Original Research

Impact of acute stress on cortical electrical activity and cardiac autonomic coupling

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Assessment of heart rate variability (reflective of the cardiac autonomic nervous system) has shown some predictive power for stress. Further, the predictive power of the distinct patterns of cortical brain activity and - cardiac autonomic interactions are yet to be explored in the context of acute stress, as assessed by an electrocardiogram and electroencephalogram. The present study identified distinct patterns of neural-cardiac autonomic coupling during both resting and acute stress states. In particular, during the stress task, frontal delta waves activity was positively associated with low-frequency heart rate variability and negatively associated with high-frequency heart rate variability. Low high-frequency power is associated with stress and anxiety and reduced vagal control. A positive association between resting high-frequency heart rate variability and frontocentral gamma activity was found, with a direct inverse relationship of low-frequency heart rate variability and gamma wave coupling at rest. During the stress task, low-frequency heart rate variability was positively associated with frontal delta activity. That is, the parasympathetic nervous system is reduced during a stress task, whereas frontal delta wave activity is increased. Our findings suggest an association between cardiac parasympathetic nervous system activity and frontocentral gamma and delta activity at rest and during acute stress. This suggests that parasympathetic activity is decreased during acute stress, and this is coupled with neuronal cortical prefrontal activity. The distinct patterns of neural-cardiac coupling identified in this study provide a unique insight into the dynamic associations between brain and heart function during both resting and acute stress states.

Keywords

1. Introduction

Stress associated with maladaptive responses and prolonged levels of cortisol has been implicated in reduced declarative memory (Lupien et al., 2002), impaired memory retrieval and decision-making (Chrousos and Gold, 1992; Dominique et al., 2009) mathematical ability, and diminished working memory capacity (Wirth, 2015), providing evidence for the neural component of stress. Further, chronic stress has been linked to an increased risk of ischaemic heart disease (Steptoe and Kivimäki, 2013). Thus, the psychophysiological impacts of stress are widespread, including both the brain and heart. Numerous theories exist to explain this neural-cardiac link. The neurovisceral integration model (Thayer and Lane, 2000) hypothesizes that cardiac vagal tone, as measured by heart rate variability (HRV), can signify the functionality of the neural networks implicated in emotion-cognition interactions. The psychophysiological coherence model draws on dynamic systems theory, and it posits a sine wave-like pattern in the cardiac rhythms, amplified synchronicity of the heart and brain, and coherence between distinct physiological systems (McCraty et al., 2009).

Heart rate variability (HRV) (Pumprla et al., 2002) is a critical component in the brain-heart axis. It can be used to assess acute stress responses via the autonomic nervous system (ANS). Using this technique, the ANS can be non-invasively examined

using spectral analysis of heart rate variability (HRV) (Pumprla et al., 2002) to indirectly quantify autonomic control of the heart (Acharya et al., 2008) and the dynamic interaction between the sympathetic and parasympathetic nervous systems (Dreifus et al., 1993; Klein et al., 1995; van Ravenswaaij-Arts et al., 1993). The two primary bandwidths of the HRV frequency domains are high frequency (HF) and low frequency (LF), indicating parasympathetic activity and a mixed sympathetic and baroreceptor reflex activity, respectively (Tulppo and Huikuri, 2004).

Electroencephalography (EEG) is often used to measure cortical electrical activity and can provide information as to the predominant EEG bandwidth associated with specific tasks or acute stress responses. The most commonly used technique to categorize EEG waveforms is by the frequency, which includes delta (0.5 to 4 Hz), theta (4 to 7 Hz); alpha (8 to 12 Hz); and beta (13 to 30 Hz). Delta rhythm is present during deep sleep and predominates in the frontocentral cerebral sites and can also be detected in awake alert people and during cognitive processes. Theta is associated with drowsiness and initial phases of sleep and predominates in the fronto-central cerebral sites. Alpha rhythms are typically present in normal awake EEG recordings in the cerebral occipital site (Nayak and Anilkumar, 2019).

Research has shown that stress varies the signals the brain sends to the heart, and the heart, in turn, responds through several complex autonomic mechanisms (Cacha et al., 2019; Pokrovskii and Polischuk, 2012). These brain signals result in neurovisceral innervation of vital body organs, including the heart, to induce biological corrections that attempt to reverse the deleterious effects of stress or threats on health and well-being.

EEG and HRV coupling can be used to monitor and assess the dynamic interaction between the brain and heart during periods of rest and acute stress-induced in the laboratory. Acute stress in the laboratory is often induced using the Trier Stress Test (TSST). In use for over 20 years, the test induces a neural and cardiac response to acute stress response of public speaking and mental arithmetic, and has been validated in many biochemical studies, and has been shown to increase heart rate and the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axis during the task (Birkett, 2011). To date, limited research has examined this acute stress task (TSST) and its relationship to brain cortical electrical function and cardiac autonomic function.

Nurses find themselves within the top 6 most stressful occupations (Cooper et al., 1987). Several occupational factors result in these nurses being viewed as a stress-vulnerable population (Hooper et al., 2010). These include the emotional nature of patient demands, long working hours, and inter-professional as well as interpersonal conflicts. Studies have shown that stress, within the workplace, is often linked with occupational demands and extrinsic effort, such as the necessity of prolonged cognitive engagement (Mark and Smith, 2012). Studies have also shown that chronic stress has detrimental effects on the psychophysiological welfare of health professionals (Jones et al., 2015). Our past studies have also shown that stress effects are prevalent in this sample, and has effects on cognitive function (Lees and Lal, 2017).

2. Materials and methods

2.1 Participants

The data from 30 clinically active nurses, aged between 18-45 years were used in the current analysis. Before inclusion, an in-house questionnaire was used to screen participants for current medication use (any prescribed medications), recent alcohol intake (previous 12 hours), smoking > 10 cigarettes per day, and chronic disease/illness. Participants were excluded if they answered yes to any of the screening questions above. The in-house designed questionnaire, adapted from the Lifestyle Appraisal Questionnaire (Craig et al., 1996), also collected demographic, lifestyle (such as exercise and smoking habits), and work-related data such as shift length, average working hours per week, years of employment, and employment site (e.g., private/public hospital). The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the UTS Human Research Ethics Committee.

2.2 Study protocol

At the commencement of the study, participants were asked to complete the in-house designed questionnaires, adapted from the Lifestyle Appraisal Questionnaire (Craig et al., 1996), to collect demographic, lifestyle, and work-related data. Following the completion of the questionnaire, participants were attached to a 32 lead electroencephalogram (EEG), which was recorded at a sampling frequency of 1,000 Hz using the $SynAmp^2$ system (Compumedics Limited, Australia) and utilizing the Scan software (Version 4.3; Compumedics Limited, Australia). The electrode positions followed the International 10-20 system (Homan et al., 1987) and were as follows: Fp_1, Fp_2, F_7, F_3, F_z, F_4, F_8, FT_7, FC_3, FC_z, FC_4, FT_8, T_7, C_3, C_z, C_4, T_8, TP_7, CP_3, CP_z, CP_4, TP_8, P_7, P_3, P_z, P_4, P_8, O_1, O_z, and O_2. Further, the reference electrode was positioned at the vertex, and the ground electrode at position AF_z; two electrooculograms (EOG) electrodes, one above and one below the left eye were also utilized. All electrodes were filled with Signal Gel (Parker Laboratories, USA), and adjusted until an acceptable direct current value was attained (less than 5 kΩ). Additionally, a 3 lead electrocardiogram (ECG) was also recorded using a Flexcomp Infiniti Encoder (Thought Technology Ltd., Canada) combined with the Biograph Infiniti software (Thought Technology Ltd., Canada), with three disposable Ag/AgCl electrodes were placed on the participant's chest, one in the left and right second intercostal space, midclavicular line and one over the xiphoid process.

A modified Trier Social Stress Test (TSST) (Birkett, 2011) was used to elicit a controlled stress response. Continuous simultaneous EEG/ECG recordings were taken during the TSST. Only the participant and the lead researcher were present during the study. The TSST involved a 10-minute resting session, which was used to determine a baseline EEG/ECG recording, before which participants were seated for 10 minutes, followed by a 10-minute preparation/anticipation task where participants were required to prepare a short speech. The preparation time was followed by a 5-minute public speaking task, followed by 5 minutes of mental arithmetic. Electrophysiological recordings were ceased after the completion of the mental arithmetic task.

2.3 Electrophysiological data processing

Before statistical analysis, both sets of electrophysiological data (ECG and EEG) were processed to obtain the relevant variables.

2.3.1 Heart rate variability

The recorded ECG data was processed utilizing the Kubios HRV Premium software (Version 3.1.0; Kubios Oy, Finland) to derive the activity for the following HRV frequency bands: very low frequency (VLF; 0 - 0.04 Hz), low frequency (LF; 0.04 - 0.15 Hz), and high frequency (HF; 0.15 - 0.4 Hz). Further, it should be noted that for each of these variables, normalized units (n.u.) were utilized. Additionally, the ratio between LF and HF (LF/HF), as well as overall or total power (TP) was also computed. These components were chosen based on their effectiveness of representing acute stress (Kim et al., 2014). These variables were derived from approximately 10 minutes of ECG, utilizing Welch's periodogram method (Welch, 1967) applied to a 300-second window with a 50% overlap. Furthermore, artefacts and ectopics were removed from the trace before analysis.

2.3.2 Electroencephalography data

Before analysis, all raw time-domain EEG data were bandpass filtered using a Butterworth IIR filter set at 0.5 and 50 Hz, followed by a Hanning window. Then the aligned-artifact average procedure (Croft and Barry, 1998) was applied, which used the collected EOG data to minimize eye artefacts. Next, all recordings (baseline and active) were partitioned into approximately 300 two-second epochs and the periodogram power spectral density estimate was used to calculate the activity in the delta (0.5 - 4 Hz), theta (4 - 8 Hz), alpha (8 - 13 Hz), beta (13 - 35 Hz) and gamma (35 - 50 Hz) frequency bands (Rowan and Tolunsky, 2003). Outlying activity values across all epochs were removed using a modified z-score statistic (Leys et al., 2013) greater than or equal to 5, which was calculated using the following equations (Leys et al., 2013):

$$Z = \frac{X - \tilde{x}}{MAD} \qquad (1)$$

where X = Epoch value, $\tilde{x}$ = Median value and MAD = Median Absolute Deviation.

The median absolute deviation was calculated using the following equation (Leys et al., 2013):

$$MAD = \tilde{x}_i \left(|X_i - \tilde{x}_i (X_j)| \right) \qquad (2)$$

where $\tilde{x}$ = Median and X = Epoch value

After removing outliers, the retained activity values were averaged to derive a single value in each frequency band for each electrode location. Finally, the activity values for all recordings were collated, and outliers were again removed using the modified Z-score statistic, with a removal threshold greater than or equal to 10 (Leys et al., 2013).

2.4 Statistical analysis

STATISTICA (Version 10, 1999, StatSoft, USA) was used to conduct the present statistical analysis, and statistical significance was set at $P < 0.05$. Partial Pearson's correlation analysis (controlling for age and BMI) examined the associations between the collected EEG and HRV data. Least absolute shrinkage and selection operator analysis (LASSO) (Tibshirani, 1996) also examined the relationship between EEG and HRV data and supplemented the correlation analysis. LASSO was computed using Matlab (Version, 2018b, Mathworks, USA), as per the least absolute shrinkage and selection operator equation (Tibshirani, 1996):

$$\min_{\beta_0 \beta} \left(\frac{1}{2N} \sum_{i=1}^{N} \left(y_i - \beta_0 - x_i^T \beta \right)^2 + \lambda \sum_{j=1}^{p} |\beta_j| \right) \qquad (3)$$

where: N is the number of observations, y_i is the response at observation i., x_i is data, a vector of P values at observation i., λ is a nonnegative regularization parameter corresponding to one value of Lambda, the parameters β_0 and β are scalar and p-vector respectively. Note: As λ increases, the number of nonzero components of β decreases. The lasso problem involves the L^1 norm of β, as contrasted with the elastic net algorithm.

LASSO is a statistical technique that provides coefficients or weights (that can equal zero) that evaluate the importance of input variables for ensuing analysis (Tibshirani, 1996); a normalized weight with an absolute value of 0.75 or greater was utilized to identify important EEG variables. Additionally, before LASSO analysis, all previously removed EEG values were imputed by calculating the mean of the previous and next non-missing value for the variable containing the missing value (Keil et al., 2014).

Finally, if significant relationships between one dependent and three or more independent variables were identified, general linear multiple regression analysis was undertaken to evaluate the relationship further.

3. Results

3.1 Participant descriptive

The average age of participants was 29.7 ± 6.3 years $\pm$ SD, with an average body mass index of 25.0 ± 4.1. 6% of the population were male (n = 2). The cohort consisted of registered nurses (n = 22, 66%), midwives (n = 6, 18%) and assistants in nursing (n = 2, 6%), who worked in the public hospital system (n = 25, 75%), the private hospital system (n = 4, 12%) and in a home care setting (n = 1, 3%). On average, participants had spent 5.8 ± 4.7 years in their role and worked 8.4 ± 1.5 hours each shift. The average blood pressure readings (+ standard deviation) were as follows; Pre-study diastolic blood pressure: 73.5 ± 9.2 mmHg, Pre-study systolic blood pressure: 114.5 ± 9.7 mmHg, Post-study diastolic blood pressure: 72.0 ± 8.1 mmHg, Post-study systolic blood pressure: 114.6 ± 8.0 mmHg.

3.2 Baseline
3.2.1 Low Frequency Heart Rate Variability (normalized units)

Baseline Low Frequency Heart Rate Variability (normalized units) (LFn.u.) was significantly negatively correlated with frontotemporal delta and frontocentral gamma EEG parameters, and positively correlated with a parietal gamma EEG variable. All other EEG variables were not significantly correlated to baseline LFn.u.

Also, the LASSO analysis demonstrated the importance of baseline F_4 theta activity and P_4 gamma activity for predicting LFn.u.

Table 1. Stepwise forward general linear regression analysis between baseline LFn.u. and the significantly correlated EEG variables.

| | | | R = 0.612; R^2 = 0.375; AR^2 = 0.345; | | | |
| | | | F = 12.59; df = 1, 21; P < 0.001* | | | |

Variable	b	SE of b	B	SE of B	t	P
Intercept			78.03	3.66	21.33	< 0.000*
g-FC3	-0.612	0.172548	-41.278628	11.634643	-3.547907	< 0.001*

Table 1 displays a stepwise forward general linear regression analysis between baseline LFn.u. and the significantly correlated EEG variables. Of the 5 EEG variables originally entered into the model, the analysis retained 1: FC3 gamma.
Key: bold = P value of < 0.01; C = Central; df = Degrees of Freedom; F = Frontal; γ = gamma; LFn.u. = Low Frequency Heart Rate Variability (normalized units); * = Statistical Significance; $\leq$ Less than

Table 2. Stepwise forward general linear regression analysis between baseline HFn.u. and the significantly correlated EEG variables.

| | | | R = 0.22; R^2 = 0.387; AR^2 = 0.359 | | | |
| | | | F = 13.91, df = 1,22; P < 0.001* | | | |

Variable	b	SE of b	B	SE of B	t	P
Intercept			21.64	3.45	6.26	< 0.000*
g-FC3	0.622	0.167	41.79	11.21	3.73	< 0.001*

Table 2 displays a stepwise forward general linear regression analysis between baseline HFn.u. and the significantly correlated EEG variables. Of the 4 EEG variables originally entered into the model, the analysis retained 1: FC3 gamma.
Key: bold = P value of < 0.01; C = Central; df = Degrees of Freedom; F = Frontal; γ = Gamma; HFn.u. = High Frequency Heart Rate Variability (normalized units); * = Statistical Significance; $\leq$ Less than

A forward stepwise general linear regression informed by the correlation and LASSO analysis retained 1 of the 5 originally entered variables (FC_3 gamma activity) and had an overall significance of $P \leq$ 0.001 (Table 1). This variable explained 38% of the variance in LFn.u. (F = 12.59, DF = 1; P < 0.001; R = 0.61; R^2 = 0.38; AR^2 = 0.35).

3.2.2 High Frequency Heart Rate Variability (normalized units)

Baseline High Frequency Heart Rate Variability (normalized units) (HFn.u.) was significantly positively correlated with delta and gamma EEG parameters and negatively correlated to a gamma EEG variable. Further, all other EEG variables were not significantly correlated to baseline HFn.u. The LASSO analysis, again, reduced the weights of all investigated EEG variables to zero.

As multiple significant correlations were identified for baseline HFn.u, a forward stepwise general linear regression was undertaken to establish predictive capability. The regression analysis retained 1 of the 4 originally entered variables (FC_3 gamma activity) and had an overall significance of $P \leq$ 0.001 (Table 2). This variable explained 39% of the variance in HFn.u. (F = 13.91, DF = 1; P < 0.001; R = 0.622; R^2 = 0.39; AR^2 = 0.36).

3.2.3 Total power

Baseline TP was significantly positively correlated with frontal beta and gamma EEG parameters, and all other EEG variables were not significantly correlated to baseline TP. The LASSO analysis for EEG variables and baseline TP HRV reduced the weights of all investigated EEG variables to zero.

The regression analysis for baseline TP HRV retained 1 of the 4 originally entered variables (F_4 beta activity) and had an overall significance of $P \leq$ 0.001 (Table 3). This variable explained 39% of the variance in baseline TP (F = 14.96, DF = 1; P < 0.001; R =

0.63; R^2 = 0.39; AR^2 = 0.38.

3.2.4 Low Frequency to High Frequency Ratio

Baseline Low Frequency to High Frequency Ratio (LF : HF) was significantly positively correlated with delta, theta, alpha, beta, and gamma EEG parameters; all other EEG variables were not significantly correlated to baseline LF : HF. The LASSO analysis reduced the weights of all investigated EEG variables to zero.

The forward stepwise general linear regression for baseline LF : HF regression analysis retained 4 of the 14 originally entered variables (F_z delta, F_z theta, TP_8 gamma and P_4 gamma activity) and had an overall significance of P < 0.001 (Table 4). This variable explained 79% of the variance in LF : HF (F = 11.06, DF = 4; P < 0.001; R = 0.89; R^2 = 0.79; AR^2 = 0.72).

3.3 Stress
3.3.1 Low Frequency Heart Rate Variability (normalized units)

Low frequency (normalized) HRV during the stress task was significantly positively correlated with delta and theta EEG parameters. All other EEG variables were not significantly correlated to stress LFn.u. The LASSO analysis was investigating EEG variables and stress LFn.u. They have reduced the weights of all EEG variables to zero.

The forward stepwise regression for stress LFn.u. retained 1 of the 10 originally entered variables (F_z delta activity) and had an overall significance of $P \leq$ 0.001 (Table 5), and this variable explained 20% of the variance in stress LFn.u. (F = 12.26, DF = 1; P < 0.001; R = 0.61; R^2 = 0.20; AR^2 = 0.19).

3.3.2 High Frequency Heart Rate Variability (normalized units)

High Frequency Heart Rate Variability (normalized units) (HFn.u.) during the stress task was significantly negatively cor-

Table 3. Stepwise forward general linear regression analysis between baseline TP and the significantly correlated EEG variables.

| | | | R =0.628; R^2 = 0.394; AR^2 = 0.368 | | | |
| | | | F = 14.96, df = 1,23; $P \leq 0.001$* | | | |
Variable	b	SE of b	B	SE of B	t	P
Intercept			734.39	248.68	2.95	0.007*
b-F4	0.63	0.16	141.58	39.6	3.87	< 0.001*

Table 3 displays a stepwise forward general linear regression analysis between baseline TP and the significantly correlated EEG variables. Of the 4 EEG variables originally entered into the model, the analysis retained 1: F4 beta.

Key: bold = P value of < 0.01; df = Degrees of Freedom; F = Frontal; β = beta; * = Statistical Significance; $\leq$ Less than

Table 4. Stepwise forward general linear regression analysis between baseline LF : HF and the significantly correlated EEG variables.

| | | | R = 0.887; R^2 = 0.787; AR^2 = 0.716 | | | |
| | | | F = 11.064, df = 1,12; $P < 0.001$* | | | |
Variable	b	SE of b	B	SE of B	t	P
Intercept			0.057	0.015	3.71	< 0.001*
q-Fz	1.54	0.3	0.53	0.102	5.2	< 0.001*
d-Fz	-1.1	0.3	-0.06	0.015	-3.71	0.001*
g-TP8	0.58	0.26	0.13	0.058	2.21	< 0.001*
g-P4	0.84	0.25	3.52	1.056	3.34	< 0.001*

Table 4 displays a stepwise forward general linear regression analysis between baseline LF : HF and the significantly correlated EEG variables. Of the 5 EEG variables originally entered into the model, the analysis retained 4: Fz delta, Fz theta, TP8 gamma, and P4 gamma.

Key: bold = P value of < 0.01; df = Degrees of Freedom; F = Frontal; LF : HF = Low Frequency to High Frequency Ratio; P = Parietal; T = Temporal; z = Midline; δ = Delta; θ = Theta; γ = gamma; * = Statistical Significance; $\leq$ Less than

Table 5. Stepwise forward general linear regression analysis between stress LFn.u. and the significantly correlated EEG variable.

| | | | R = 0.451; R^2 = 0.203; AR^2 = 0.187 | | | |
| | | | F = 12.26, df = 1,48; $P < 0.001$* | | | |
Variable	b	SE of b	B	SE of B	t	P
Intercept			67.31	1.91	35.16	< 0.000*
d -Fz	0.45	0.128823	0.086644	0.024748	3.50106	< 0.001*

Table 5 displays a stepwise forward general linear regression analysis between stress LFn.u. and the significantly correlated EEG variables. Of the 10 EEG variables originally entered into the model, the analysis retained 1: Fz delta.

Key: bold = P value of < 0.01; df = Degrees of Freedom Model; F = Frontal; z = Midline; δ = Delta; LFn.u. = Low Frequency Heart Rate Variability (normalized units); * = Statistical Significance; $\leq$ Less than

related with delta and theta EEG parameters, and all other EEG variables were not significantly correlated to stress HFn.u. Also, the cut-off weight for the LASSO analysis demonstrated the importance of F_z delta activity and O_z delta activity for predicting stress HFn.u.

The correlation and LASSO informed forward stepwise general linear regression for stress HFn.u retained 1 of the 10 originally entered variables (F_z delta activity) and had an overall significance of $P = 0.001$ (Table 6). This variable explained 20% of the variance in stress HFn.u. (F = 12.09, DF = 1; $P < 0.001$; R = 0.45; R^2 = 0.20; AR^2 = 0.18).

3.3.3 Total power

Stress TP was significantly negatively correlated with theta EEG parameters (Table 7). All other EEG variables were not significantly correlated to stress TP. Also, the LASSO analysis

demonstrated the importance of T_7 theta activity for predicting stress TP; all other weights were reduced to zero.

As numerous EEG variables were determined to be important for total HRV power during a stress task, a forward stepwise general linear regression was performed, and retained 1 of the 4 originally entered variables (FC_z theta activity) with an overall significance of $P \leq 0.002$ (Table 7). This variable explained 10% of the variance in stress TP (F = 5.27, DF = 1; $P < 0.002$; R = 0.32, R^2 = 0.10; AR^2 = 0.08).

3.4 Low Frequency to High Frequency Ratio

Low Frequency to High Frequency Ratio (LF : HF) during the stress task was significantly positively correlated with delta and theta EEG parameters. The LASSO analysis for Stress LF : HF reduced the weights of all investigated EEG variables to zero.

Finally, as multiple EEG variables were indicated to be important for LF : HF during a stress task a forward stepwise general

Table 6. Stepwise forward general linear regression analysis between HFn.u. during the stress task and the significantly correlated EEG variables.

| | | | R = 0.448; R^2 = 0.201; AR^2 = 0.185 | | | |
| | | | F = 12.09, df = 1,48; $P \leq 0.001$* | | | |
Variable	b	SE of b	B	SE of B	t	P
Intercept			32.51	1.91	17.04	< 0.000*
d-Fz	-0.09	0.02	-0.45	0.13	-3.48	< 0.001*

Table 6 displays a stepwise forward general linear regression analysis between HFn.u. during the stress task and the significantly correlated EEG variables. Of the 10 EEG variables originally entered into the model, the analysis retained 1: Fz delta.

Key: bold = P value of < 0.01; df = Degrees of Freedom; F = Frontal; z = Midline; γ = gamma; HFn.u. = High Frequency Heart Rate Variability (normalized units); * = Statistical Significance; $\leq$ Less than

Table 7. Stepwise forward general linear regression analysis between stress TP and the significantly correlated EEG variables.

| | | | R =0.321; R^2 = 0.103; AR^2 = 0.083 | | | |
| | | | F = 5.27, df = 1,23; $P \leq 0.002$* | | | |
Variable	b	SE of b	B	SE of B	t	P
Intercept			19	0.62	30.68	< 0.000*
q-FCz	0.32	0.14	-0.44	0.19	-2.3	0.026*

Table 7 displays a stepwise forward general linear regression analysis between stress TP and the significantly correlated EEG variables. Of the 4 EEG variables originally entered into the model, the analysis retained 1: FCz theta.

Key: bold = P value of < 0.01; C = Central; df = Degrees of Freedom; F = Frontal; θ = Theta; * = Statistical Significance; $\leq$ Less than

linear regression was performed and retained 3 of the 12 originally entered variables (F$_z$ delta, T$_7$ delta and O$_z$ delta) and had an overall significance of $P = 0.001$ (Table 8). This variable explained 29% of the variance in stress LF : HF (F = 6.291; DF = 4; $P = 0.001$; R = 0.53; R^2 = 0.29; AR^2 = 0.25).

A summary of correlation findings for the baseline resting phase is presented in Table 9.

A summary of correlation findings for the stress phase is presented in Table 10.

4. Discussion

The present study identified distinct patterns of neural-cardiac coupling during both resting and acute stress states. During the stress task, frontal delta wave activity was positively associated with LF HRV and negatively associated with HF HRV. Low HF power is associated with stress and anxiety, and reduced vagal control has been linked to increased morbidity and mortality (Thayer et al., 2010). It has been proposed that LF HRV is associated with the baroreceptor reflex rather than sympathetic nervous system activity alone (Goldstein et al., 2011; Rahman et al., 2011; Vaschillo et al., 2002). During the stress task, LF HRV was positively associated with frontal delta activity. That is, as the parasympathetic nervous system is reduced during a stress task, so too is frontal delta wave activity. Delta wave activity is associated with drowsiness and sleep, and previous studies have shown that during stress, inhibition of our REM-on hormones ensures adequate vigilance and attentiveness (Krueger et al., 2018). The cognitive and neural functions associated with delta waves have been mapped to prefrontal structures and awake EEG delta activity.

Additionally, deeper anatomical structures associated with

deep subcortical delta activity also map well to areas associated with autonomic control. It is also known that cognitive tasks that require verbal memory and mental arithmetic both increase significant broad areas of prefrontal EEG delta activity (Harmony, 2013). This waking delta activity has been suggested to suppress other cognitive systems for better attention to the task activity. At the same time, others have also suggested such activity will likely trigger emotive cognitions. Hence a cognitive task that elicits prefrontal delta activity is likely also associated with acute stress response and deeper thalamocortical and brainstem regions that can control cardiac autonomic responses (Riganello et al., 2019). In summary, delta activity, as recorded in prefrontal areas, is well described and increases during different complex cognitive processes that can be stressful (Massimini et al., 2000).

The inverse relationship was identified when examining HF ECG derived parameters, as HF HRV was negatively correlated with frontal cortex delta wave activity. That is, as cardiac parasympathetic nervous system activity increases, delta wave activity decreases. The frontocentral region, or prefrontal cortex, is associated with complex cognitive behaviors, decision making, and behavioral responses (Euston et al., 2012). This may infer a psychophysiological response to acute stressors. This may have implications for an extrapolative model of HRV analysis, which utilizes HF and LF HRV patterns to predict behavioral responses to stress, as inferred by prefrontal cortex activity.

The present study also identified a positive association between resting HF HRV and frontocentral gamma activity, the direct inverse relationship of the LF HRV-gamma wave coupling at rest. That is, the findings suggest a link between parasympathetic nervous system activity and frontocentral gamma activity

Table 8. Stepwise forward general linear regression analysis between stress LF : HF. and the significantly correlated EEG variables.

R = 0.539; R^2 = 0.291; AR^2 = 0.245

F = 6.291, df = 3,46; P = 0.001*

Variable	b	SE of b	B	SE of B	t	P
Intercept			1.6	0.729	2.19	0.033*
d-Fz	0.31	0.15	0.02	0.008	2.04	0.047*
d-T7	0.53	0.18	0.06	0.019	2.98	0.005*
d-Oz	0.56	0.19	0.1	0.033	3.04	0.004*

Table 8 displays a stepwise forward general linear regression analysis between LF : HF during a stress task, and the significantly correlated EEG variables. Of the 12 EEG variables originally entered into the model, the analysis retained 3: Fz delta, T7 delta, and Oz delta.

Key: bold = P-value of < 0.01; df = Degrees of Freedom; F = Frontal; O = Occipital; T = Temporal z = Midline; δ = Delta; * = Statistical Significance

Table 9. Summary of findings from stepwise forward linear regression analysis between baseline HRV parameters and significantly correlated EEG variables.

HRV Parameter	EEG Correlate	EEG Correlate location	Direction of relationship
LF n.u.	Gamma wave activity	Frontocentral	Inverse
HF n.u.	Gamma wave activity	Frontocentral	Direct
Total Power	Beta wave activity	Frontal	Direct
LF : HF	Delta wave activity	Frontal	Direct
	Theta wave activity	Frontal	
	Gamma wave activity	Parietotemporal	
	Gamma wave activity	Parietal	

Table 9 presents a summary of electroencephalography and electrocardiography correlation findings for the baseline resting phase.

Key: HFn.u.: High-frequency heart rate variability normalized units; LFn.u.: Low-frequency, heart rate variability, normalized units; LF : HF: Low frequency to High-frequency ration (sympathovagal balance)

Table 10. Summary of findings from stepwise forward linear regression analysis between stress HRV parameters and significantly correlated EEG variables.

HRV Parameter	EEG Correlate	EEG Correlate location	Direction of relationship
LF n.u.	Gamma wave activity	Frontal	Direct
HF n.u.	Gamma wave activity	Frontal	Inverse
Total Power	Theta wave activity	Frontocentral	Inverse
LF : HF	Delta wave activity	Frontal	Direct
	Delta wave activity	Temporal	
	Delta wave activity	Occipital	

Table 10 presents a summary of electroencephalography and electrocardiography correlation findings for the stress phase.

Key: HFn.u.: High-frequency heart rate variability normalized units; LFn.u.: Low-frequency, heart rate variability, normalized units; LF : HF: Low frequency to High-frequency ration (sympathovagal balance)

at rest. Frontocentral gamma activity is associated with memory formation (Basar et al., 1991; Singer and Gray, 1995), language processing (Pulvermüller et al., 1995), perception (Pulvermüller et al., 1997; Steriade et al., 1996), and associative learning (Miltner et al., 1999). The parasympathetic system predominates during quiet, resting conditions (McCorry, 2007). This coupling pattern during the resting phase lends itself to the psychophysiological coherence model proposed by (McCraty et al., 2009). This model suggests that distinct emotions and environmental conditions such as relaxation infer psychophysiological synchronicity, such that the bod-

ily systems work in unison. The findings from the present study suggest a distinct neurocardiac coupling pattern of HRV and frontocentral gamma activity at rest. That is, during rest, there is a negative correlation between LF HRV and frontocentral gamma activity, and a positive correlation between HF HRV and frontocentral gamma activity.

Total power (TP) is defined as the sum of the variance in the four spectral bands; LF, HF, Ultra Low Frequency, and Very Low Frequency. In the present study, resting TP was positively correlated with frontal beta wave activity. It is well accepted in the

literature that increases in prefrontal beta wave activity can represent anticipatory responses to stimuli (Haenschel et al., 2000). During the stress phase, TP was positively correlated with frontocentral theta wave activity. Previous studies have suggested that a predominance of theta waves during active tasks may suggest cognitive fatigue (Lal and Craig, 2002). Prolonged cognitive acuity is often a requirement of those within the nursing occupation. The predominance of theta waves during the stress task may indicate the cognitive fatigue associated with the task. Further, the relationship between TP and frontal theta waves may provide a future neurophysiological biomarker of cognitive fatigue.

Several limitations warrant comment. We have used heterogeneous nursing participation samples; as such, we have not controlled for baseline chronic stress upon entry into the study or epidemiological factors such as years of nursing experience. On the other hand, we are using within the design to explore acute stress states during a stressful activity versus baseline that we have captured. In doing so, we have found associations with cortical EEG and cardiac HRV coupling. Any population that we choose will likely be heterogeneous with respect to their background stress levels, and people will have different social cognitions that mitigate both chronic stresses and burn out at baseline. There is a significant body of literature that indicates that baseline stress levels are challenging to capture (Epel et al., 2018). The acute stress task chosen (Trier Social Stress Test) is robust and reliably induced an acute stress response as per our associations reported during the task. Given the baseline level of stress experienced by this sample, it can be inferred the stress response couplings that were recorded can be extrapolated to a broader stressed population. If the resultant stress neural-coupling responses are evident in a population with a high resting baseline stress level, within whom stress accommodation is likely being physiologically engaged, these relationships may be present to an even greater degree in a non-stressed population. The task engages several cognitive domains during the stress task itself that can elicit an emotional stress response, and this has been validated previously by other investigators concerning biological markers of salivary cortisol, heart rate, and the hypothalamic-pituitary-adrenal axis (Birkett, 2011; Hellhammer and Schubert, 2012). Finally, given the exploratory nature of the paper, the data were not corrected for multiple comparisons. As such, findings should be interpreted with caution given the multiple correlations and the chance of Type 1 error. We have, however, highlighted results with a *P*-value of < 0.01, which conforms to reducing type 1 error.

Future research may benefit from the exploration of neural-cardiac relationships identified within this study, in particular, the inverse relationship between LF and HF HRV and frontocentral delta waves. The delta waves demonstrate a consistent pattern of neural cardiac coupling, which could be further examined by exploring different frequencies in the delta range to assess the power of this relationship further and to explore acute stress recovery. We have not explored cognitive parameters in the present study and how these may interact with specific coupling and was not our aim to do so. Where appropriate, we have drawn reference to the interaction of cognitive states that may affect the EEG biomarkers and also explain an underlying stress response.

5. Conclusions

The distinct patterns of neural-cardiac coupling identified within this study provide a unique insight into the dynamic associations between brain and heart function during both resting and acute stress states. Moreover, the findings from this study contribute to a growing body of literature that suggests HRV may be used to predict behavioral responses to stress. This study provides the foundations for future research regarding possible ubiquitous patterns of neural-cardiac stress patterns and may allow for early identification of a physiologically stressed state. This, in turn, may allow for early intervention and management of deleterious stress responses in occupations where stress impairs functionality. Moreover, the findings underscore the hypothesis of response stereotypy in that neural and cardiac responses to stress are often universal despite possible differing individual coping strategies.

Abbreviations

ANS: Autonomic nervous system; ECG: Electrocardiogram; EEG: Electroencephalogram; HF: High Frequency Heart Rate Variability; HFn.u.: High Frequency Heart Rate Variability normalized units; HPA: Hypothalamic-pituitary-adrenal axis; HRV: Heart rate variability; LF: Low Frequency Heart Rate Variability; LFn.u.: Low Frequency Heart Rate Variability normalized units; LF : HF: Low Frequency to High Frequency Ratio; LF:HFn.u.: Low Frequency to High Frequency Ratio normalized units; SAM: Sympathetic-adrenal-medullary axis; TP: Total Power.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the UTS Human Research Ethics Committee.

Acknowledgment

Conflict of Interest

The authors declare no conflict of interest.

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