattern reversal are described. Part (c) of this section describes a tentative effort to extract the elusive fast optical evoked response. The results presented here are preliminary and qualitative in nature.

(a) Measuring PPG

As a preliminary procedure to subsequent experiments, blood flow in the area of the visual cortex was measured with the developed system to check if these changes could be seen in real time. This signal is used to test if the optode placement is correctly positioned to pick up optical changes inside the skull. The dominant component is due to the heart, which causes changes in blood pressure and hence blood flow on a beat-by-beat basis. This signal is clearly evident in Figure 5 although there is a large slowly changing component also visible. Physiologists refer to this particular signal as the Mayer wave and its origins are as yet unclear.

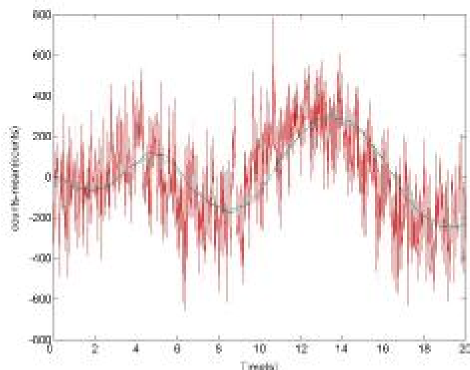

Figure 5: Measurement of the PPG in the visual cortex using present technique. The Mayer wave is also visible.

The successful acquisition of the PPG is a prerequisite for further experimentation, as it is an omnipresent signal acquired from inside the skull. An inability to extract this signal would suggest serious problems with the optical measurement system.

(b) Measuring slow visual evoked responses

The slow optical brain response was measured using the protocol described in subsection IV. The checkerboard was placed 0.5m from the subject. The software controlling the visual stimulus also controlled the triggering of the MSC and a signal in the area of the visual cortex was acquired (see Figure 6).

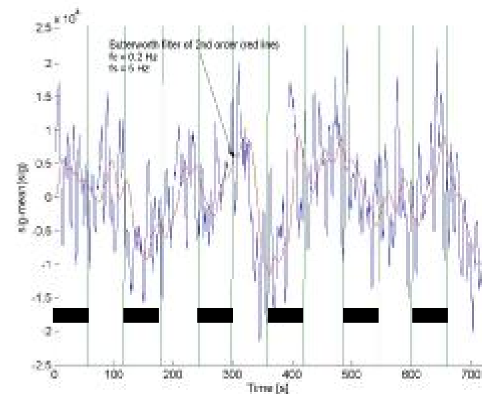

Figure 6: Slow vascular response of the brain in the result of visual stimulus.

The black bars indicate areas of changing visual stimulation while the periods in between illustrate periods of invariant stimulation. In this data a modulation of the optical intensity detected is clearly visible with as period commensurate with that of the rest / stimulation period (120 seconds). This is to be expected as the visual cortex is more active during periods of visual change resulting in an increased metabolic demand for oxygenated blood which manifests itself as an increase in blood flow in the cortex. It is this increased blood flow that is measured optically.

(c) Measuring fast visual evoked responses

As it was already mentioned, some preliminary attempts were made to capture the fast optical response of the human brain using the protocol described in subsection IV. The subject was placed in front of the flat-panel monitor for total time of around 23 minutes. Due to the very smnall size of the signal averaging was used to enhance the singal to noise ratio. In the results presented here 4000 trials were acquired and averaged to produce a final signal.

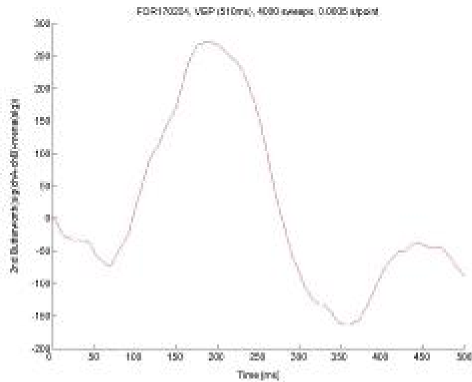

Figure 7: Fast optical response of the human brain as a result of the visual stimulus.

Figure 7 shows the final filtered signal (Butterworth filter, 2nd order). The signal clearly exhibits the features expected [5] for such a fast signal with a peak in optical intensity at around 200ms. Interestingly the electrical analogue of this signal which is called the visual evoked potential [12] is almost identical to the signal shown in above.

At this stage it is not possible to ascertain for certain that this is indeed the elusive fast optical signal and many more tests need to be done. While it could be argued that by definition the signal shown above is that fast optical response as elicited by the visual pattern we cannot say for certain that the photons measured here are in any way related to the neuronal firing and not due to some other associated physiological artifact. Regardless what is evident as a result of this experiment is that the photon counting apparatus we have put together for this experiment has the capabilities of very accurate optical measurement of photon flux changes in the active human cortex.

VI CONCLUSIONS

The development of appropriate apparatus and experiment protocols for the robust acquisition and measurement of both slow haemodynamic and fast optical responses is essential for ivNIRS to realise its potential for understanding brain function. It is our hypothesis that such robust techniques can be developed and applied to a variety of neuroscientific problems in much the same way as electrical evoked responses are in electroencephalography. The developed system described here proves the possibility of monitoring blood flow and heart rate in the visual cortex of the human head using a photon counting technique and provides a platform for the detection of signals on even shorter time scales and lower intensities. Our monitoring of the slow vascular response showed some interesting changes in blood flow but this was to be expected given that it is well known that such tasks elicit only changes in tissue oxygenation. The monitoring of tissue oxygenation as opposed to merely tissue perfusion requires a multiple wavelength system in order to separate out the two processes. We are currently working on extending this photon counting system to encompass this idea. As a first step, it was important to show that developed system is able to capture these changes. Measurement of fast optical response of the brain in the result of visual stimulus was done using simple signal processing and the obtained data are comparable with those, obtained by other authors. We are in the midst of testing the system much more comprehensively using a number of other experimental procedures as well as refining the instrumentation. It is hoped that soon we will be able to more robustly and rigorously acquire fine resolution optical signals associated with brain activity at a cortical-neuronal level.

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