UNIVERSITY OF CANBERRA

Development of an Objective Pain Assessment using Functional Near-Infrared Spectroscopy and Machine Learning

by

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ABSTRACT

Pain is a subjective experience, and no objective clinically available diagnosis test exists to assess it. In clinical practice, the most accepted and valid method is self-reports, this method relies on a patient's ability to communicate a self-assessment of pain. However, the absence of verbal (or writing) communication in some patients (also referred as non-verbal) is an obstacle to the evaluation of pain, which may derived in risk to death and under- or over-treatment. Patients with impaired communication, unconscious patients, infants, stroke survivors, the critically ill, and persons suffering from advance dementia are examples of vulnerable individuals who are unable to communicate. Therefore, the need for a reliable and objective pain assessment to assist medical practitioners in the diagnosis and management of pain.

Attempts to use neuroimaging and computational methods to identify pain in healthy humans have shown potential to aid the assessment of pain. Previous studies using functional Magnetic Resonance Imaging (fMRI), Electroencephalography (EEG) and Near-Infrared Spectroscopy (NIRS), to predict and identify patterns of noxious signals (e.g., heat, cold) from non-painful stimuli have proved the use of brain signals to retrieve pain information. These results show that pain recognition and classification is plausible using neuroimaging methods, also the results from these studies advocate for the use of machine learning techniques to predict human pain.

The objective of this PhD research is to investigate the use of functional NIRS (fNIRS) and machine learning techniques to objectively estimate the pain status of non-verbal patients. This PhD research also aims to expand previous studies by exploring the classification of fNIRS signals according to different types of thermal (cold and hot) pain and corresponding pain intensity (low and high) using machine learning models. In addition, another purpose of this PhD research is the identification of a potential *biomarker* of pain based on fNIRS.

Based on the literature reviewed, the methodology created in this PhD thesis consisted of data collection, data analysis and interpretation. This included designing a noxious stimulation procedure using the thermal test following the Quantitative Sensory Testing (QST) method to obtain the pain threshold and pain tolerance in eighteen ($n = 18$) volunteers while recording their haemodynamic activity using an fNIRS sys-

tem. This database was labelled according to their corresponding type of stimuli: low-cold, low-heat, high-cold, and high-heat. Then, from the fNIRS signals a total of 69 features were established, 9 features in time, 23 features in frequency, and 37 features in wavelet domain; these features represent different distinctive characteristics in each domain. The features were evaluated by five feature selection methods and ranked based on relevance to the task and redundancy according to: Information Gain (IG), Joint Mutual Information (JMI), Student's t-test (t-test), Chi-squared (X^2), and Fast Correlation Based Filter (FCBF). The feature rankings were used to train and test three classifiers separately, the Linear Discriminant Analysis (LDA), K-Nearest Neighbour (K-NN) (with $K = 1, 3, 5, 7, 9$), and Support Vector Machines (SVM) (linear, Gaussian, and polynomial kernels).

The results of the this PhD research proved the adequacy of the designed methodology. The stimulation paradigm showed a haemodynamic response in the primary somatosensory cortex (S1) and opposite to the hand of application, which was consistent with similar published literature. Most of the obtained features showed a normal distribution, while other presented a slightly positive skewed distribution; some features also showed high correlation among them, suggesting redundancy. Feature selection methods ranked the obtained features, showing that *timemax* (time to maximum amplitude) and *F7* (Fourier coefficient) were among the top ranked features. The classification models tested the significance of each ranking to classify the data in four types of noxious stimuli, these results showed that the best classifiers were 1-NN, the Gaussian SVM and the polynomial SVM. The highest accuracy (94.16%) was exhibited by the Gaussian SVM using the top 25 features ranked by (JMI), however, using only 13 features this classifier showed an accuracy of 89.44%. Therefore, this subset of 13 features was identified as probable *biomarker* of pain using fNIRS.

The major contributions of this PhD research can be summarized in five items: a) presenting the classification of four types of noxious stimuli, b) showing that pain threshold and pain tolerance from the QST could be used to obtain pain information from non-verbal patients, c) increasing generalization by taking measurements from different domain representations, d) presenting a comparison between feature selection methods and learning models, to obtain the best representation of the pain database, e) finding a subset of features to be defined as potential *biomarker* of pain using fNIRS.

This PhD research demonstrates the application of fNIRS in the development of a physiologically-based diagnosis of human pain that would benefit vulnerable patients who cannot self-report pain, and presents a set of features as possible *biomarker* of pain as measured by fNIRS. However, there is still further research need to develop a bedside monitor for the diagnosis of pain in clinical settings.

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LIST OF PUBLICATIONS

Some of the research leading to this thesis has appeared previously in the following publications.

Journal Articles

- **Raul Fernandez Rojas**, Xu Huang, Keng-Liang Ou: Toward a Functional Near-Infrared Spectroscopy-based Monitoring of Pain Assessment for Nonverbal Patients. – *Journal of Biomedical Optics*, **ERA A**, October 2017.
- **Raul Fernandez Rojas**, Xu Huang, Keng-Liang Ou: Region of Interest Detection and Evaluation in Functional Near Infrared Spectroscopy. – *Journal of Near Infrared Spectroscopy*, **ERA B**, October 2016.
- **Raul Fernandez Rojas**, Xu Huang, Keng-Liang Ou: Spatiotemporal Analysis of Brain Activity Response using Near Infrared Spectroscopy. – *International Journal of Pharma Medicine and Biological Sciences*, March 2016.
- **Raul Fernandez Rojas**, Xu Huang, Keng-Liang Ou, Dat Tran, Sheikh Islam: Analysis of Pain Hemodynamic Response using Near-Infrared Spectroscopy (NIRS). – *International Journal of Multimedia and its Applications*, **ERA C**, July 2015.

Refereed Conference Papers

- **Raul Fernandez Rojas**, Xu Huang, Julio Romero, Keng-Liang Ou: fNIRS Approach to Pain Assessment for Non-verbal Patients. – *International Conference on Neural Information Processing (ICONIP)*, **ERA A**, November 2017, Guangzhou, China.
- Xu Huang, **Raul Fernandez Rojas**, Keng-Liang Ou, Sheikh Md Rabiul: A Computational Investigation of an Active Region in Brain Network Based on Stimulations with Near-Infrared Spectroscopy. – *International Conference on*

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- **Raul Fernandez Rojas**, Xu Huang, Jesus Hernandez-Juarez, Keng-Liang Ou: Physiological fluctuations show frequency-specific networks in fNIRS signals during resting state. – *Engineering in Medicine and Biology Society (EMBC), 39th Annual International Conference of the IEEE*, **ERA A**, June 2017, Jeju Island, South Korea.

- **Raul Fernandez Rojas**, Xu Huang, Keng-Liang Ou, Jesus Hernandez-Juarez: Exploring the use of optical flow for the study of functional NIRS signals. – *SPIE Medical Imaging*, February 2017, Orlando Florida, USA.

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- Sheikh Md Rabiul, Xu Huang, Keng Liang Ou, **Raul Fernandez Rojas**, Hongyan Cui: Novel Information Processing for Image De-noising Based on Sparse Basis. – *International Conference on Neural Information Processing (ICONIP)*, **ERA A**, November 2015, Istanbul, Turkey.

LIST OF ACRONYMS

ACC Anterior Cingulate Cortex

BCI Brain Computer Interface

BOLD Blood Oxygen-Level Dependent

CNS Central Nervous System

CPT Cold Pressor Test

CWT Continuous Wavelet Transform

DFT Discrete Fourier Transform

DWT Discrete Wavelet Transform

EEG Electroencephalography

FCBF Fast Correlation Based Filter

fMRI functional Magnetic Resonance Imaging

FN False Negative

fNIRS functional NIRS

FP False Positive

FS Feature Selection

HbO Oxygenated Haemoglobin

HbR Deoxygenated Haemoglobin

Hb Total Haemoglobin

HIT Hot-water Immersion Test

ICA Independent Component Analysis

IG Information Gain

JMI Joint Mutual Information

***K*-NN** K-Nearest Neighbour

LDA Linear Discriminant Analysis

LFO Low Frequency Oscillations

LOOCV Leave-One-Out Cross Validation

MEG Magnetoencephalography

MI Mutual Information

ML Machine Learning

NIR Near Infrared

NIRS Near-Infrared Spectroscopy

OF Optical Flow

PCA Principal Component Analysis

PET Positron Emission Tomography

QST Quantitative Sensory Testing

ROI Region of Interest

S1 Primary Somatosensory Cortex

S2 Secondary Somatosensory Cortex

SDS Source-Detector Separation

SVM Support Vector Machines

TN True Negative

TP True Positive

***t*-test** Student's t-test

VLFO Very Low Frequency Oscillations

X^2 Chi-squared