STRESS RESPONSE INDEX FOR ADVERSE CHILDHOOD EXPERIENCE BASED ON FUSION OF HYPOTHALAMUS PITUITARY ADRENOCORTICOL AND AUTONOMIC NERVOUS SYSTEM BIOMARKERS

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ABSTRACT

Early life exposure to stress such as adverse childhood experiences has been suggested to cause changes in physiological processes and alteration in stress response magnitude which might have significant impact on health later in life. For this reason, detection of this altered stress response can be used as an indicator for future health. To date, there is no study that utilized this information to indicate future health. In order to detect the altered stress response, biomarkers that represent both Autonomic Nervous System (ANS) and Hypothalamic-Pituitary-Adrenocorticol (HPA) is proposed. Among the available biomarkers, Heart Rate Variability (HRV) has been proven as a powerful biomarker that represents ANS. Meanwhile, salivary cortisol has been suggested as a biomarker that reflects the HPA. Even though many studies used multiple biomarkers to measure the stress response, the results for each biomarker were analysed separately. Therefore, this study fuses the biomarker that represents both ANS and HPA as a single measure, proposes a new method to classify the stress response based on adverse childhood experience in the form of stress response index as a future health indicator. Electrocardiograph, blood pressure, pulse rate and Salivary Cortisol (SCort) were collected from 23 participants, 12 participants who had adverse childhood experience while the remaining 11 act as the control group. The recording session was done during a Paced Auditory Serial Addition Test (PASAT). HRV features were then extracted from the electrocardiograph (ECG) using time, frequency, time-frequency analysis, and wavelet transform. Following this, genetic algorithm was implemented to select a subset of 12 HRV features from 83 features. Next, the selected HRV features were combined with other biomarkers using parallel and serial fusion for performance comparison. Using Support Vector Machine (SVM), results showed that fused feature of the parallel fusion, so-called Euclidean distance (e_d), demonstrated the highest performance with 80.0% accuracy, 83.3% sensitivity and 78.3% specificity. Finally, the fused feature of the Euclidean distance was fed into SVM in order to model the stress response index as an indicator for future health. This index was validated using all samples and achieved 91.3% accuracy. From this study, a new method based on HRV-SCort biomarker using Euclidean distance and SVM named as e_d-SVM was proven to be an effective method to classify the stress response and could further be used to model a stress response index. This index can then be benefited as an indicator for future health to improve the health care management in adulthood.

ABSTRAK

Pendedahan terhadap tekanan di awal usia seperti pengalaman buruk semasa zaman kanak-kanak telah dicadangkan mampu mengubah proses fisiologi dan magnitud tindak balas tekanan yang akan memberi kesan kepada kesihatan di kemudian hari. Pengesanan pada perubahan tindak balas tekanan ini boleh digunakan sebagai indikator kesihatan masa hadapan. Sehingga kini, tiada lagi kajian yang menggunakan maklumat ini sebagai indikator kesihatan pada masa hadapan. Untuk mengesan tindak balas tekanan ini, penanda biologi yang mewakili Sistem Saraf Autonomi (ANS) dan hypothalamic-pituitari-Adrenocorticol (HPA) telah dicadangkan. Dalam kebanyakan penanda biologi yang sedia ada, kadar variasi jantung (HRV) telah terbukti sebagai penanda biologi yang baik bagi ANS. Sementara kortisol saliva pula telah dicadangkan sebagai penanda biologi yang memaparkan HPA. Walaupun banyak kajian menggunakan beberapa penanda biologi untuk mengukur tindak balas tekanan, keputusan untuk setiap penanda biologi telah dianalisis secara berasingan. Oleh itu, kajian ini menggabungkan penanda biologi yang mewakili ANS dan HPA sebagai satu pengukuran induk sebagai pendekatan baru bagi mengelaskan tindak balas tekanan berdasarkan pengalaman buruk zaman kanak-kanak untuk membina indeks tindak balas tekanan sebagai indikator kesihatan masa depan. Elektrokardiograf (ECG), tekanan darah, kadar denyutan dan kortisol saliva dikumpul dari 23 peserta, 12 peserta yang mempunyai pengalaman pahit semasa zaman kanak-kanak dan 11 peserta bertindak sebagai kumpulan kawalan. Sesi rakaman dijalankan semasa Ujian Auditori Penambahan Bersiri (PASAT). Ciri-ciri HRV kemudiannya diekstrak dari ECG dengan menggunakan analisis masa, frekuensi, masa-frekuensi, dan transfomasi wavelet. Algoritma genetik kemudiannya diimplimentasi untuk memilih 12 subset ciri HRV daripada 83 ciri. Ciri HRV yang dipilih kemudiannya digabungkan dengan penanda biologi lain menggunakan kaedah gabungan selari dan bersiri untuk perbandingan prestasi. Dengan menggunakan Mesin Vektor Sokongan (SVM), keputusan menunjukkan gabungan ciri yang menggunakan kaedah gabungan selari, juga dikenali sebagai jarak Euclidean (e_d) menunjukkan prestasi tertinggi dengan ketepatan 80.0%, kepekaan 83.3% dan kekhususan 78.3%. Akhir sekali, gabungan ciri dengan kaedah jarak Euclidean kemudiannya dimasukkan ke dalam SVM untuk menghasilkan indeks tindak balas tekanan sebagai indikator kesihatan masa hadapan. Indeks ini disahkan dengan menggunakan semua sampel dan mencapai ketepatan 91.3%. Daripada kajian ini, satu kaedah baru berdasarkan penanda biologi HRV-SCort dengan menggunakan kaedah jarak Euclidean dan SVM yang dikenali sebagai e_d-SVM terbukti berkesan dalam mengklasifikasikan tindak balas tekanan dan seterusnya digunakan untuk menghasilkan indeks tindak balas tekanan. Indeks ini kemudiannya boleh digunakan sebagai indikator kesihatan pda masa hadapan bagi menambah baik pengurusan penjagaan kesihatan semasa dewasa.

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LIST OF SYMBOLS

$\boldsymbol{b}$	-	Blood Pressure Feature Vector
$\boldsymbol{c}$	-	Combination of HRV, BP and PR Feature Vector
$\boldsymbol{c}$	-	Salivary Cortisol Feature Vector
C_p	-	Cross over probability
E_c	-	Elite Children
e_d	-	Euclidean Distance
E_r	-	Classification error
f_e	-	Parallel Fusion
f_s	-	Serial Fusion
$\boldsymbol{h}$	-	HRV Feature Vector
i	-	Imaginary Unit
k	-	Number of *k* for *k*-Nearest Neighbor
k_l	-	Linear kernel
M_p	-	Mutation probability
N	-	Total window length
N_5	-	5 minutes window lenght
$\boldsymbol{p}$	-	Pulse Rate Feature Vector
p_A	-	AR model order
RR	-	Normal-to-Normal time interval
S	-	Sample
Y_D	-	Maximum of the sample density distribution
β	-	MBD kernel parameter
σ	-	Radial Basis Function (RBF) Scaling Factor
ψ	-	Wavelet family function

LIST OF ABBREVIATIONS

A	-	Approximation coefficient
Acc	-	Accuracy
ACTH	-	Adrenocorticotropin
ANS	-	Autonomic Nervous System
ApEn	-	Approximate entropy
AR	-	Autoregressive
BP	-	Blood pressure
BVP	-	Blood volume pulse
C-DIS-IV	-	Computerized Diagnostic Interview Schedule IV
CNS	-	Central Nervous System
Cort	-	Cortisol
CRH	-	Corticotrophin-Releasing Hormone
CTQ	-	Childhood traumatic questionnaire
CWD	-	Choi William Distribution
CWT	-	Continuous Wavelet Transform
D	-	Detail coefficient
db8	-	Eight-order Daubechies mother Wavelet
DWT	-	Discrete Wavelet transform
E	-	Energy
ECG	-	Electrocardiogram
EEG	-	Electroencephalogram
EMG	-	Electromyogram
E_r	-	Error rate
FA	-	Frequency domain analysis
FFT	-	Fast Fourier Transform
FitFunc	-	Fitness Function
FN	-	False negative

FP	-	False positive
FPE	-	Final prediction error
Fs	-	Sampling Frequency
GA	-	Genetic algorithm
GSR	-	Galvanic skin response
HF	-	High Frequency
HFnu	-	Normalized unit of high frequency
HPA	-	Hypothalamus Pituitary Adrenocorticol
HR	-	Heart Rate
HRV	-	Heart Rate Variability
HTI	-	Heart Rate Variability Triangular Index
IHD	-	Ischemic Heart Disease
kNN	-	k-Nearest Neighbor
Kur	-	Kurtosis
LF	-	Low Frequency
LFM	-	Low Frequency Modulation
LFnu	-	Normalized unit of Low Frequency
M	-	Mean
MBD	-	Modified-B Distribution
NB	-	Naive Bayes
PASAT	-	Paced Auditory Serial Addition Test
PD	-	Pupil Diameter
PNS	-	Parasympathetic Nervous System
PR	-	Pulse rate
PSD	-	Power Spectral Density
RBF	-	Radial Basis Function
Resp	-	Respiration rate
RIS	-	Rissanen’s minimum description length
RMSSD	-	Root Mean Square of Standard Deviation
ROC	-	Receiver Operating Characteristic
RO	-	Research objective
SampEn	-	Sample Entropy
SC	-	Skin conductance
SCort	-	Salivary Cortisol

SD	-	Standard Deviation
SDNN	-	Standard deviation of N-N interval
Sen	-	Sensitivity
Skw	-	Skewness
SNS	-	Sympathetic Nervous System
SP	-	Spectrogram
Spe	-	Specificity
SPWVD	-	Smoothed Wigner Ville Distribution
SRi	-	Stress Response Index
ST	-	Skin Temperature
STFT	-	Short Time Fourier Transform
SV	-	Support vector
SVM	-	Support vector machine
TA	-	Time domain analysis
TF	-	Time Frequency
TFD	-	Time Frequency Distribution
TFSA	-	Time Frequency Signal Analysis
TN	-	True negative
TP	-	Total Power
VLF	-	Very Low Frequency
WL	-	Wavelet
WLT	-	Wavelet transform
WVD	-	Wigner Ville Distribution

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CHAPTER 1

INTRODUCTION

1.1 Background of the Research

Stress is an individual's adaptive process to external and internal challenges that is regulated on the systemic and cellular level. In the resistance stage, stress heightens awareness, increases mental alertness, and leads to superior cognitive and behavioral performance such as seen in sports. However, stress in the long run will enter its exhaustion stage and could eventually cause exhaustion of hormonal, cardiovascular, neural and muscular system due to insufficient time for recovery and repair (Rice, 2012). In addition, stress has been proven to be one of the main risk factor for serious illnesses and lead to mortality (Schneiderman, Ironson and Siegel, 2005). Due to the significant impact of stress on health, the study of stress with its various modalities has drawn the attention of several researchers. For example, the effects of stress and its relationship with certain diseases have been widely discussed, and a number of treatments have been proposed (Rice, 2012; Schneiderman, Ironson and Siegel, 2005).

When the body is under stress, there are two primary systems that are particularly involved in adapting to the situation which are the Autonomic Nervous System (ANS) and the Hypothalamus Pituitary Adrenocorticol (HPA) axis (Applegate, 1995; Michels *et al.*, 2013b). In times of stress, basically, ANS will increase heart rate (HR), (blood pressure) BP and breathing rate (Applegate, 1995). Heart Rate Variability (HRV), a signal derived for electrocardiograph (ECG) allows a much more accurate and detailed determination of the functional regulatory characteristics of the ANS than simple HR and BP alone. For this reason, HRV is recognized as a quantitative biomarker of the ANS (Task Force, 1996) and thus as a powerful biomarker of psychological stress (Acharya *et al.*, 2006; Allen *et al.*, 2014; Thayer *et al.*, 2012). Meanwhile, the second body system that activates upon stress, HPA, stimulates the adrenal cortex to increase the cortisol secretion (Michels *et al.*, 2013a; Michels *et al.*, 2013b; Nevid, Rathus and Greene, 2011). As HPA plays a significant role in the stress response, the measurement of the cortisol level is regarded as a biomarker in stress related studies. It has been found that the salivary cortisol concentrations is closely correlated to the serum cortisol concentration and thus it has been suggested as a possible biomarker that reflects the HPA system (Hamer *et al.*, 2010; Nomura *et al.*, 2009).

The detection and classification of stress is another research area that has become popular recently (Soman, Sathiya and Suganti, 2014; Sharma and Gedeon, 2012; Widjaja *et al.*, 2013; Wijsman *et al.*, 2013; Zhai and Barreto, 2006). Results and innovations that spring from such studies are very important in providing information by which accurate and reliable treatment can be given to patients. Apart from this, the results can be also used for the development of an early detection tool for certain diseases. Stress classification can be a big challenge since certain biomarkers are too complex to be processed such as, HRV. However, this complex biomarker has been proven able to represent important information of the heart as well as autonomic function in responding to the stress (Acharya *et al.*, 2006; Allen *et al.*, 2014; Task Force, 1996; Thayer *et al.*, 2012). Throughout the years, the method of processing this signal has been improved to a satisfying stage. However, as the health problems grow rapidly, the demand of more advanced treatment, diagnosis as well as health monitoring has increased. These demands lead to the investigation and development of a new processing method for specific application, in this case, stress classification for the development of a health indicator and potentially may provide better health care.

In this study, HRV which was derived from ECG has been studied as one particular biomarker in investigating stress response. Other than ECG, BP, PR and salivary cortisol (SCort) is also studied. The following section outlines the problem statement that led to the present work. This is followed by the objectives, scopes, and finally the contributions of this study.

1.2 Problem Statement

Early life exposure to stress has been suggested to be predictive of a range of health outcomes (Anda *et al.*, 1993; Felitti *et al.*, 1998). Reports spring from the area of disease control and prevention linking early life adversity to a wide range of psychological and physical health outcomes such as alcohol addiction, obesity, depression, smoking, use of substance, sexual behavior problem (Anda *et al.*, 2006) and also serious illnesses such as cardiovascular disease (Batten *et al.*, 2004; Dong *et al.*, 2004) depression (Batten *et al.*, 2004; Danese *et al.*, 2009; Kendall-Tackett, 2000), irritable bowel syndrome (Kendall-Tackett, 2000) as well as cancer (Jacobs and Bovasso, 2000). Motivated from these findings, recent work in the area of childhood trauma discovered that adverse childhood exposure might cause changes in physiological processes such as cardiovascular stress reactivity. For example, individuals with a history of one or more significant adverse events earlier in their lives showed altered cortisol and heart rate responses to acute psychological stress (Lovallo *et al.*, 2012; Lovallo, 2013). Children from aggressive family environments have also been shown to have altered cardiovascular reactivity to stress task (Luecken and Roubinov, 2012). These evidences suggest that stress reactivity is determined through events occurring at quite an early age, and that exposure to stress can determine the magnitude of stress reactivity which might have significant impact on health later in life (Boyce and Ellis, 2005; Ellis, Essex and Boyce, 2005). For this strong reason, detection of this altered stress response caused by adverse childhood experiences is important to be used as an indicator for the future health. However, until recently, there has been no study that utilized this information as an indicator for future health thus a study that fills this gap is needed.

In order to detect the altered stress response, selection of appropriate biomarker is crucial. Among the available biomarkers, HRV has been proven as a powerful biomarker that represents autonomic nervous system (Acharya *et al.*, 2006; Allen *et al.*, 2014; Task Force, 1996; Thayer *et al.*, 2012). Time and frequency domain analyses are the conventional approaches applied by many previous studies in HRV analysis during stress classification (Deepak *et al.*, 2014; Karthikeyan, Murugappan and Yaacob, 2014; Muaremi, Arnrich and Tröster, 2013). Due to the non-stationary nature of the HRV, valuable information embedded within the signal might not be completely extracted by these conventional methods. Therefore, more advanced analysis such as Time Frequency Distribution (TFD) and Wavelet transform (WT) are proposed (Acharya *et al.*, 2015; Boashash, 2003; Carvalho *et al.*, 2003; Neto *et al.*, 2016; Wachowiak, Hay and Johnson, 2016). However, in studies related to adverse childhood experience, very few studies were found using HRV to measure the stress response and only conventional frequency domain method was used (Carroll *et al.*, 2013; Ockenburg *et al.*, 2014; Winzeler *et al.*, 2017). Therefore, HRV analysis, using both conventional and more advanced approaches for stress response on individual who have had adverse childhood experience should be carried out.

Since ANS and HPA are two major body systems that play important role in stress response regulation, combination of the biomarkers that represent both ANS and HPA is recommended (Michels *et al.*, 2013a; Michels *et al.*, 2013b). Even though many studies used multiple biomarkers to measure the stress response, the results for each biomarker however were analysed separately (Ginty *et al.*, 2012a; Phillips, 2011; Phillips *et al.*, 2012). Hence, the combination or fusion of those biomarkers as a single measure, need to be done.

Therefore, to address these research gaps, a new approach to the fusion method for stress response classification of adverse childhood experience is proposed. Since the irregularity of stress response caused by adverse childhood experience can be used as essential indication of the adult's health status, a stress response index is proposed as an indicator for future health. The detection of this stress response irregularity is important so that preventive measures can be taken and if needed, further thorough diagnosis can be done. This perhaps might improve the health care management during adulthood. Next, the objectives and scopes of this thesis is explained in detail in the next section.

1.3 Objectives of Study

The main objective of this study is to fuse the biomarker that represents both ANS and HPA in order to classify the stress response of a group of people who had adverse childhood experience and propose a stress response index as an indicator for future health. The main objective is achieved through the following objectives.

1. To extract the HRV features of stress response from mental stress test of normal participants who had adverse childhood experience and normal participant who had no adverse childhood experience.

2. To select the relevant sub-set HRV features in classifying two classes of stress response using feature selection algorithm.

3. To investigate the stress response through fusion of biomarkers that represent both ANS and HPA using serial and parallel fusion method.

4. To propose a stress response index by using HRV and Salivary Cortisol (HRV-SCort) based on adverse childhood experience as an indicator for future health.

1.4 Scopes of the Study

The scopes of the study are listed as follow:

1. In this study, the participants were restricted to University of Birmingham United Kingdom students, aged 17 to 23 years old with no history of cardiovascular disease, current endocrine or immune disorder, acute infection or other chronic illnesses, and who are non-smokers as well as not on any medication.

2. Even though there are several other factors that may affect how the individual responds to a mental stress test, this study only focused on adverse childhood experience since the irregularity of stress response caused by this factor can be used as essential indication of future health.

3. There are several biomarkers that represent ANS and HPA either direct or indirectly. However, this study only focused on measuring significant biomarkers which are HRV, BP, PR and salivary cortisol as the biomarker for stress response classification.

4. All analysis starting from pre-processing, feature extraction, feature selection, feature fusion until stress response classification were computed using MATLAB software.

5. In order to stimulate the stress, a mental stress task was needed. In this study stimulated arithmetic stress test named Paced Auditory Serial Addition Test (PASAT) was used.

1.5 Contributions of the Study

The contributions of the current study are:

1. This study proposed HRV and salivary cortisol named as HRV-SCort as the most effective measure for stress response classification compared to either

different combinations of biomarkers or single biomarkers. It is important to be noted that, this combined biomarker represents both ANS and HPA, which are two main body systems that are activated during stress. Therefore, this new approach to measurement is believed to be more reliable and accurate compared to the existing measures as it is able to assess both essential systems simultaneously and thus minimize the errors and limitations caused by single biomarkers.

2. A new method for classification of stress response based on HRV-SCort biomarker using Euclidean distance and SVM named as e_d-SVM is proposed. The robustness of this method is crucial in contributing to the effectiveness of the proposed stress response index.

3. Based on adverse childhood experience and the fused biomarkers, HRV-SCort, by using e_d-SVM, a stress response index was proposed. This stress response index differentiates how the individual responds to stress by classifying between irregular stress response and normal stress response. This index can then be used for an indicator for future health. The detection of this stress response irregularity is important so that preventive measures can be taken and if needed, further thorough diagnosis can be done. This perhaps might improve the health care management during adulthood.

1.6 Thesis Organization

The thesis consists of five chapters. The organization of the thesis is as follows:

Chapter 1 is an introductory chapter. The chapter starts with a brief explanation of background of stress and stress classification. It presents the problem statement that leads to this research. Then, the chapter explains the objectives, scope and contributions of this study and outlines the overview of this thesis.

Chapter 2 provides a comprehensive review to a number of topics that were used as a base in developing the material of this thesis from both medical and signal processing perspectives. It gives a brief description on background of stress, stress factor and mechanism of stress response. Next, the chapter reviews the measurement of stress and analysis of HRV. The analysis of HRV included the feature extraction and feature selection. It is followed by a review of the fusion of biomarkers for stress classification.

Chapter 3 explains the implementation of the method used in the present work. This chapter starts with a brief description of data acquisition, including the recruitment of the participants and the procedure of measuring the stress response using various biomarkers. It is followed by the pre-processing of HRV and continued with HRV feature extraction and selection. The fusion of biomarkers is discussed next and finally the algorithm for the stress response index is presented in the last section.

Chapter 4 discusses the findings of this study. It starts by discussing the results of the HRV pre-processing and followed with the HRV feature extraction by using time, frequency, TF and wavelet analysis method. Then, the HRV feature selection using Genetic Algorithm (GA) is discussed. It is then followed with the presentation of the performance of the fused feature using different fusion methods. Finally, the proposed stress response index based on the adverse childhood experience is discussed in the last section.

Chapter 5 gives some conclusions based on the results obtained in the thesis and recommends some directions for further research.

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