A new framework for modeling the bidirectional interplay between brain oscillations and cardiac sympathovagal activity

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Abstract— **The study of functional brain-heart interplay (BHI) aims to describe the dynamical interactions between central and peripheral autonomic nervous systems. Here, we introduce the Sympathovagal Synthetic Data Generation Model, which constitutes a new computational framework for the assessment of functional BHI. The model estimates the bidirectional interplay with novel quantifiers of cardiac sympathovagal activity gathered from Laguerre expansions of RR series (from the ECG), as an alternative to the classical spectral analysis. The main features of the model are time-varying coupling coefficients linking Electroencephalography (EEG) oscillations and cardiac sympathetic or parasympathetic activity, for either ascending or descending direction of the information flow. In this proof-of-concept study, functional BHI is quantified in the from-heart-to-brain direction on data from 16 human volunteers undergoing a cold-pressor test. Results show that thermal stress induces heart-to-brain functional interplay originating from sympathetic and parasympathetic activities and sustaining EEG oscillations mainly in the δ and γ bands. The proposed computational framework could provide a viable tool for the functional assessment of the causal interplay between cortical and cardiac sympathovagal dynamics.**

I. Introduction

The communication between central and autonomous nervous systems may occur through different pathways, including pain, visceroceptive, spino-thalamo-cortical, and somatosensory pathways [1][2]. Such communication may occur through several mediators including hormonal and electrical/mechanical signaling, the ensemble of which has been referred to functional brain-heart interplay (BHI) at a holistic, comprehensive, and high-abstraction level. To this extent, functional BHI has been demonstrated to be dynamically involved in numerous physiological processes, including cognitive functioning [3], as well as somatosensory perception [4], and emotions [5][6].

The quantification of functional BHI has recently received attention from the scientific community. For example, computational approaches based on non-invasive recordings as electroencephalography (EEG) and heartbeat dynamics (derived from the electrocardiogram, ECG) have recently been proposed, including the analysis of spontaneous neural responses to heartbeats, and synchronization analysis between cortical and heartbeat oscillations [7]. However, most of the state-of-the-art methodologies for a BHI assessment rely on spectral analysis of heart rate variability (HRV) series, which is unable to provide accurate estimates of cardiac sympathetic activity [8][9]. In fact, the sympathetic control on heartbeat dynamics acts in the 0.04-0.15Hz frequency band, in overlap with the cardiac parasympathetic (vagal) activity. To overcome this limitation, here we introduce a novel computational framework that accounts for sympathovagal measurements of both ascending heart-to-brain and descending brain-to-heart interplay, namely, the Sympathovagal Synthetic Data Generation (SV-SDG). The model provides time-varying BHI estimates for both sympathetic and vagal activities as linked to a specific EEG oscillation at a given frequency. The framework embeds an *ad hoc* heartbeat generation model and exploits the Sympathetic Activity Index (SAI) and Parasympathetic Activity Index (PAI) [9], which are defined from a Laguerre expansions of the heartbeat series.

We test our model using real data gathered from 16 healthy subjects undergoing thermal stress through a cold-pressor test. Thermal stress, in fact, is known to elicit changes in HRV as a result of a sympathetic activity increase and a vagal activity decrease [10]. EEG studies showed that these stimuli induce an increase in the power in the δ and γ bands, mainly over the fronto-temporal areas [11]–[16]. In the frame of functional BHI, thermal stress induces changes in the bidirectional interplay mainly sustained by EEG oscillations in the δ and γ bands [17], and a suppression of heartbeat-evoked potentials [18]. In this proof-of-concept study, we focus on the assessment of heart-to-brain interplay considering both sympathetic and parasympathetic activities, based on existing evidence on the influence of ascending inputs in somatosensory perception [4]. Methodological details of the proposed framework, as well as description of results and related discussion follow below.

II. Materials and Methods

A. Dataset description

This study comprises 16 healthy right-handed subjects undergoing a cold-pressor test (age range 21–41 years, 7 males). The experimental protocol consists in 3-minute rest followed by up to 3-minute cold-pressor test. Subjects were asked to sit comfortably, keep their eyes closed to minimize artifacts, and guided to put their left hand in ~4°C water. The recordings include EEG (128-channel, EGI) and ECG series sampled at 500 Hz.

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The study was approved by ethics committee Area Vasta Nord-Ovest Toscana and followed the declaration of Helsinki requirements.

B. Data pre-processing

Data were pre-processed using MATLAB R2017a and Fieldtrip Toolbox [19]. EEG data were bandpass filtered with a Butterworth filter of order 4, between 0.5-45 Hz. An independent component analysis was applied to remove large artifacts, including eye movements and cardiac-field artifacts. EEG channels were marked as corrupted if their area under the curve exceeded 3 standard deviations of the mean of all channels, or if their weighted-by-distance correlation coefficient with neighbors was less than 0.6. Corrupted EEG channels were replaced through a spherical interpolation of neighbor channels. According to previous findings [7], EEG signals were re-referenced using a common average. The EEG spectrogram was computed using a 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, the spectrogram was integrated within the frequency bands δ: 1-4 Hz, θ: 4-8 Hz, α: 8-12 Hz, β: 12-30 Hz, γ: 30-45 Hz, to obtain time-varying power series.

The R peaks from ECG series were automatically identified following the procedure reported in [7]. Then, a visual inspection analysis was performed on RR series to check for gross artifacts. Finally, a point-process based procedure was applied to identify and correct remaining algorithmic and physiological artifacts (e.g., ectopic beats) [20].

C. The proposed Sympathovagal Synthetic Data Generation Model

We describe the Sympathovagal Synthetic Data Generation model (SV-SDG), which provides time-variant estimates of the bidirectional functional coupling between different heartbeat and brain components.

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 [21] for further details). Briefly, we generate heartbeats 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 (PAI) activities through their respective control coefficients C_{SAI} and C_{PAI} representing the proportional central nervous system contribution:

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

The modulation function is then taken as input to an integrate-and-fire model [21]. 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:

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

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

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 [22]. The model is fitted using a least-square auto-regressive process to estimate cardiac sympathovagal contributions to the ongoing fluctuations in EEG power as:

$$EEG_F(t) = \kappa_F \cdot EEG_F(t\text{-}1) + \Psi_F(t\text{-}1) + \varepsilon_F \quad (3)$$

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:

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

where $X \in \{SAI, PAI\}$. For further details, please see [23].

D. Statistical analysis

Averaged, within-session BHI estimates in the heart-to-brain direction were derived from resting state and cold-pressure conditions and were statistically compared using a cluster-based permutation analysis based on non-parametric Wilcoxon's tests, preceded [23]. The preliminary mask was identified in space, time, and frequency with $\alpha = 0.01$. A minimum cluster size of 3 channels was imposed. Adjacent candidate clusters on time were wrapped if they had at least one channel in common. The overall minimum duration of the cluster was imposed to 5 seconds. Cluster statistics are Monte Carlo p-value (p_{mc}) from 10,000 random partitions. with significance at $\alpha = 0.01$, and the Wilcoxon's absolute maximum Z-value obtained from all the samples of the mask.

III. Results

Fig. 1A shows the group-median time course of sympathetic and parasympathetic activities, i.e., SAI and PAI, respectively, and Fig. 1B shows the group-median EEG power series in the δ and γ bands, averaged in frontal channels. We observe that the cold-pressor triggers an increase in the sympathetic activity, which remains high for no less than 30s from the cold-pressure onset. Similarly, the parasympathetic activity decreases after the stimulus onset. EEG power increases after the stimulus onset, although it starts to return to resting state levels after about 10s.

Results from the statistical analysis on the functional estimation of heart-to-brain interplay are shown in Table I considering both SAI and PAI indices and EEG power series. A clustered effect was found during the cold-pressor phase, with respect to the resting state, from SAI and PAI to δ, β and γ. From the cold-pressure onset, the interplay SAI/PAI → γ occurs earlier than the other interplays. The directed interplay originating from parasympathetic activity shows also statistical differences between experimental conditions in relation to EEG power series in the θ band.

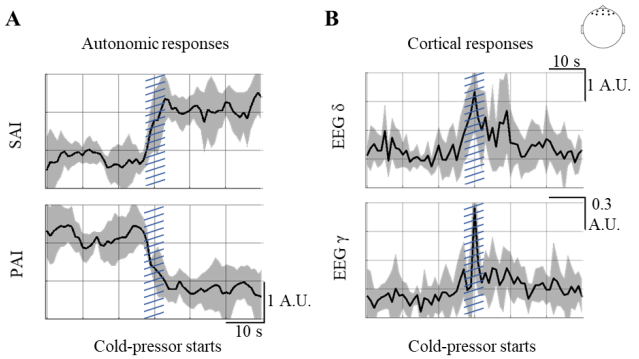

Figure 1. Physiological responses to cold pressure. The black line indicates the group-median, and the shaded gray area indicates its median absolute deviation. The cold-pressor onset is marked with striped, blue lines. (A) Autonomic changes measured as SAI and PAI. (B) Frontal EEG power changes in δ and γ bands.

TABLE I. RESULTS FROM THE CLUSTER PERMUTATION ANALYSIS

Interplay	Cluster statistics		
	latency (s) [a]	p_{mc} [b]	*Z*
SAI→δ	1-101	< 0.0001	3.46
SAI→β	1-9	0.0008	2.84
SAI→γ	0-93	0.0001	3.52
PAI→δ	5-103	< 0.0001	3.52
PAI→θ	68-101	< 0.0001	3.41
PAI→β	1-99	< 0.0001	3.52
PAI→γ	0-96	< 0.0001	3.52

a. earliest-latest sample in the cluster, b. Monte Carlo p-value from 10,000 permutations

IV. DISCUSSION

Computational methods for the measurement of functional BHI aim to quantify the neural information exchange between brain and cardiac dynamics. To this end, we proposed a novel framework to estimate functional BHI through cardiac sympathetic and parasympathetic activities. The framework relies on the definition of SAI and PAI [9], derived from HRV series. As BHI is actively and dynamically involved under sympathovagal elicitation driven by thermal stress, we tested the proposed methodology on real EEG and ECG data gathered from healthy subjects undergoing a cold-pressor test. Speculatively, the model captures the multiple communication pathways involved in body temperature changes, including the spino-thalamo-cortical pathway [1].

Our results suggest that, with respect to resting state, several changes in ascending BHI occur through EEG oscillations in the δ and γ band, primarily involving midline frontal and posterior regions. Accordingly, previous studies on EEG correlates of thermal stress showed that the spectral power in the δ-θ range is increased in frontal areas, and power in the β-γ range increases as well; the power in the α band decreases, with slight differences between studies [11]–[16].

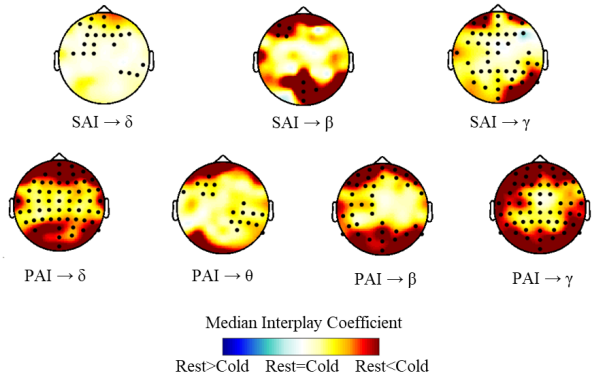

Figure 2. Clustered effects found in the ascending brain-heart interplay. Scalp topographies indicate an overall increase of the ascending interplay under cold pressure, with respect to resting state. Major increase is found in frontal and parietal regions. Thick channels indicate cluster $p_{mc} < 0.01$

We observed that BHI changes involving EEG oscillations in the α band were not triggered by the change in the experimental conditions. This may be due to the fact that the cold-pressor test does not require active cognitive participation. Therefore, a change in α activity or in the interplay with the autonomous nervous system may indeed cause minor changes.

Cortical responses to tactile, thermal, and painful stimuli usually occur within 200-350ms [24][25]. Our results suggest that such response is directly linked to the ascending interplay from SAI/PAI mainly to the cortical activity in the γ band, as we found clustered effects from the cold pressure onset. The previously reported peripheral responses to thermal stress include heart rate increase as a result of an increase in sympathetic activity and decreased cardiac vagal outflow [10]. Consistently, we observed such changes through the estimators of cardiac sympathovagal activity, SAI and PAI.

The relation between cardiovascular and brain responses to somatosensory stimulation and thermal stress has been previously described through the baroreceptor modulation of heart rate due to physiological arousal [26][27]. Consistently, it was reported that heartbeat-evoked potentials under cold stimuli shows a prominent deflection mainly over the frontal and central scalp locations [18]. In this frame, we recall that cold temperature perception may be modulated by the cardiac cycle [28]. Different mechanisms may be employed by the nervous system to ensure an optimal energy use, including anticipation processes in parallel to local feedforward regulatory processes [29].

Activation of specific brain-body interactions during cognitive processes has been shown experimentally, suggesting possible cognitive/affective modulations of autonomic responses to cold and pain [30]. The evidence on heartbeat-evoked potentials during cold stimuli showed significant changes in BHI, but this effect was minimized when subjects performed mental calculations [18]. Therefore, the described mechanisms of BHI may not be related to homeostatic control exclusively, but also describing the disruption of the ongoing neural dynamics.

Further endeavors will be directed towards the application of the SV-SDG model to a large data cohort, aiming to uncover the specific physiological and anatomical mechanisms that allow the neural information exchange between the brain and autonomic activity.

V. Conclusion

The proposed SV-SDG model promisingly constitutes a viable tool for the time-resolved assessment of functional BHI. The advantages of assessing directionality and latency of functional BHI are numerous in the neuroscientific and clinical domains, together with the quantification of cortical and cardiac sympathovagal coupling.

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