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The Effect of Adverse Childhood Experience on Heart Rate Variability and Salivary Cortisol.

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***Abstract*— Adverse childhood exposure has been discovered might alter physiological processes such as cardiovascular stress response. When the body is in a stressful condition, it triggers two primary systems that are particularly involved in adapting the body to the stress: the Autonomic Nervous System (ANS) and the Hypothalamic-Pituitary-Adrenocorticol (HPA) axis. To detect the altered stress response, biomarkers that represent both systems: ANS and HPA are 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. This study will investigate the stress response on individual who have had adverse childhood experience and no adverse childhood experience by using HRV and salivary cortisol. Electrocardiograph and salivary cortisol were collected from 23 healthy participants (age, 19 to 23 years old), 12 participants who had adverse childhood experience while the remaining 11 acted as the control group. The recording session was done during a Paced Auditory Serial Addition Test (PASAT). HRV was then computed from the ECG and the HRV features were extracted. From the result, it can be seen that irregular stress response detected by HRV and salivary cortisol was found associated with adverse childhood experience with moderate classification performance; accuracy 61.7% and 59.4% respectively. To achieve a better classifier performance, an approach to the fusion method for stress response detection of adverse childhood experience is proposed for the future study.**

***Keywords*— stress, heart rate variability, cortisol, PASAT, children, signal processing**

I. Introduction

Early life exposure to stress has been suggested to be predictive of a range of health outcomes [1-2]. 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 [3] and also serious illnesses such as cardiovascular disease [4-5] depression [4, 6-7], irritable bowel syndrome [7] as well as cancer [8]. Motivated from these findings, recent work in the area of childhood trauma discovered that adverse childhood exposure might alter the physiological processes such as cardiovascular stress reactivity [9-10]. For this reason, detection of this altered stress response caused by adverse childhood experiences is important to be used as an indicator for health outcome.

Stress response is the way the body reacts to a stressor or factor that is causing the stress [11]. When the body is in a stressful condition, it triggers two primary systems that are particularly involved in adapting the body to the stress: the Autonomic Nervous System (ANS) and the Hypothalamic-Pituitary-Adrenocorticol (HPA) axis [12]. 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 [13-16]. The HRV, is easier to collect and less complex, yet has a direct connection with the ANS, where changes in the ANS directly affect cardiovascular reactivity.In addition, it has been proven that HRV provides predictive information for patients with autonomic function-related diseases and is a valuable biomarker for the investigation of sympathetic and parasympathetic functions, including diabetes [17-18] and cardiovascular disease [19]. HRV is also used to assess the autonomic response to physiological differences or activities under different conditions such as meditation [19-21], mental stress [22-23], physical exercise [24-25] and acupuncture [26].

As HPA plays a significant role in the stress response, the measurement of the cortisol level is also regarded as biomarker in stress related studies. It has been found that the salivary cortisol concentration is closely correlated to the serum cortisol concentration and thus it has been suggested as a possible biomarker that indirectly reflects the HPA system [27-28]. Furthermore, the salivary cortisol is also regarded as a more practical assessment tool, the sample collection is easier and stress-free compared to the collection of blood and urine samples for stress research [29-30].

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 [12, 31]. Therefore this study investigates the stress response on individual who have had adverse childhood experience and no adverse childhood experience using HRV and salivary cortisol.

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II. Method

A. Data Acquisition

A total of 609 participants, comprised of 511 females and 98 males (age, M = 19.2, SD = 2.99 years), who were the students of University of Birmingham, United Kingdom, were screened using the lifetime adversity inventory based on C-DIS-IV items, as conducted by Lovallo et al. (2012) and the Childhood Traumatic Questionnaire (CTQ) [32]. The C-DIS-IV questionnaire covers two different aspects of adversity which are physical or sexual adversity and emotional adversity. Meanwhile, CTQ measured five different aspects which emotional, physical, and sexual abuse as well as emotional and physical neglect. This measure summarizes the picture of the severity, duration, and frequency of abuse during childhood. Their consent was obtained during the online screening, where the participants agreed to be invited for the laboratory session if they fulfilled the selection criteria.

All the individuals with scores of 2 to 5 on the lifetime adversity measure and those with scores of 2 or higher on the CTQ were invited to the laboratory session as the adverse childhood experienced group while the control group was comprised of those who scored 0 on the lifetime adversity and CTQ measures [9, 32]. From the screening, 23 participants, 11 participants with highest score on the lifetime adversity criteria and 12 with lowest score (healthy control group) managed to attend the further recruitment in the laboratory. The participants were non-smokers with no history of cardiovascular disease, an acute infection or other chronic illnesses, a current endocrine or immune disorder, and who were not on any medication. The informed consent was obtained and the study was approved by the University of Birmingham Ethics Committee.

B. Mental Stress Test: The Paced Auditory Serial Addition Test (PASAT)

The Paced Auditory Serial Addition Test (PASAT) was used as the mental stress test in this study. To ensure the standardization of the stimulation procedure, the test was executed using an audio cassette tape. A series of single-digit numbers were presented to the participants, and they were required to add the new numbers that they had previously heard to the current numbers, and to say aloud their answers. In order to increase the level of difficulty of the test, the intervals between the numbers were shortened towards the end of the task.

Throughout the test, an examiner stood near the participant to mark the answers given. The participant heard a loud buzz during the last five numbers of every block of 10 numbers, mostly subject to an error or a hesitation. It should be noted that all the participants heard the same number of loud buzzes. They were told that the buzzes indicated the mistakes that they had made, including giving wrong or no answers, and not looking at the television screen. The participants had to look at the television screen, which mirrored their own image. The test took approximately 10 minutes to complete.

C. Procedure

Before attending the laboratory session, the participants were asked to refrain from smoking and caffeine two hours before the session, not to consume alcohol for at least 12 hours, not to consume any meal for one hour, and not to engage in any vigorous exercise 4 hours before the lab test. These details were reconfirmed before the testing began. On entering the laboratory, the participants were asked to sit on a chair facing the television set. Next, Lead II ECG, with a standard three-lead ECG placement, were attached to the participants. The ECG was then captured continuously using LabChart Software at a sampling rate of 1 kHz, and was used for later analysis. The participants were reminded that no talking was allowed throughout the testing. The recording session took place between 2.00 pm and 6.00 pm.

The test started with the adaptation phase for 10 minutes, followed by a further resting baseline period of another 10 minutes. Three saliva samples were obtained from each participant. The first saliva sample was collected at the final minute of the baseline period. Before starting the next phase, the participants were asked to read the instructions of the mental stress task, and to rehearse the task first to ensure better understanding. The participants then completed the 10-minute PASAT. Immediately after the test, a saliva sample was again collected, and this was followed by a 10-minute recovery period. The last saliva sample was obtained after the 10minutes of recovery. The ECG was recorded throughout the testing.

D. Saliva Sampling and Cortisol Assays

To collect the saliva samples, a salivette dental swab was placed in the mouth and was gently chewed by the participant for one minute. The swab was then returned to the salivette tube. In this study, three stimulated saliva samples were collected. The first sample was obtained at the 10-minute baseline period, while the second sample was collected immediately after the stress test, and the final sample was obtained 10 minutes prior to the task. At the end the laboratory session, the salivettes were centrifuged at 3500 rpm for five minutes at room temperature, and the saliva was then aliquoted and frozen at -20 degrees until the time to be assayed.

The cortisol was assayed from the saliva samples in duplicate by an enzyme-linked immunosorbent assay (ELISA) using a commercial kit (DRG Diagnostics). This assay is based on the competition principle and microplate separation. An unknown amount of cortisol present in the sample, and a fixed amount of cortisol conjugated with horseradish peroxidase, competed for the binding sites of a polyclonal cortisol-antiserum coated onto wells. After one hour of incubation, the microtiterplate was washed to stop the competition reaction. A substrate solution was added and incubated for 15 minutes at room temperature. After a stop

solution was added, the optical density was measured at 450 nm. The concentration of cortisol (nmol/l) was then determined from the measurement of the optical density using a regression program (DRG Instruments).

E. HRV Signal Analysis

The recorded ECG signals were pre-processed to quantify the HRV using MATLAB software. The 50 Hz power line interference was removed using a notch filter. The QRS waves were then detected using Pan and Tompkin's algorithm. This method was chosen, because it has been proven to detect 99.3% of adult QRS using the MIT/BIH database [33].

Next, time, frequency, non-linear time-frequency and Wavelet analysis were used to extract the HRV features. In total, 83 HRV features were extracted. These features were selected to be used in this study since it has been proven to provide significant results in discriminating HRV reactivity upon mental stress task

From the feature extraction process, a vector of 83 features may contain irrelevant and redundant features. Therefore, a feature selection technique was required to identify the most representative features so as to improve the performance of the classification. In this study, the Genetic Algorithm (GA) was exploited as a feature selection method.

In this study, GA was exploited using GA MATLAB Toolbox for the feature selection process. GA involves an iteration process, which manipulates the chromosomes to produce a new population using genetic functions such as crossovers and mutations. According to the theory, the fittest species will survive the evolution process, while the weak will perish. From the GA feature selection, 12 best features were finally selected and are presented in Table I.

TABLE I. FEATURE EXTRACTED FROM FEATURE SELECTION BY GENETIC ALGORITHM

Type of Analysis		Feature
Time Domain	-	RMSSD
Frequency Domain	Autoregressive with Burg Estimation	HFnu
Wavelet	Level 5 Db8	Mean LF
		SDNN D1
		SDNN D4
		Apen D4
		SampEn D3
		Kurtosis D4
		Skew D5
Time- Frequency	Modified-B Distribution	ShanEn LF
		ShanEn HF
		ShanEn LFHFr

*Notes: SDNN: Standard deviation of N-N interval; RMSSD: root mean square successive difference; LF: low frequency; HF: high frequency; LFnu: Normalized unit of low frequency; HFnu: Normalized unit of high frequency; ShanEn: Shannon entropy, SampEN: Sample entropy; Apen: Appoximate entropy.

F. Performance Analysis

A classifier is needed to predict the output class of an input where the data is already in existence. In this study, the stress response between two groups of people, one group with adverse childhood experiences and the other as a normal control group, was classified using a Support Vector Machine (SVM) classifier.

The SVM, which is a classifier that is being extensively used in the biomedical field, constructs a separating hyperplane in a feature space which splits the training data into two stress response classes. An SVM classifies the data by searching the best hyperplane that splits all the data points of two classes. The hyperplane with the largest margin between the two classes is selected as the best hyperplane for an SVM. The margin means the maximal width of the slab parallel to the hyperplane that has no interior data points. The support vectors are the data points that are closest to the separating hyperplane. These points are on the boundary of the slab [11].

In this study, 10-fold cross validation method was then used to evaluate the classifier [34]. The dataset was first randomly divided into 10 disjointed sets of equal parts, where each part had roughly the same class distribution. Then, nine parts were used for training the classifier and the one remaining part was used to test the performance. This whole process was repeated 10 times with different parts of training and test set.

- **Classifier Performance Evaluation**

The performance of classifiers can be estimated through a number of different approaches. One of the most commonly used performance measures is the accuracy of the classification. Usually, the classifier is trained by using a set of training data, and the performance measure is calculated from a set of test data. In this study, the performance measures derived from the confusion matrix. From the confusion matrix, accuracy (Acc), sensitivity (Sen) and specificity (Spe) were implemented as the performance measures [35-36].

III. Result and Discussion

From Table II, it can be seen that irregular stress response detected by HRV and salivary cortisol was found associated with adverse childhood experience with moderate classification performance; accuracy 61.7% and 59.4%. Even though the HRV performance was slightly higher than salivary cortisol, the performance in term of sensitivity and specificity indicated inconsistent result. As mentioned earlier, 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 [12, 31].

TABLE II. COMPARISON OF THE PERFORMANCE BETWEEN HRV AND SALIVARY CORTISOL FOR STRESS RESPONSE CLASSIFICATION BY USING SVM

Biomarkers	Accuracy, %	Sensitivity, %	Specificity, %
HRV	61.7	48.3	76.7
Cort	59.4	71.7	46.7

However, the use of single biomarker as showed in this study has drawback especially in producing consistent result. In addition, many studies has been found used multiple biomarkers to measure the stress response, however the results for each biomarker were analysed separately [37-39] and thus lead to unsatisfactory result. Therefore, in future, the combination or fusion of those biomarkers as a single measure can be done so that a better performance can be achieved.

IV. Conclusion

This study presented the investigation of stress response on individual who have had adverse childhood experience and no adverse childhood experience using HRV and salivary cortisol. From the results, HRV and salivary cortisol showed moderate performance as well as inconsistent result when compared with each other. Therefore, to achieve a better classifier performance, an approach to the fusion method for stress response detection of adverse childhood experience is proposed for the future study.

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.

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