Dynamic fluctuations in ascending heart–to–brain modulations under mental stress elicitation

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Keywords

Brain–heart interplay, mental stress, physiological modeling, sympathovagal control

Highlights

- We tested a model to assess brain–heart interplay under mental stress elicitation.
- The model revealed that stress levels are reflected in heart–to–brain variability.
- Interplay from sympathetic to delta and beta waves are the best markers for stress.

Abstract

Previous endeavors have revealed how the dynamical information exchange between central and autonomous nervous systems, as measured from brain–heart interplay, can explain emotional arousal and physical stress. In this study, we test our recently proposed computational framework for a functional brain–heart interplay assessment; the Sympatho-Vagal Synthetic Data Generation Model. The model estimates the causal and bidirectional neural modulations between EEG oscillations and sympathetic/parasympathetic activity. Here, mental stress is elicited by increasing the cognitive demand and quantified on 37 human volunteers. The increase on mental stress induced an increased variability on heart–to–brain functional interplay, primarily from sympathetic activity on EEG oscillations in the delta and beta bands. Existing theoretical and experimental evidence has shown that stress involves top-down neural dynamics in the brain. Therefore, our results show that mental stress involves dynamic and bidirectional neural interactions at a brain–body level as well, where bodily feedback shapes the perceived stress caused by an increased cognitive demand. We conclude that brain–heart interplay estimators are suitable biomarkers for stress measurements.

1. Introduction

Human physiology entails constant and dynamic adaptations occurring in response to cognitive demand, involving homeostatic and allostatic mechanisms. From a holistic point of view, the physiological responses to cognitive pressure are deemed as mental stress, which can be elicited by memory, arithmetic, and increased cognitive demand tasks [1]. Physical stress involves the physiological responses triggered by homeostatic regulations to bodily conditions, emerging from physical exercise or environmental changes (e.g., temperature or atmospheric pressure) [1]. Mental and physical stress encompass physiological responses from different brain structures, together with endocrine and autonomic responses [2,3]. The neurophysiology of stress sets the hypothalamus as a central component, in which the paraventricular nucleus is the main integrator of stress signals, activating stress systems such as the Sympathetic-Adreno-Medullar and Hypothalamus-Pituitary-Adrenal axes [4]. The brain structures actively participating in stress responses include the prefrontal cortex, which is actively involved in responses to overall environmental stimuli [5], and the amygdala, associated to emotional processing and stress responses [6]. The prefrontal projections to the amygdala have shown activated in stress responses [7], but also the projections from hippocampus to the amygdala and prefrontal cortex [8]. These mechanisms have been captured in EEG studies, showing a high diversity of responses, including hemispheric changes in alpha power and wide-range variability in the EEG spectrum [9,10].

There is a strong relationship between stress and autonomic activity (for a review, see Lamotte et al., 2021), in a similar direction as occurs with emotions processing [11,12]. For instance, cardiovascular dynamics are part of the steady responses to increased arousal, as elicited from mental and physical stress conditions [13,14]. Stress conditions can become emotionally challenging [15], therefore, the ability to exert control over the physiological responses to stress (i.e., stress regulation) is directly related to the physiological mechanisms of emotion regulation [16]. Recently, emotion regulation has shown to involve an active brain–heart information exchange [17]. Still, stress responses do not require the explicit mental representation of the emotional state [12], and therefore, the neurophysiology of stress may diverge in some communication pathways with respect to emotional arousal. Some studies have described and hypothesized some components of the brain–body interplay under mental stress (for a review, see Schulz and Vögele, 2015). However, the existing experimental evidence has not yet described the mutual and bidirectional interplay between central and autonomic nervous systems under stress. The existing EEG evidence is described as neural correlates, which does not imply causality between the observed parallel changes in brain and autonomic activities [19]. For instance, acute stress triggers parallel fluctuations in heart rate variability and functional connectivity between central executive and default mode networks [20]. Neural responses to heartbeats have been described as a potential indicator of stress, because of the correlations found with sympathetic

indexes [21]. Similarly with the correlations found between EEG power and autonomic indexes under mental stress [22].

To better understand the brain–heart interplay mechanisms involved in mental stress we explore the mutual modulations between EEG oscillations and cardiac sympathetic/parasympathetic activities, as proposed in the Sympathovagal Synthetic Data Generation model (SV-SDG) [23]. The evidence in physiological and cognitive conditions suggests that mental stress may encompass an active brain–heart interplay, from the bidirectional interactions observed under thermal stress [23], to the role of the central autonomic network for thermoregulatory responses to mental stress [24], and the active role of ascending vagal inputs in emotion elicitation [25]. The model provides time-varying interaction estimates for both sympathetic and parasympathetic activities as linked to a specific EEG oscillation at a given frequency band. The framework embeds a heartbeat generation model based on the estimation of sympathetic and parasympathetic activities from a Laguerre expansions of the heartbeat series [26]. We test the SV-SDG model in a dataset of 37 healthy human participants undergoing three increasing levels of mental stress, including visual stimulation and memory tasks.

2. Materials and methods

2.1 Dataset description

This study comprised 37 healthy participants undergoing a mental stress task (age median 30 years, age range 22–45 years, 20 males, 17 females). Participants were asked to sit comfortably and follow instructions on screen. The recordings include EEG (9-channel, Biopac B-Alert) and one lead ECG, sampled at 256 Hz.

This study was performed in accordance with the Declaration of Helsinki. Neurons Inc. follows the rules and laws of the Danish Data Protection Agency. Neurons Inc's data protection policy also follows the European Union law of the General Data Protection Regulation, as well as the ethical regulations imposed by the Neuromarketing Science and Business Association, Article 6. Each person's biometric data, survey responses, and other types of data were anonymized and only contained the log number as the unique identifier. Personal information cannot be identified from the log number.

2.2 Experimental protocol

The protocol included four stress load conditions presented in a parametric modulation setup: 1-minute rest and three different stress load conditions, with a total duration of 15 minutes approximately. The stressors were presented in the same order to all participants. The first stress load condition consisted in watching a documentary. The second stress load condition consisted in watching a documentary in parallel to a digit span task. The third stress load condition consisted in watching a documentary, performing the digit span task and the red box task in parallel. Participants were asked to report the level of stress of the three stressors on a discrete scale between 1 to 7.

The documentary "The Reality of Van Life", Different Media © 2018, first five minutes are projected in screen as first stressor (Figure 1A). The digit span task starts with a fixation cross for 1.5 s. Then three digits are presented for 5 s, followed by a blank screen for 4 s. Then the participant is asked to verbally say the three digits in up to 5 s (Figure 1B). The red box task, run in parallel to the digit span task (Figure 1C), starts with a fixation cross for 1.5 s. Then a red box (4x4 red and white box pattern) is presented for 3 s. Next, the three digits are presented for 5 s, followed by a blank screen for 4 s. Then the participant is asked to verbally say the three digits in up to 5 s. Consecutively, a red box is presented, and the participant is asked if the pattern matches to the previously presented one (yes or no answer).

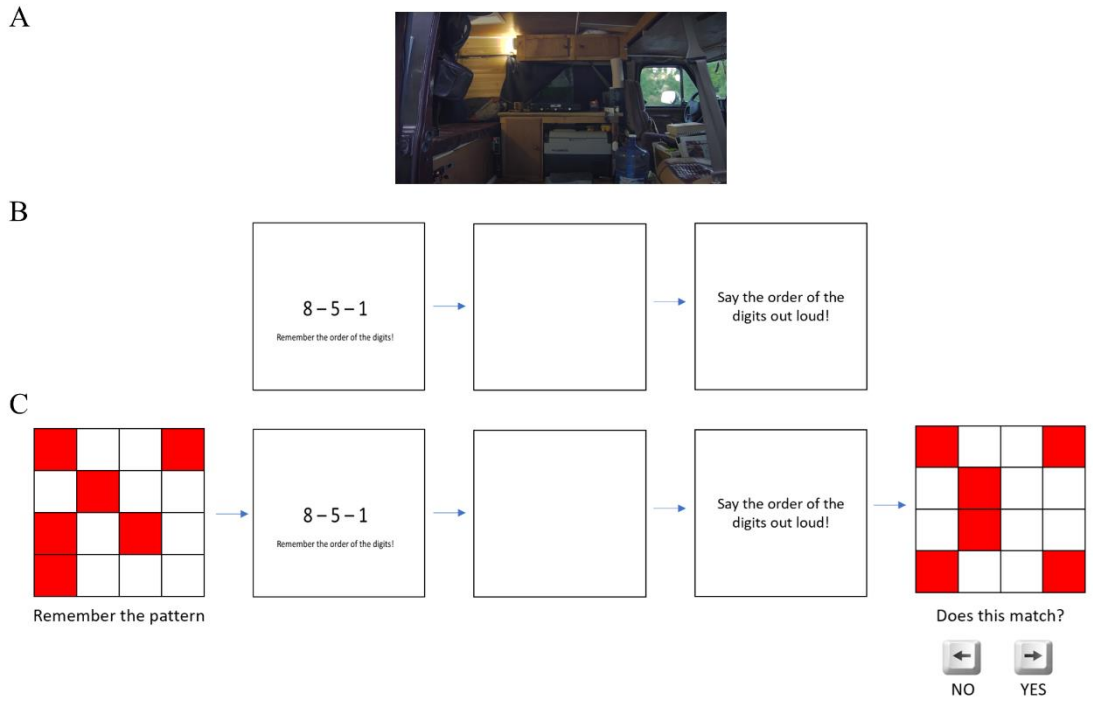

Figure 1. Experimental protocol. (A) Sample image from stress load condition 1, The Reality of Van Life, Different Media © 2018. (B) Sample image from stress load condition 2: digit span task. (C) Sample figure from stress load condition 3: digit span task + red box task.

2.3 EEG pre-processing

EEG data were pre-processed using MATLAB R2022a and Fieldtrip Toolbox [27]. EEG data were bandpass filtered with a Butterworth filter of order 4, between 0.5 and 45 Hz. Large movement artifacts were visually identified and removed manually from independent component space using wavelet filtering. Consecutively, the Independent Component Analysis (ICA) was computed to visually recognize and reject the eye movements and cardiac-field artifacts from the EEG data. One lead ECG was included as an additional input to the ICA to enhance the process of finding cardiac artifacts. Once the ICA components with eye movements and cardiac artifacts were visually identified, they were removed to reconstruct the EEG series. Channels were re-referenced using a common average, which is the most appropriate for a brain–heart interplay estimations [28].

The EEG spectrogram was computed using the short-time Fourier transform with a Hanning taper. Calculations were performed through a sliding time window of 2 seconds with a 50% overlap, resulting in a spectrogram resolution of 1 second and 0.5 Hz. Then, time series were

integrated within five frequency bands (delta: 1-4 Hz, theta: 4-8 Hz, alpha: 8-12 Hz, beta: 12-30 Hz, gamma: 30-45 Hz).

2.4 ECG data processing

ECG time series were bandpass filtered using a Butterworth filter of order 4, between 0.5 and 45 Hz. The R-peaks from the QRS waves are detected in a procedure based on template-matching method [28]. All the detected peaks were visually inspected over the original ECG, along with the inter-beat intervals histogram. Manual corrections were performed where needed and guided from the automatic detection of ectopic beats [29].

2.5 Functional brain–heart interplay assessment

The Sympathovagal Synthetic Data Generation model (SV-SDG) provides time-variant estimates of the bidirectional functional coupling between heartbeat and brain components. The model uses the estimation of sympathetic and parasympathetic activities proposed in [26,30].

2.5.1 Functional Interplay from the brain to the heart

The descending interplay is quantified through a model of synthetic heartbeat generation based on Laguerre expansions of RR series (see Candia-Rivera et al., 2021a for further details). Briefly, heartbeats generation is based on the modulation function *m(t)*, which contains the fluctuations with respect to the baseline heart rate. Such fluctuations are modeled including the sympathetic and parasympathetic interplay. In Eq. (1), the modulation function is expressed as a linear combination of sympathetic (SAI) and parasympathetic activity index (PAI), and their respective control coefficients C_{SAI} and C_{PAI} representing the proportional central nervous system contribution:

$$m(t) = C_{SAI}(t) \cdot SAI(t) + C_{PAI}(t) \cdot PAI(t) \qquad (1)$$

The modulation function is then taken as input to an integrate-and-fire model [26]. The model is fitted on the RR interval series using a 15-seconds sliding time window and a linear regression model with no constant term. Then, the interaction between heartbeat dynamics and the cortical activity is defined as:

$$SDG_{EEG\ F \rightarrow X}(t) = C_X(t) / EEG_F(t-1) \qquad (2)$$

where $X \in \{SAI, PAI\}$, and EEG_F indicates the time-varying EEG power with $F \in \{\delta, \theta, \alpha, \beta, \gamma\}$.

2.5.2 Functional Interplay from the heart to the brain

The functional interplay from heart to brain is quantified through a model based on the generation of synthetic EEG series using an adaptative Markov process [31]. The model is fitted using a least-square auto-regressive process to estimate cardiac sympathovagal contributions to the ongoing fluctuations in EEG power as:

$$EEG_F(t) = \kappa_F \cdot EEG_F(t-1) + \Psi_F(t-1) + \varepsilon_F \qquad (3)$$

where F is the EEG frequency band, κ_F is a fitting constant, ε_F is the adjusted error, and Ψ_F indicates the fluctuations of EEG *power in the F*. Then, the heart–to–brain functional coupling coefficients are calculated as follows:

$$SDG_{X \rightarrow EEG\ F}(t) = \Psi_F(t) / X(t) \qquad (4)$$

where X ∈ {SAI, PAI}. For further details, please see Candia-Rivera et al., 2022a.

The software for computation of SAI and PAI is available at *www.saipai-hrv.com*. The source code implementing the SV-SDG model is available at *www.github.com/diegocandiar/brain_heart_svsdg*.

2.6 Multivariate analysis

The multivariate analysis included a prior selection of features from SV-SDG coefficients. The selection is based on the ranking provided by the computation of Minimum Redundancy Maximum Relevance (MRMR) scores [32].

The MRMR score computation algorithm is as follows:

1. The relevance V_x of all features x is computed. The feature with the largest relevance $\max_{x \in \Omega} V_x$ is selected. The selected feature is added to an empty set of features S.

   V_x is defined as:

$$V_x = \frac{1}{S \vee \sum_{x \in S} I(x, y)} \qquad (5)$$

Where $S \vee$ is the number of features in S and $I(x, y)$ is the mutual information between the feature x and the output y:

$$I(x, y) = \sum_{ij} p(x_i, y_j) log \frac{p(x_i, y_j)}{p(x_i) p(y_j)} \qquad (6)$$

2. Next, the features with non-zero relevance V_x and zero redundancy W_x in S^c (complement of S) are identified. Then, select the feature with the largest relevance, $\max_{x \in S^c, W_x = 0} V_x$. The selected feature is added to the set S.

   W_x is defined as:

$$W_x = \frac{1}{|S|^2} \sum_{x,z \in S} I(x,z) \tag{7}$$

If S^c does not include a feature with non-zero relevance and zero redundancy, skip step number 3

1. Repeat step number 2 until the redundancy W_x is not zero for all features in S^c.
2. Select the feature with the largest MIQ, with non-zero relevance and non-zero redundancy in S^c, and add the selected feature to the set S.
   MIQ is defined as:

$$\max_{x \in S^c} MIQ = \max_{x \in S^c} \frac{V_x}{W_x} = \max_{x \in S^c} \frac{I(x,y)}{\frac{1}{|S|} \sum_{z \in S} I(x,z)} \tag{8}$$

3. Repeat Step 4 until the relevance is zero for all features in S^c.
4. Add the features with zero relevance to S in random order.

The multivariate analyses are performed in a 5-fold cross-validation. Linear regressions to the stress level are performed using least squares kernel regression, using MATLAB 2022a default parameters. The stress level was defined at rest = 0, and the three experimental conditions as the group median reported level of stress (stressor 1 = 1, stressor 2 = 4, stressor 3 = 5). The regression performance is measured with Root Mean Squared Error (RMSE) in the estimation of group median level of stress. Binary classifications are performed using kernel naïve Bayes classifier, using MATLAB 2022a default parameters. To perform binary classifications, the four experimental conditions were divided in either low or high stress, where low stress encompass rest and stressor 1, and high stress the stressors 2 and 3. The classification performance is measured through the accuracy on identifying high or low stress.

2.7 Statistical analysis

Group-wise statistical analysis between resting state and the three stressors studied through non-parametric Friedman test and two-conditions comparisons through Wilcoxon signed-rank test. The statistical tests were performed over individual EEG channels, in which the inputs correspond to SV-SDG coupling coefficient computed at different experimental conditions. The

significance level of the *p*-values was corrected in accordance with the Bonferroni rule for 9 channels, with an uncorrected statistical significance set to alpha = 0.05. The samples were described group-wise using the median, and related dispersion (variability) measures were expressed as the median absolute deviation (MAD).

3 Results

The experimental protocol consisted in a resting state period and consequent three levels of stress. The participants' reports on the perceived level of stress are displayed in Figure 2, where the group median reported stress levels are 1, 4 and 5, for stress load conditions 1, 2 and 3, respectively. All three stress load conditions reports are significantly different from each other.

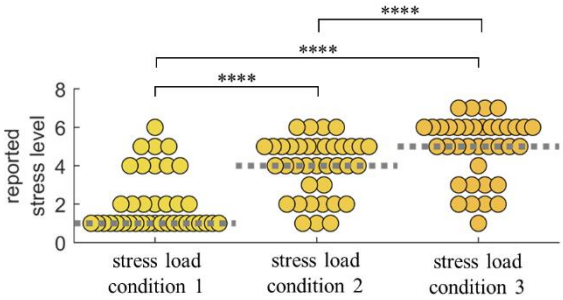

*Figure 2. Reported stress level for the three stressors: i) stress load condition 1: documentary, ii) stress load condition 2: documentary + digit span task, iii) stress load condition 3: documentary + digit span task + red box task. **** < 0.00005*

The autonomic dynamics are assessed with estimators of sympathetic and parasympathetic activity (SAI and PAI, respectively). Figure 3 depicts the group distributions of SAI and PAI median and variability values. Significant differences are observed between experimental conditions, in which the three stress load conditions cause an increase in the autonomic variability, as compared to rest.

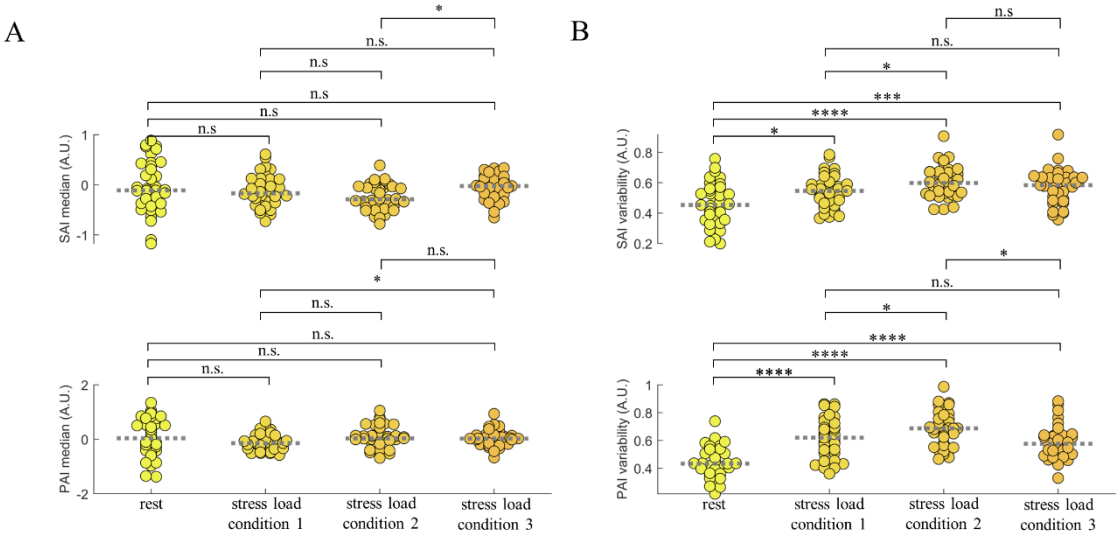

Figure 3. (A) SAI and PAI median. (B) SAI and PAI variability as measured with median absolute deviation (M.A.D.), at the four experimental conditions. The time-varying autonomic indexes were z-score normalized for the whole experimental protocol duration before computing median and M.A.D values. Stress load condition 1 consists of

*documentary visualization. Stress load condition 2 consists in documentary visualization and performing the digit span task in parallel. Stress load condition 3 consists in documentary visualization, performing the digit span and red box tasks in parallel. * < 0.05, ** < 0.005, *** < 0.0005, **** < 0.00005*

We further explored whether the strong differences observed in the autonomic markers variability relate to brain–heart interplay. Figure 4 illustrates the Friedman tests results, in which are assessed the group-wise changes among all experimental conditions. Ascending interactions present a stronger change on brain–heart interplay variability, as compared to descending interactions. In contrast, the cortical power variability is not significantly increased by mental stress (see Figure 4 bottom row), as compared to brain–heart interplay markers.

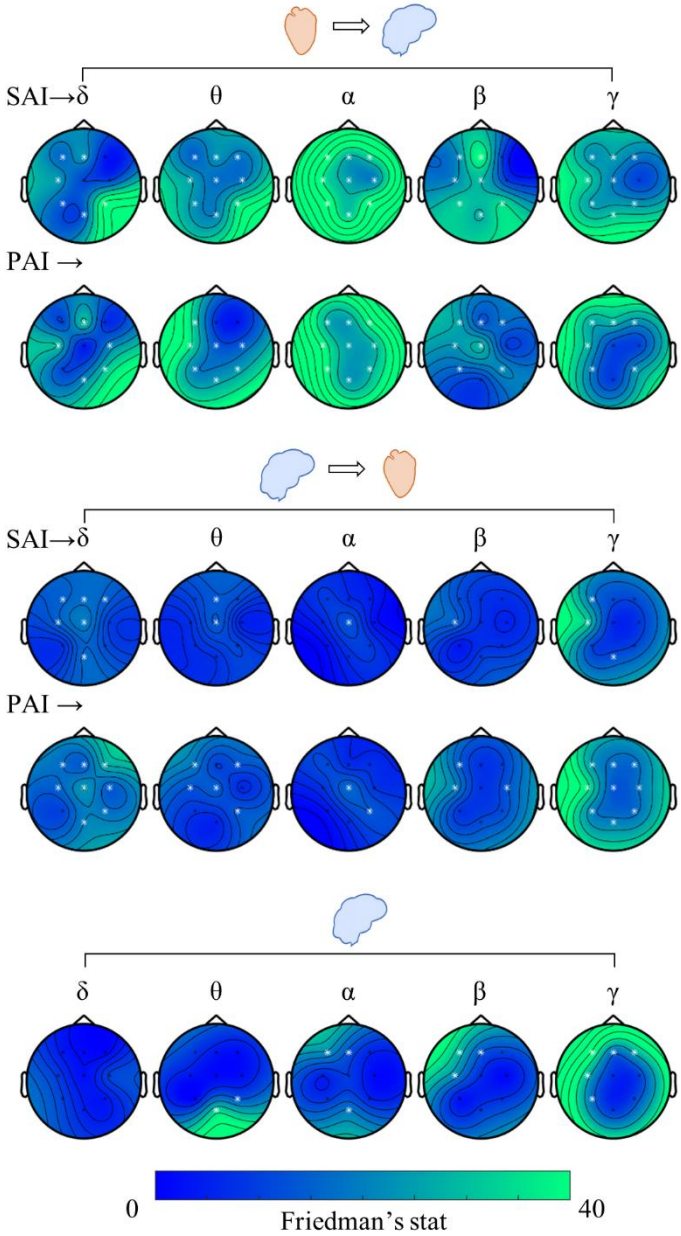

Figure 4. Friedman test on brain–heart interplay variability and EEG power variability at the four experimental conditions. Colormaps indicate the Friedman test statistic. White electrodes indicate p < 0.05/9.

To further explore the potential interactions and complementarity between brain–heart interplay markers, we performed multivariate analyses. The MRMR was computed over the 180 markers (180 = 2 directions x 2 autonomic markers x 5 brain oscillations x 9 channels) in two conditions: (i) linear regression to the group median reported stress level in each condition, and (ii) binary classification between low vs high stress level. The best five markers for the two cases are reported in Figure 5A and B. In both multivariate analyses, ascending markers from SAI and PAI are prevalent. The regression to the median stress level ranks SAI→beta as best marker, as measured with MRMR scores. The binary classification to low vs high stress level ranks PAI→gamma as best marker but showing a better separability in SAI→beta and SAI→delta. Using the best five selected markers (see Table 1) under the MRMR criteria to the regression to group median, the obtained RMSE is 1.6851. The regression output shows a significant difference to all pair comparisons, with exception of the stressor 2 vs stressor 3 comparison (Figure 5C). Using the best five selected markers (see Table 1) under the MRMR criteria to the binary classification obtained an accuracy of 77% (Figure 5D).

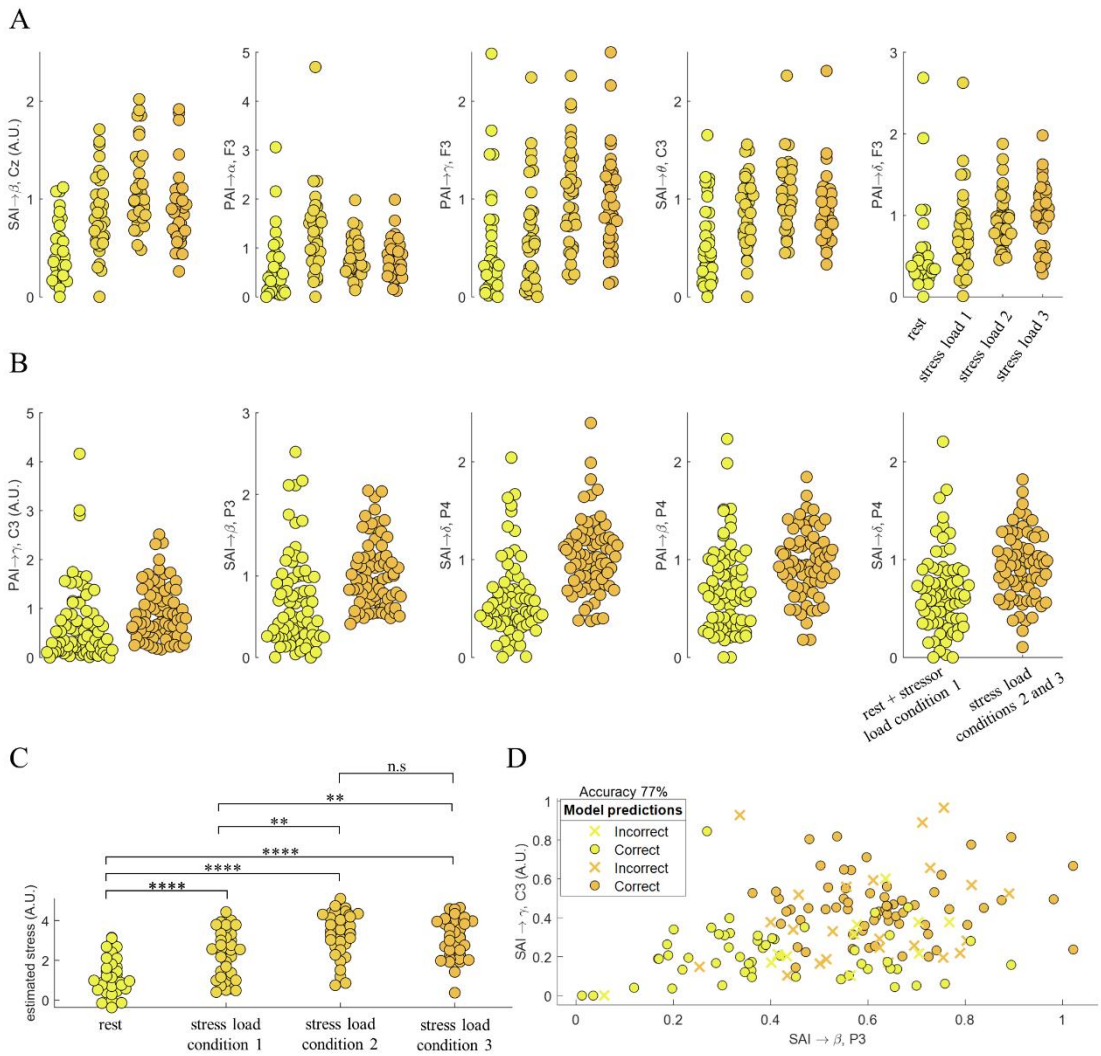

*Figure 5. (A) Best five brain–heart interplay markers to regress the stress level (regression to the group median stress level: rest=0, stressor1=1, stressor2=4, stressor3=5). (B) Best five brain–heart interplay markers to classify low vs high stress level (low: rest + stressor1, high: stressor2 + stressor3). (C) Model output to the stress level linear regression using the best five markers under the MRMR criteria. (D) Model output to the stress level linear binary classification using the best five markers under the MRMR criteria. Yellow circles are low stress and orange circles are high stress conditions. **** $p < 0.00005$.*

Table 1. Minimum redundancy maximum relevance (MRMR) scores of the best five features for regression to the level of stress (rest=0, stressor1=1, stressor2=4, stressor3=5) and for the binary classification low vs high stress (low=rest+stressor1, high=stressor2+stressor3).

	1st feature	2nd feature	3rd feature	4th feature	5th feature
Regression	SAI→β, Cz MRMR=0.2395	PAI→α, F3 MRMR=0.2247	PAI→γ, F3 MRMR=0.1771	SAI→θ, C3 MRMR=0.1669	PAI→δ, P4 MRMR=0.1521
Binary classification	PAI→γ, C3 MRMR=0.1464	SAI→β, P3 MRMR=0.1399	SAI→δ, P4 MRMR=0.1156	PAI→β, P4 MRMR=0.0473	SAI→δ, F3 MRMR=0.0453

In Figure 6 is shown one single subject example. The evolution of SAI→beta and SAI→delta modulations is presented for the whole experimental protocol. An overall increased variability of both markers can be observed in stress load conditions 2 and 3, as compared to rest and stress load condition 1, which can be clearly observed in the case of SAI→beta, Fz channel.

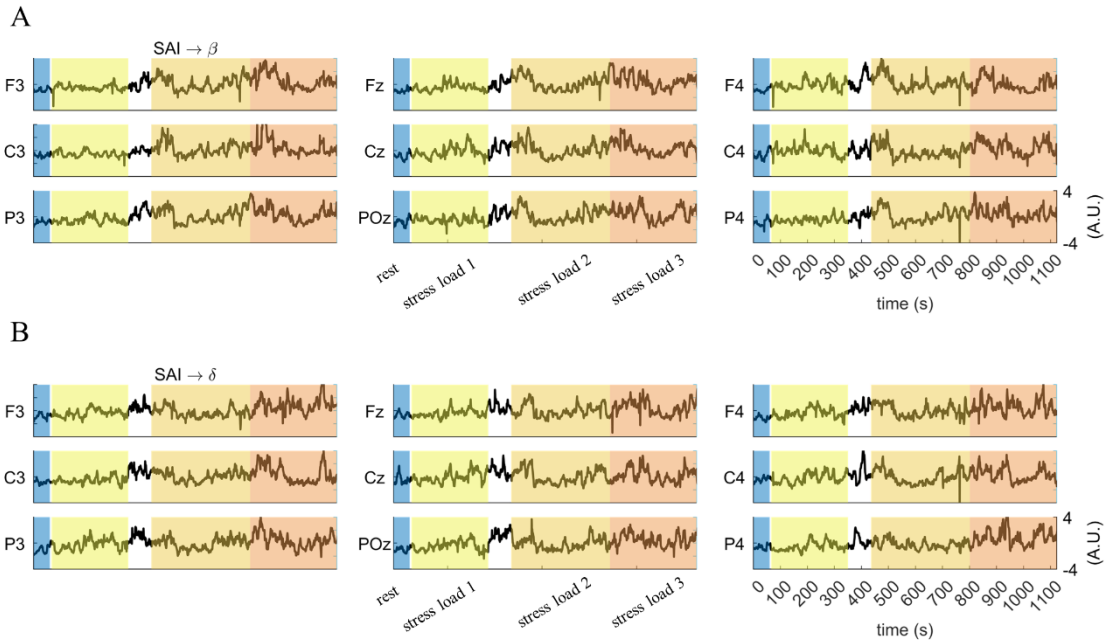

Figure 6. Exemplary participant during the experimental protocol in their fluctuations in (A) SAI→beta and (B) SAI→delta modulations.

4 Discussion

Building upon existing evidence on brain–heart interplay in emotional arousal [25], thermal stress [23], and thermoregulation under mental stress [24], we hypothesized a direct brain–heart interplay involvement under mental stress. The existing literature highlights the presence of parallel changes in brain dynamics and heart-rate variability. However, very little is known whether these parallel changes have a functional relationship and whether mutual modulations exist on time.

The median values of SAI and PAI are less successful on separating the stress conditions, as compared to the variability. We observed an increase of SAI variability with respect to the stress level. However, PAI values did not follow an increased variability as compared to SAI, where the highest stress condition (stress load condition 3) presented a lower group median compared to stress load condition 2, although non-significant. These results indicate a dynamical and nonlinear behavior of autonomic dynamics under mental stress.

We observed that the variability of autonomic markers gave higher separability between the experimental conditions, as compared to the median values. Therefore, we analyzed the brain–heart interplay variability under four different levels of stress. Our results showed that ascending heart–to–brain modulations better reflect the level of stress, as compared to descending brain–to–heart modulations. We observed an active and dynamic fluctuations of both branches of the autonomous nervous system, as measured by SAI and PAI markers. The measured ascending modulations from SAI and PAI are observed over all frequency bands studied. In this study. the main component involved in stress levels is SAI→beta. The involvement of beta waves in mental stress has been previously reported [33]. However, the existing evidence on EEG and stress shows high diversity and heterogeneity of results, being all bands from delta to gamma involved in stress elicitation. Some studies suggest that different dimensions of stress are associated with the interactions between different frequency bands, such as alpha-beta interactions [10,34,35], theta-beta interactions [34,36], alpha-gamma interactions [37–39], and theta-alpha interactions [38]. The high variability of the existing studies may be related to the subjectivity associated to either reported or perceived stress [37], but also to the mental strategies used when performing the different stress tasks [40]. For instance, the processing of multiple signals in parallel requires access to the working memory system, which dynamically resets to adapt to environmental demands [41]. Another source of variability may be associated with the level of cognitive demand during the tasks, which may not be directly related to the stress level [42]. In this study, the digit span task involved a verbal report, which is also associated to differentiated EEG signatures in parieto-occipital desynchronizations of lower alpha [43]. We observed an activation in both frontal and parietal regions, confirming their involvement in stress for overall stimulations in

frontal and prefrontal structures [5], and for general cognitive operations in parietal structures [44].

On the autonomic side, sympathetic activity is associated with mental stress elicitation, as measured from systolic blood pressure, heart rate, ventricular ejection fraction, and skin conductance [21]. The measurements on heart rate variability show that mental stress induced from mental arithmetic tasks causes increase in low frequency fluctuations, and a decrease in high frequency [35,45–47], suggesting an increase in the sympathetic tone, and a decrease in the parasympathetic one. More recently, stress showed changes in heart-rate's non-linear dynamics [48], indicating more complex dynamics, beyond an increase or decrease of autonomic nervous system activities. These autonomic variations have been reported as well to be associated with fluctuations in attention [49]. High frequency activity is associated with memory retrieval, as it correlated with performance and reaction times [50,51]. The existing evidence indicates that mental stress elicitation through mental calculation and memorizing tasks involves a dynamic interaction between sympathetic and parasympathetic activities, in which sympathetic activity is involved in slow-paced stress elicitation and parasympathetic activity is involved in memory retrieval and action execution [46]. The active role of autonomic activity has been previously suggested in executive functioning as well (e.g., self-control and working memory) [52–55].

With respect to the directionality of the modulations between brain and heart, the existing evidence suggests that stress systems performs a top-down control at brain level [6,56]. However, under psychological stressors, if the activity of the amygdala and hippocampus becomes more prevalent, the stress system can switch to a bottom-up control [57]. Experimental evidence shows that brain responses precede the cardiac responses, as measured in EEG [35,39] and fMRI [58,59]. While top-down signaling may be predominant, the bidirectional interactions exists [59], as the ascending arousal system shapes brain dynamics to mediate awareness of mental states [60] and to facilitate performance at different tasks [61,62]. In fact, stress regulation encompass the processes involved in emotion regulation [16], and ascending sympathetic-vagal inputs shape physical and emotional arousal [23,25]. The role of ascending visceral inputs show that the anterior insula integrates interoceptive signals during emotional and cognitive processing, being these processes involved to the monitoring of the physiological state of the body [63]. The projection neurons from interoceptive networks in the brain target autonomic control areas, which are relevant to predict the physiological states of the body, and then send them through cortico-cortical projections to the posterior insular cortex [64]. These brain predictions and adjustments using information from bodily activity may trigger both emotional feelings and homeostatic responses [12]. The functional brain–heart interplay under stress elicitation has been shown in heartbeat-evoked potentials correlating with stress-induced changes in cardiac output [21], and correlates of functional connectivity with heart rate variability [20]. The role of cardiac inputs in

the neurophysiology of stress is also supported by the experimental evidence showing an increased information flow from heart-to-brain during increased attention [49] and disrupted abilities on detecting cardiac and respiratory signals from oneself under anxiety [65,66].

We showed that a multivariate analysis can help to better distinguish between stress levels, as compared to individual autonomic markers, given that ascending sympathetic modulations to delta and beta oscillations provide complementary information. The use of low-density EEG in this study is certainly a limitation to understand the brain mapping and cortical dynamics of stress neurophysiology, but also confirms the usability of this kind of devices to detect levels of stress with potential commercial applications. The study of mental stress elicited in other paradigms, such as mental arithmetic, could give a broader view of the physiological processes involved in brain–heart information exchange. Our study confirms the advantages of analyzing the interactions between brain and heart, instead of studying heart rate and brain dynamics separately [19,67], to understand the origin and potential pathways of the observed physiological changes. The understanding of brain–heart dynamics and the neurophysiological substrates of stress has clinical relevance. Heart rate variability markers are acknowledged to reflect autonomic dysregulation, which may lead to morbidity and mortality [68,69]. The evidence also shows differences in heart rate variability between healthy humans and different mood disorders, but also as a marker of the effects of antidepressant medications [68]. The description of stress mechanisms can enlighten the apparent relationships with cardiac death [70], cardiovascular disease [71], sudden death [72], and psychiatric disorders [73]. The evidence in other markers of brain–heart interplay shows as well that the dynamic interaction of these systems may relate to different aspects of mental health [21,74,75].

5 Conclusions

Our results demonstrate that stress neurophysiology comprises dynamic and bidirectional cortico-cortical and brain–body interactions, where bodily feedback is involved in shaping the perceived mental stress. These results are in line with the experimental evidence showing a dynamical information exchange between central and autonomous nervous systems in emotional arousal and physical stress. We conclude that stress levels can be effectively measured from brain–heart interplay estimators.

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7 Authors’ contributions

Conceptualization: D. Candia-Rivera and T. Z. Ramsøy; Data curation: K. Norouzi; Formal analysis and Investigation: D. Candia-Rivera and G. Valenza; Methodology: D. Candia-Rivera; Supervision: T. Z. Ramsøy and G. Valenza; Writing - original draft: D. Candia-Rivera; Writing - review & editing: All authors.

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