# Measures and Models of Brain-Heart Interactions

Diego Candia-Rivera*, Luca Faes, Fabrizio de Vico Fallani, Mario Chavez

***Abstract*— Exploring brain-heart interactions within various paradigms, including affective computing, human-computer interfaces, and sensorimotor evaluation, has demonstrated enormous potential in biomarker development and neuroscientific research. A range of techniques, from molecular to behavioral approaches, has been proposed to measure these interactions. Different frameworks use signal processing techniques, from estimating brain responses to individual heartbeats to interactions linking the heart to changes in brain organization. This review provides an overview of the most notable signal processing strategies currently used for measuring and modeling brain-heart interactions. It discusses their usability and highlights the main challenges that need to be addressed for future methodological developments. Current methodologies have deepened our understanding of the impact of physiological disruptions on brain-heart interactions, solidifying it as a biomarker. The vast outlook of these methods could provide tools for disease stratification in neurological and psychiatric disorders. As we tackle new methodological challenges, gaining a more profound understanding of how these interactions operate, we anticipate further insights into the role of peripheral neurons and the environmental input from the rest of the body in shaping brain functioning.**

***Index Terms*—Autonomic neuroscience, brain-heart interplay, cardiovascular research, heart rate variability, physiological signal processing, physiological modeling**

## I. Introduction

As early as 1938, evidence suggesting a functional brain-heart interaction was reported in a patient with a brain injury, showing distinctive electrocardiography patterns [1]. Since then, numerous clinical cases have provided abundant evidence linking cardiovascular, neurological, and psychiatric disorders to changes in the brain-heart interaction. For example, severe brain damage can lead to sudden cardiac death [2], while cardiac arrhythmias can cause cerebrovascular accidents such as ischemic attacks [3].

The brain and heart communicate with each other to participate in various processes involved in sensing, integration, and regulation of bodily activity [4], [5], namely interoception. This communication is essential for maintaining neural homeostasis and the overall physiological state of the body [6]. The interoceptive mechanisms operating within the brain-heart axis span various components (Fig. 1), from genetic factors, molecular mechanisms, and hormonal and neural pathways [7]. Evidence on genetic factors comes from the links between genomic loci associated with both cardiac and brain anatomy, but also between cardiovascular issues and genetic risk for psychiatric disorders, such as major depression, schizophrenia, and bipolar disorder, emphasizing the association between brain function and increased cardiovascular risks [8], [9], [10].

Brain-heart interaction can occur through cellular mechanisms involving extracellular vesicles [11]. In the context of stroke, evidence indicates an elevated level of circulating extracellular vesicles [12] and in the permeability of the blood-brain barrier [13], eventually leading to posterior cardiac dysfunctions [14]. Stroke may also cause the downregulation of certain microRNAs [15], which are non-coding RNAs that play important roles in regulating gene expression, and their transportation through extracellular vesicles may likely target and influence heart physiology. Conversely, cardiac damage can trigger protein-specific release that can induce thrombosis [16] but also alter the regulation of gene expression at the brain level [17].

Heartbeat pulsations during each beat create mechanical and electromagnetic effects in the brain. The mechanical force generated by the heartbeat sends pressure waves through the blood vessels, influencing cerebral blood flow and promoting efficient oxygen and nutrient delivery, but also influencing neural dynamics [18], which is mediated by mechanosensitive ion channels. These ion channels are expressed in sensory neurons that contribute to the baroreflex, a mechanism to regulate blood pressure [19]. Simultaneously, the electrical activity generated by the heart produces electromagnetic fields at the brain level [20] that can influence neural oscillations, while heartbeats can also reach cortical and subcortical structures through different neural pathways. These pathways include visceroceptive and spino-thalamocortical pathways [21], which are mediated by the autonomic nervous system through its sympathetic and parasympathetic branches [4].

In the context of the brain-heart axis, “connection” typically refers to any structural or functional link between brain and heart systems, such as nerve links or synchronized activity. “Interaction” implies the presence of dynamic influences, either through direct or indirect signaling. “Interplay” implies a direct, bidirectional exchange between the systems. Finally, “coupling” refers to the synchronization of physiological activities, emphasizing how these systems act in a coordinated

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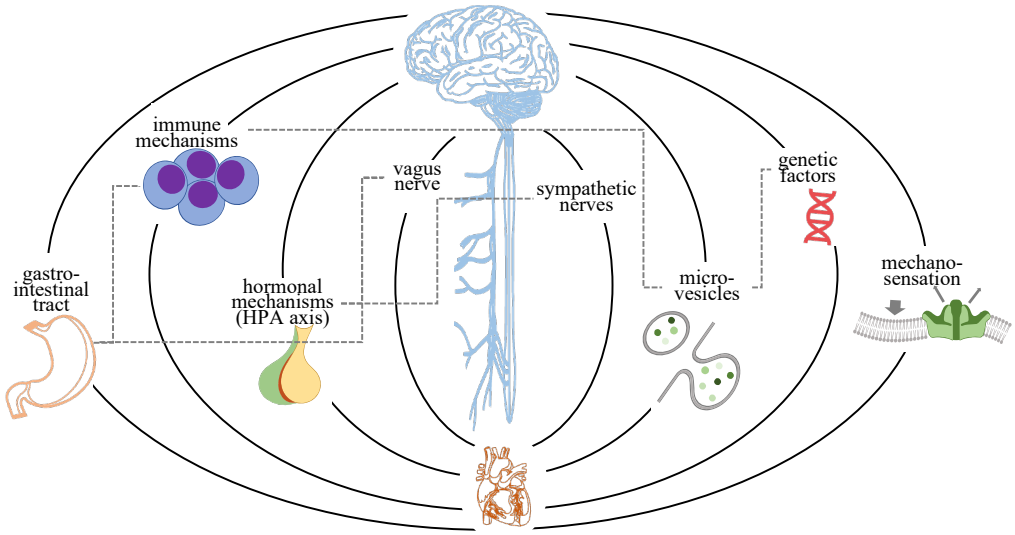


Fig. 1. Pathways of the brain-heart connection. These pathways, which facilitate direct or indirect interactions between the brain and heart, encompass various physiological systems beyond the commonly discussed vagus nerve and sympathetic nerves. Additional pathways involve hormonal mechanisms within the Hypothalamic-Pituitary-Adrenal axis, and immune mechanisms primarily linked to neuroinflammatory processes initiated by the brain and affecting the heart. The gastrointestinal tract contributes through mechanisms related to the innervation of gut pacemaker cells by parts of the autonomic nervous system, as well as through gut-mediated effects associated with microbiota and gut dysbiosis, implicated in conditions such as stroke. Interorgan communication occurs through microvesicles, which contain gene regulation messengers such as microRNAs. Recently, common genetic factors have been identified in brain and heart pathologies, although the mechanisms involved require further elucidation, with some likely associated with genetic regulation through microRNAs. Mechanosensation is another mechanism of brain-heart communication, evidenced by baroreceptor mechanisms and mechanosensitive ion channels that respond to each pulsation. Interactions between systems (dashed links) can indirectly influence brain-heart communication, as part of visceral crosstalk and large systems' mechanisms.

manner. Within this rich repertoire of crosstalk modalities along the brain-heart axis, state-of-the-art noninvasive methodologies for estimating these brain-heart interactions in humans include different approaches. The present review offers a comprehensive overview of these approaches, classifying them in six different categories.

The first approach, reviewed in Section II, involves measuring transient neural responses to heartbeats, known as heartbeat-evoked responses, which rely solely on analyzing brain activity in between heartbeats. Experimental findings demonstrate that heartbeats and the associated cardiac cycle have an impact on perception, information processing, and reaction [22]. Cardiac inputs to the brain are hypothesized to influence the generation of spontaneous cognition, which involves developing a first-person perspective [23].

In Section III is presented the study of brain-heart axis through identification of the brain regions consistently activated by the autonomic nervous system, which in turn is known to influence cardiac rhythmicity. Autonomic correlates in the brain identify the so-called central autonomic network [24], playing a leading role in this form of brain-heart interaction.

Other proposals use signal processing techniques to examine statistical pairwise correlations (Section IV), directional (causal) modulations (Section V), and higher-order interdependencies (Section VI) between brain and cardiac autonomic dynamics. These approaches involve time- and frequency-domain measures as well as tools taken from information theory or dynamical system theory to operationalize and quantify concepts like time delay stability [25], spectral coherence [26], mutual information [27], Granger causality and information transfer [28], redundancy and synergy [29], cross-mapping [30], or state-space correspondence [31], within the frame of brain-heart interactions; more recent methods focus on analyzing neural systems using generative models of brain and cardiac dynamics that leverage prior physiological knowledge to assess causal connections between changes in the brain and heartbeat dynamics [32], [33]. Lastly, the newer frameworks reviewed in Section VII focus on measuring complex, parallel interactions among various brain regions, occurring alongside with autonomic processes [34], [35]. These frameworks explore how brain networks assessed at different levels of resolution evolve in response to physiological fluctuations from other organs.

A summary of the strategies adopted for measuring and modeling brain-heart interactions across the different methodologies outlined in this review is presented in Table I. Many of these strategies are versatile and can be extended to study interactions with other bodily systems, including gastric rhythms, respiration, skin conductance, or body temperature. The development and application of these methodologies in different contexts may help to elucidate the physiological underpinnings of the appropriate processing of interoceptive inputs, which plays a crucial role in maintaining a healthy brain. To achieve this, we analyze the practicality of these methods, address current methodological challenges, and outline the most notable clinical translations.

TABLE I
BRAIN-HEART INTERACTION METHODOLOGY SUMMARY

| Approach | Key references |
|---|---|
| Responses to heartbeats | |
| *Heartbeat-evoked potentials* | [36], [37] |
| *Heartbeat-evoked oscillatory responses* | [38], [39], [40] |
| *Other heartbeat-evoked responses (information, complexity, variability)* | [41], [42] |
| Brain correlates of autonomic cardiac rhythms | |
| *Functional brain imaging + autonomic outflow measures* | [24], [43], [44] |
| Brain-heart oscillatory couplings | |
| *Correlation, coherence* | [25], [26], [45] |
| *Information theory, nonlinear coupling* # | [27], [31], [46] |
| *Symbolic representations* # | [47], [48] |
| Brain-heart causal interactions † | |
| *Granger causality ‡, Transfer Entropy* # | [28], [49], [50] |
| *Synthetic data generation modeling ‡ §* | [32], [51], [52] |
| *Convergent cross-mapping* # | [30], [53] |
| Higher-order interactions ¶ | |
| *Multivariate correlation ‡ ¶* | [54] |
| *Partial information decomposition ‡ ¶* # | [29], [55], [56] |
| *Global brain dynamics ¶* # | [35] |
| *Brain connectivity ¶*# | [34], [57] |
| *Multilayer ¶* | [58] |

† allows directionality estimation, ‡ model-based, # detects nonlinear interactions, § time-varying estimation, ¶ collective interactions (3 or more nodes)

## II. COUPLING BEHAVIOR AND NEURAL ACTIVITY WITHIN THE CARDIAC CYCLE

The cardiac cycle consists of two phases: systole, the muscle contraction phase; and diastole, the relaxation phase (Fig. 2a). Experimental findings reveal that the cardiac phase is associated with perceptual awareness and behavior [22]. Specifically, humans are more likely to detect a stimulus when presented during the diastole, as reported in visual [59], auditory [60], and somatosensory detection [61]. Conversely, processes such as saccades during visual search [62], visual attention [63], active information sampling [64], active tactile discrimination [65], reaction time, and motor excitability [66], [67] are enhanced during the systole phase. Therefore, in behavioral and perceptual awareness research, synchronizing neural dynamics with the approximate onset of systole and diastole emerges as a compelling approach for analyzing brain-heart interactions [68]. This approach has recently been suggested for extension into fMRI analysis to present stimuli as a function of the cardiac phase [69].

The analysis of brain responses to heartbeats using heartbeat-evoked potentials (HEPs) was initially proposed by Schandry and colleagues in 1986 [36]. Typically, the computation of these potentials involves averaging brain signals across windows that are time-locked to the R- or T-peak of the cardiac cycle [37] (Fig. 2b). However, there is currently no consensus on how to compute them, including aspects like baseline correction, cardiac-field artifact removal, and overall preprocessing [37]. HEPs have been linked to markers of cortical processing of cardiac signals, as they are modulated in various conditions, such as perceptual awareness in a healthy state [23]. However, there is considerable diversity in the specific latencies relative to the cardiac cycle and the scalp locations where these effects are observed [70]. Moreover, HEPs capture merely the average brain response to heartbeats,

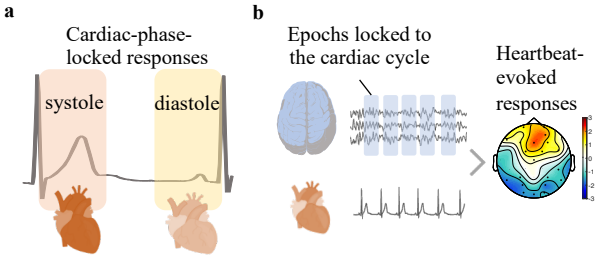


Fig. 2. Measures of brain-heart interaction based on changes in behavioral responses and brain activity with respect to the cardiac cycle. (a) Cardiac phase methods aim at contrasting responses occurring in the systole and diastole phases of the cardiac cycle. (b) Heartbeat-evoked responses aim at providing a signature of the evoked brain responses to individual heartbeats by averaging brain epochs with respect to a defined phase of the cardiac cycle.

disregarding its complexity. To uncover the ambiguities of heartbeat-evoked potential, further methodological analyses have been proposed to highlight these biomarkers, including information-based techniques [42], time-frequency analysis [38], [39], [40], variability [71], complexity and network properties [41].

The primary limitation of cardiac cycle-based approaches lies in the dynamic variations of sympathetic and parasympathetic autonomic activities influencing the cardiac cycle. These variations may intricately connect with brain dynamics in afferent and efferent manners, leading to a lack of specificity regarding the involved physiological dynamics. Some intracranial studies have identified specific brain regions, such as the anterior cingulate, right insula, prefrontal cortex, and left secondary somatosensory cortex [72], [73], as origins for heartbeat-evoked potentials. However, identifying the cortical and sub-cortical regions involved in heartbeat-evoked potentials using non-invasive techniques remains challenging.

Moreover, limitations also arise from cardiac electric currents associated with ventricular contractions [20], which can induce artifacts in computing heartbeat-evoked potentials. Importantly, it remains to be further elucidated whether heartbeat-evoked responses have a direct relationship with the recently uncovered pathways from the mechanical effects of the brain due to changes in blood pressure caused by each heartbeat [22], where recent research in rodent models has shed light on this aspect [18].

Current protocols to study heartbeat-evoked responses typically set a fixed value of latencies and duration for each heartbeat to define a baseline. This approach can, however, be biased by the heart rate variability of the subject during the task. Although some strategies can mitigate the effect of this variability (e.g., discarding short intervals, or adapting the baseline to the events cycles), the conventional procedure for computing and analyzing ECG-based cortical responses is rarely questioned.

## III. CO-OCCURRENCES OF AUTONOMIC DYNAMICS IN THE BRAIN

Links between the brain function assessed in specific regions and cardiac rhythmicity have been reported in both neuroimaging and intracranial studies. The associations of autonomic and brain region activities in healthy subjects have

been related to direct autonomic control, although the causal relationship is not directly assessed. The estimation of the sympathetic and parasympathetic activities is traditionally done through heart rate variability (HRV) spectral integration at low (LF: 0.04–0.15 Hz) and high frequencies (HF: 0.15–0.4 Hz), respectively [74], although with some variability in the bands' definitions. Because some studies have shown that the estimation of sympathetic activity from HRV can be biased [75], sympathetic markers are also gathered from other physiological activity, such as sympathetic nerve neurogram or electrodermal activity [24].

Neuroimaging studies have employed diverse approaches to capture the central autonomic network, involving brain regions correlated with autonomic activity. Most studies either correlated autonomic signal time courses with voxel time courses or confirmed stimulus-induced autonomic modulation, while fewer studies used parametric or conjunction designs [24]. As presented in Fig. 3, meta-analyses on fMRI studies [24], [43] revealed that the most reported brain regions involved in autonomic correlates are the thalamus, hippocampus, amygdala, right anterior insula, left posterior insula, cingulate cortices, and a few structures from parietal lobes. Intracranial electrophysiological recordings have further confirmed the involvement of the anterior and posterior insula, along with limbic system components such as the amygdala, hippocampus, and anterior and mid-cingulate regions [76]. Altogether, this evidence highlights the involvement of numerous high-order regions and the forebrain, but also several nuclei in the medulla, such as the nucleus of the tractus solitarius, nucleus ambiguous, parabrachial Kolliker fuse nucleus [2], [77]; but also in the cerebellum [44], [78]. Further regions have been described in relationship to complex HRV patterns [77], including temporal gyrus, planum temporale, frontal orbital cortex, opercular cortex, paracingulate gyri, cingulate gyri, temporal fusiform, superior and middle frontal gyri, lateral occipital cortex, angular gyrus, precuneus cortex, frontal pole, intra-calcarine, supra-calcarine cortices; although, lacking specificity with respect to their sympathetic or parasympathetic origin.

Region-specificity with associations to sympathetic and parasympathetic activations has also been reported [24]. Sympathetic activations are generally associated with regions pertaining to executive and salience networks, while parasympathetic activations are more associated with regions in the default mode network. However, those regions represent a trend and should not be considered as sympathetic- or parasympathetic-exclusive structures *per se*.

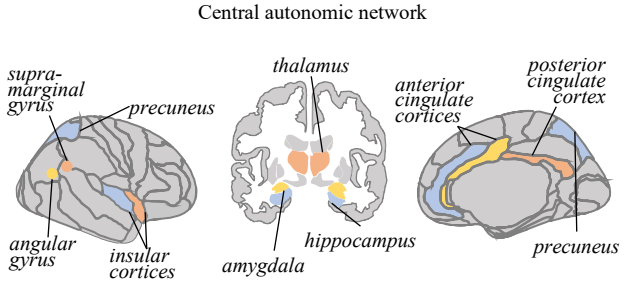


Fig. 3. Central autonomic network components, based on a meta-analysis of autonomic correlates [66]: parietal lobe substructures, including the precuneus, angular gyrus, and supramarginal gyrus; anterior and posterior insular cortices; subgenual, pregenual, and dorsal anterior cingulate cortices; posterior cingulate cortex; and subcortical structures, including the thalamus, amygdala, and hippocampus.

## IV. Approaches for Quantifying Coupling Between Brain-Heart Time Series

Pairwise methods measuring the statistical association between variables have been exploited to explore brain-heart interactions. The adopted techniques span from conventional linear correlation methods [25], [45], [54] to frequency approaches such as cross-spectrum and spectral coherence, also combined with information-theoretic methods [55], [79] and other nonlinear interdependence measures [27], [31], [80], [81]. With an approach as simple as the correlation function, analyses on source-reconstructed EEG signals have validated some of the findings from earlier neuroimaging studies [82], showing that the insula, amygdala, hippocampus, anterior and mid-cingulate cortices are involved in autonomic changes. Nevertheless, a crucial procedural prerequisite before applying such measures is the extraction of relevant variables from the brain and cardiac signals, typically in the form of time series that capture synchronous information about brain and cardiovascular oscillations. This is usually done by building time series that map the dynamics of EEG oscillations via spectral analyses and correlating them with HRV expressed by the series of the cardiac interbeat intervals at the scale of ~1 sec [25], [47], [48], [54], or with series mapping the sympathetic or parasympathetic component of HRV at longer time scales of ~1 min [26], [28], [31], [49]. On the other hand, alternative approaches looking directly at the cross-spectrum or spectral coherence between electrocardiogram and brain activity have been proposed [83], [84], but it is important to note that these approaches may not necessarily capture functional coupling. Instead, they often quantify isoelectric properties shared by the brain and the heart, which can sometimes arise as mere artifacts. Therefore, coherence analysis, particularly concerning HRV features [26], [48], should be prioritized to better understand the functional aspects of brain-heart coupling.

Correlation and spectral coherence-based analyses assume linear interactions between the analyzed signals. As a model-free alternative, coupling and synchronization measures have been proposed to detect nonlinear dependencies between pairs of signals. In particular, the phase-space approach of synchronization likelihood [81] was proposed as a brain-heart coupling measure and tested on sleep EEG, showing a close relationship between a broad part of the EEG spectrum and high-frequency HRV, being especially prominent in the delta-alpha range [31]. Further methodologies, such as Joint Symbolic Dynamics, detect patterns emerging from the interactions between time series by coarse-graining the series into sequences of symbols [85]. This approach was tested on patients diagnosed with schizophrenia, showing insights into the effects of the antipsychotic medication on the relationships between HRV, baroreflex, and cortical dynamics [48], [85].

Approaches framed in dynamical information theory dynamics have shown relevance in studying physiological couplings with a high presence of non-linear dynamics [86]. Understanding the complex dynamics of information exchange between variables over time is crucial in various fields, particularly in studying complex systems like the nervous

system. Formal quantification of information has become a basis for unraveling the complexities of information processing within physiological systems. The methodologies relying on information measures include mutual information, joint entropy, and instantaneous information shared between processes. It is worth noting that the computation of these measures involves discretizing random variables through uniform quantization or rank ordering, thus introducing discretization parameters which have to be set reaching a tradeoff between resolution and computational reliability [87].

The Maximal Information Coefficient quantifies linear and non-linear correlations between time series [80]. The computation is based on the mutual information between time series, normalized by the minimum joint entropy. The method does not require symbolic transformations. Furthermore, it may capture non-linear relationships, as similarities between time series are quantified regardless of their related distributions. This method has been tested in emotion elicitation, revealing insights into the brain-heart dynamics associated with arousal [27].

Among the plethora of methodologies available, the combination of cross-spectral and information-theoretic approaches stands out as a promising tool for analyzing brain-heart interactions [55], [79]. Whereas spectral analysis provides a frequency-specific lens through which to examine the interactions between multiple time series, multivariate information measures allow the detection of information exchanges that may not be discernible through traditional time-domain analyses or spectral measures alone.

While the methods reviewed so far assume stationarity, physiological systems often exhibit non-stationary behavior. Consequently, time-varying approaches have been proposed [46]. These methods enable, for instance, the estimation of information storage at each instant [88], capturing abrupt and gradual changes in stored information over time. By applying these techniques to study brain-heart interactions, distinct patterns may appear over time-varying information-storage across different phases of the cardiac cycle. This highlights the importance of considering non-stationarity in understanding dynamic processes within physiological systems.

Further methods exist to study linear interactions in the time and frequency domains as well as synchronizations and nonlinear interdependencies between pairs of time series [89], [90], [91], [92], [93], [94], [95]. However, most of these methods are derived from dynamical systems theory, in which the signals are used to reconstruct the underlying state-space of a latent dynamical system at every time. Although these methods can capture nonlinear couplings, they require a large amount of data to provide robust and unbiased estimators and are extremely sensitive to artifacts and nonstationary trends.

## V. Causality in brain-heart interplay: estimation of bottom-up and top-down information flow

Causality holds significant relevance due to increasing evidence indicating a higher incidence of certain brain conditions in the presence of cardiovascular conditions and vice versa. The bidirectional brain-heart relationship underscores the importance of understanding the causal pathways between the cardiovascular system and brain health. Identifying causal links can inform preventive strategies and interventions aimed at mitigating the risk and progression of cardiovascular and neurological disorders.

Causal mechanisms in brain-heart interplay have been demonstrated experimentally through invasive methods combining neuromodulation, lesion and pharmacological approaches across human and animal models. Neuromodulation targeting either brain or peripheral nerves has shown measurable effects on the other system. For example, transcranial magnetic stimulation of brain areas within the central autonomic network can modulate heart rate [96], while vagus nerve stimulation can influence brain oscillatory patterns [97]. Beta-blockers, commonly used to manage irregular heart rhythms, also impact brain activity, likely mediated by brain-heart pathways [98], [99]—even in cases where these drugs do not cross the blood-brain barrier. Pharmacological interventions have further clarified causal brain-heart communication during tasks involving heartbeat perception [100]. Recently, heart rate modulation through optogenetics has shown behavioral changes [101], suggesting that altering cardiac rhythms can affect brain activity.

In a non-invasive manner, different signal processing techniques have been employed to estimate functional brain-heart interactions. Brain connectivity measures [102] and methods investigating causal interactions in physiological signals [89], [103] are potential candidates to unveil brain-heart interactions. Existing tools aim to uncover the interactions within systems composed of multiple components. Key insights lie in discerning coupling direction, strength, and occurring time lags. Most used approaches rely on Granger-causality-based and entropy-based techniques quantifying the directed information transfer between signals and implemented via linear model-based or nonlinear model-free estimators [103], mutual nonlinear predictions detecting asymmetric relations in pairs of signals [89], [104], [105], and synthetic causal models of the underlying generative neural dynamics, among other connectivity measures [106].

Granger causality (GC) is a statistical method to determine whether a time series can forecast another [107]. Therefore, GC can assess directional interactions between time series. GC estimation consists of comparing the extent to which the putative driver improves the prediction of the target above the extent to which the target can be predicted by its own past states. While traditional GC approaches rely on linear regression, nonlinear prediction models can also be adopted [108], [109]. GC has been primarily used to describe brain network connectivity [110], [111] and cardiovascular interactions [112], [113], but also to gather brain-heart interactions.

For instance, Duggento and colleagues revealed that some regions previously described as correlated with autonomic dynamics are actually associated with brain-to-heart neural control [78], [114]. Faes et al. [28] characterized the topology of brain-heart interaction networks during sleep using GC, highlighting bidirectional communications between the cardiac parasympathetic variability and the beta EEG activity and unidirectional brain-to-heart interactions when slower brain waves are considered [28]. Further evidence on GC applied to EEG showed that brain-to-heart coupling increases in the left hemisphere for positive emotional valence and in the right

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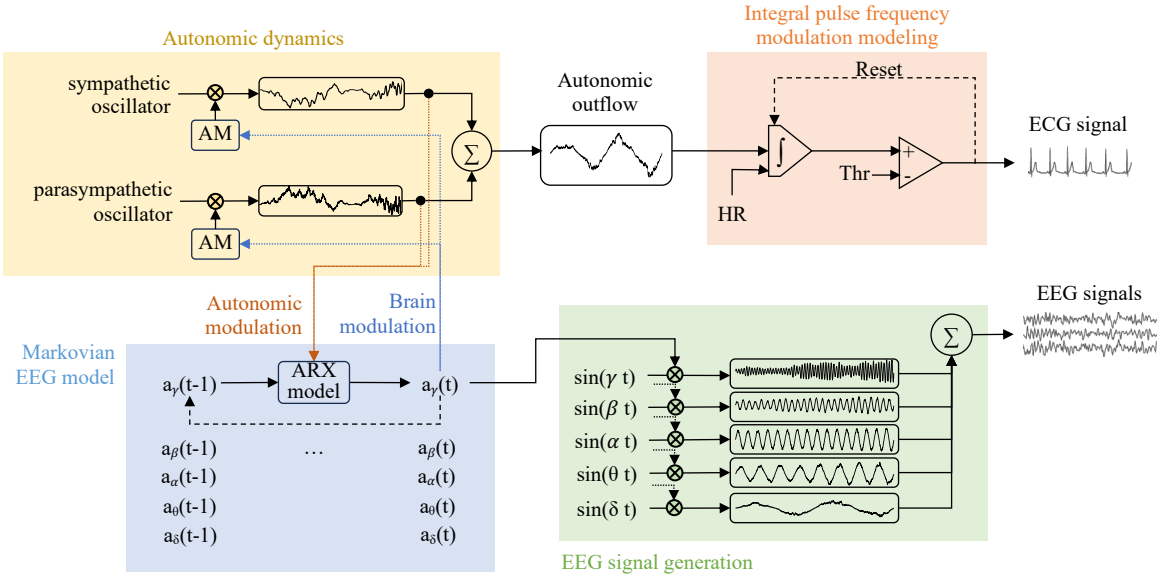


Fig. 4. Modeling bidirectional brain-heart interaction through block diagrams of the coupled heartbeat and brain signal generation systems. The heartbeats' generation in the sinoatrial node is an integrate-and-fire model (red block), the integral pulse frequency modulation model, which receives the sum of sympathetic and parasympathetic inputs and the baseline heart rate (HR). The model generates the heartbeats as a train of pulses each time the integration reaches a defined threshold (Thr). Autonomic dynamics (yellow block) are disentangled in the sympathetic and parasympathetic components, which are individually modeled as oscillators whose amplitude is modulated (AM) on time as a function of the changes in EEG power. In the brain part, EEG signals are modeled as the sum of five frequency bands (green block), typically, δ: 0-4 Hz, θ; 5-8 Hz, α: 9-12 Hz, β=13-30 Hz, γ: 31-50 Hz, whose powers ($a_F$; with F: δ, θ, α, β, γ) are individually modeled (blue block) as an autoregressive process that receives autonomic modulations as an external term (ARX model).

hemisphere for negative valence, as gathered from prefrontal, somatosensory, and posterior cortices [50].

Clinical evidence has been provided for the cases of sleep apnea and epilepsy. During sleep recordings, GC revealed differences between healthy controls and patients suffering obstructive sleep apnea, where a bidirectional brain-heart coupling in the lower frequency ranges could distinguish between the participants' groups [115]; an impaired brain-to-heart communication during severe sleep apnea-hypopnea syndrome was detected using GC computed across whole-night recordings [116], also showing the potential of long-term ventilation therapy to recover the physiological brain-heart interaction patterns. In epilepsy, GC revealed a dominance of the brain-to-heart causality, over the heart-to-brain counterpart, suggesting the central control of autonomic dynamics during the ictal phase of the seizures [29].

Granger-causal information can be gathered also from entropy-based methods, such as the Transfer Entropy (TE), which provides a model-free probabilistic tool to assess the information transfer between time series [117]. TE provides a viable alternative to nonlinear GC models, bringing the advantage of generality (no functional forms are imposed for the analyzed nonlinearities) at the cost of lower computational reliability (longer datasets are required for reliable probability estimation). Therefore, TE has been proposed as an alternative measure of effective connectivity[118] and to detect potential asymmetries in the interactions [117], [119].

In the context of brain-heart interplay, TE has been tested in sleep and schizophrenia. In sleep EEG, TE revealed that the beta power conveys the largest amount of bidirectional brain-heart information flow across different sleep stages, being weaker in the transitions from light sleep to deep sleep and to REM sleep [49]; a direct comparison between linear GC and nonlinear TE evidenced the role of nonlinear correlations in driving brain-heart interactions during sleep [28].

In schizophrenia, TE revealed a stronger heart-to-brain interplay as compared to healthy controls [47]. A normalized version of the TE, estimated via non-uniform embedding [119] between the time series of HRV and EEG complexity, was employed as well by Yu and colleagues [120], who revealed the existence of unidirectional effects of the cardiac period length on the irregularity of the brain waves in the resting and mental stress states. Similarly, distinguishing between physiological changes induced by internally-driven attention, linked with short-term memory assessment, and externally-driven attention, associated with automatic and transient responses to external stimuli; the findings revealed that heart-to-brain information flow increased, while the brain-to-heart flow decreased during externally-driven attention compared to internally-driven attention [121].

Alternative approaches for estimating directional interactions between time series use the concept of cross-predictability, whereby embedding vectors from one series are used to predict future states of the other. These approaches lay their ground on the theory of dynamical systems, based on the concept of state-space correspondence [105], whereby it is assumed that it should be possible to cross-map between the variables observed from a system and extract predictability measures from such cross-mapping. The most popular method in this context is Convergent Cross-Mapping (CCM) [89], a statistical tool for cross-prediction that exploits the idea that the reconstructed states from a responding signal can be used to cross-map the driver signals. Convergent Cross-Mapping has been used to study brain-heart interactions [53], with particular evidence on epilepsy [30], [122], [123], [124]. Interestingly,

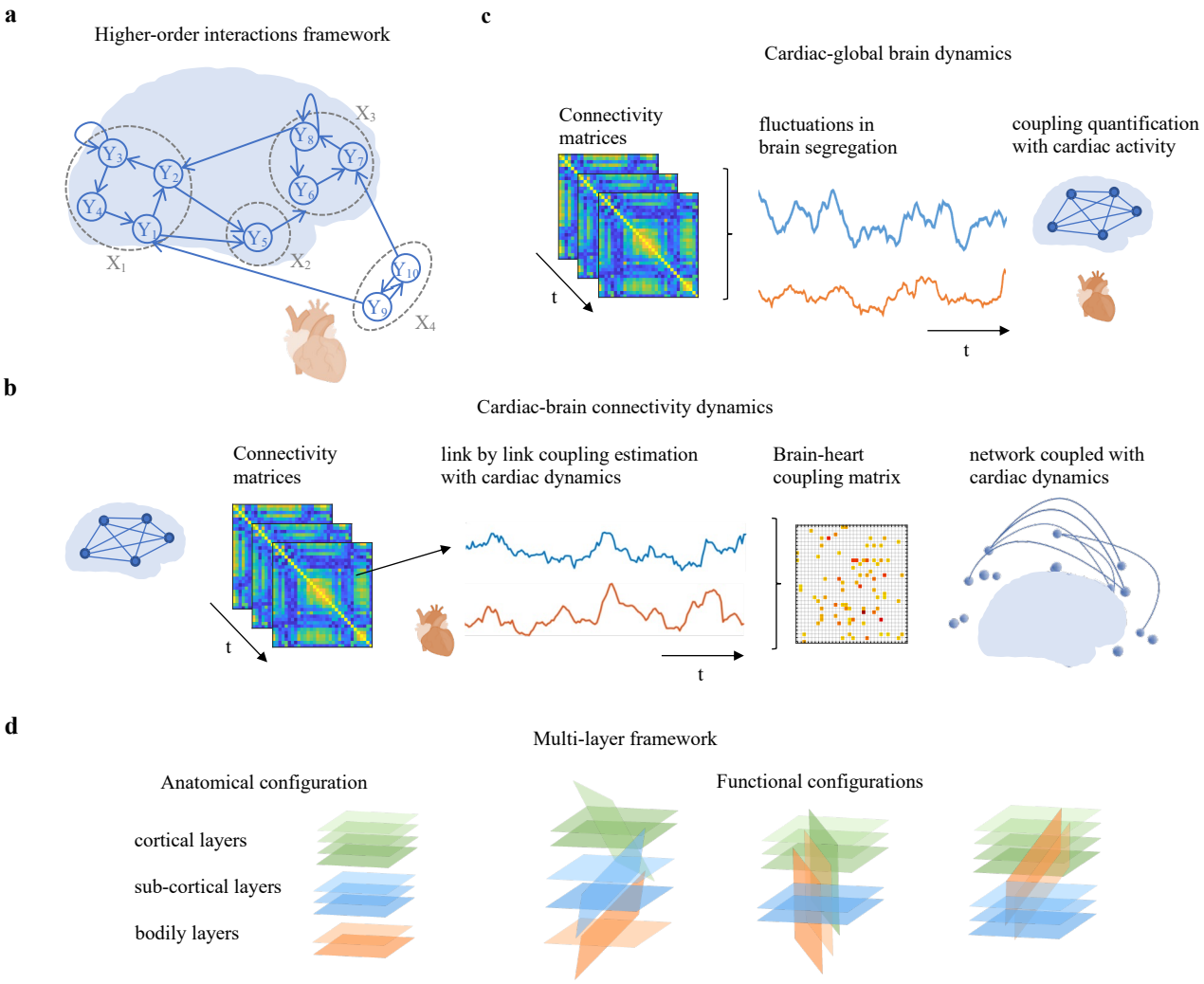


Fig. 5. Frameworks of higher-order brain-heart interactions. (a) Brain-heart interactions as a complex network system analyzed via multi-node interplay. (b) Cardiac-brain connectivity framework draws relationships between brain connectivity and cardiac dynamics by capturing the individual brain links that covary with cardiac dynamics, to identify the whole network associated with these changes. (c) Cardiac-global brain dynamics aims at quantifying the relationship of network measures, such as integration and segregation, and parallel changes in cardiac dynamics. (d) Multi-layer frameworks in brain-heart interactions model the different nodes within pre-defined layers and re-refined ones as per their functional relationships.

although the underlying concept and assumptions are different, CCM and GC yielded overlapping results on the analysis of time series of HRV features and the envelopes of delta and alpha EEG activity [29], [30]. These consistent findings suggest that cortical oscillations drive the autonomic activity before, during, and after the development of epileptic seizures.

Synthetic data generation models are frameworks that aim to estimate the directionality of the interactions following a logic of generative neural dynamics (Fig. 4). These models assess the directed modulations between EEG oscillations (at a given frequency band) and cardiac sympathetic/parasympathetic activity time series [32], [51], [52]. The estimates of brain-to-heart interplay are quantified through Integral Pulse Frequency Modulation models [125], [126], [127], which are represented as an integrate-and-fire computation that receives as inputs the linear combination of autonomic inputs and their respective amplitude modulation coming from the brain. The heart-to-brain interplay is quantified through a model based on the generation of synthetic EEG series using an adaptative Markov process on brain power series [128]. The model estimates the ascending modulations from the heart to the brain using least squares in a first-order auto-regressive process, in which the Markovian neural activity generation uses its previous neural activity and the current heartbeat dynamics as inputs. This approach offers a time-resolved estimation of bidirectional brain-heart interactions, which has been used to model the physiological dynamics in emotions, showing that ascending cardiac inputs modulate brain dynamics in different contexts of arousal [33], [51], [129]. This modeling has also been tested in clinical conditions, including mood disorders [130] and patients in coma [131].

## VI. Brain-Heart Higher-Order Interactions

Complex systems often exhibit interactions among multiple components beyond simple pairwise connections, involving higher-order interactions among three or more nodes [132]. These higher-order interactions can significantly impact collective network behavior but are often overlooked in traditional analyses. To address this gap, characterizations of

pairwise and higher-order interactions among multivariate time series focus on assessing the equilibrium between redundant and synergistic information (Fig. 5a).

Synergy arises from collective statistical interactions within a network that cannot be inferred when the sources of information are considered in isolation; as such, synergy amplifies the efficiency of information exchange by leveraging interactions among multiple system elements. Redundancy, on the other hand, encapsulates information conveyed equally by more sources; it ensures system robustness but at the expense of not fully utilizing the available information capacity [133]. These characterizations offer a more detailed understanding of how information flows and how it is used within complex systems.

Frameworks conceptualized for the analysis of higher-order interactions include those based on the Shannon theory of information, which captures the balance between redundant and synergistic information among groups of three or more variables via measures of information transmission [134] and its generalizations, such as the O-information [135]. The framework of partial information decomposition [88] is more powerful as it provides separate measures of synergy and redundancy but is also more complicated because its unequivocal formulation requires going beyond classical information theory [136]. Additionally, implementing these higher-order frameworks is challenging, as they require computing entropies in high-dimensional spaces. Consequently, their reliable application has so far depended on linear parametric models [56], [137]. However, despite being still under active development, these frameworks are gaining strong relevance for the analysis of multivariate biological systems, for instance, in the brain and cardiovascular system, where redundancy and synergy have been found to play distinct roles in explaining the mechanisms that govern robust and flexible physiological regulation [133], [137], [138]. Therefore, higher-order interaction frameworks could become pervasive in the analysis of brain-heart interaction. In the following we illustrate how novel analytical frameworks can bring new insights into the study of the functional coupling of brain and heart signals.

While some studies have started analyzing the spatial distribution of the brain activity associated with cardiac dynamics in terms of high-order brain-heart interactions [29], [54], the investigation of multi-scale behavior has been limited by the fact that the theoretical frameworks have been formalized with focus on random variables, thus with no explicit account of temporal correlations. However, the recent introduction of a dynamic framework for the analysis in networks of random processes, formalized via measures of entropy and mutual information rates [55], [56], [139], has introduced an approach to assess higher-order interactions in rhythmic processes with rich oscillatory content. The O-information rate, quantifying the equilibrium between redundancy and synergy from a novel dynamic perspective [56], exploits spectral representations of vector autoregressive and state space models to assess interactions among groups of processes in specific time and frequency bands after whole-band integration. It allows for highlighting redundant and synergistic interactions emerging at defined frequencies, offering insights not detectable using traditional time-domain measures. One can relate the O-information rate to pairwise measures of dynamic coupling like spectral coherence [139], decompose it into measures quantifying Granger causality and instantaneous influences in different frequency bands [56], or examine its gradients to derive low-order descriptors offering insights into the individual contributions of variables in shaping high-order informational circuits [140]. These recent developments hold great promise for ongoing and future investigations on the dynamic interplay between cardiovascular and neural oscillations.

Further statistical inference methodologies can be embedded in these frameworks of higher-order interactions [141] to characterize functional links within physiological networks. Validation on theoretical and numerical simulated networks demonstrated its ability to represent higher-order interactions, but also to detect cascades, by dynamically identifying drivers and targets within the networks. These approaches aim at further describing the hierarchical dynamics within the system, allowing the evaluation of dynamic networks depicted by multivariate time series [139], offering versatility and scalability for exploring interactions beyond pairwise connections.

## VII. Cardiac-related brain network dynamics

Most previous studies have predominantly focused on the interaction between specific brain or scalp regions and heartbeat dynamics, disregarding the dynamic nature of brain networks and their role in numerous neural functions [25], [56], [142], [143]. In line with this, there have been proposals for frameworks to study brain-heart interactions that explore the relationship between ongoing brain network organization and cardiac oscillations. Some fMRI studies have explored the relationship between HRV and connectivity in certain brain regions [57], [144], [145]. However, these approaches rely on the definition of a seed, typically defined as one of the main nodes of the central autonomic network. In a more agnostic manner, these frameworks can be extended to the identification of the brain networks associated with changes in cardiac dynamics in certain conditions. In a recent study, authors examine the interplay between pairwise brain connectivity and cardiac dynamics (Fig. 5b). This framework explores the relationship between triads by quantifying the coupling between the pairwise brain region connectivity and the cardiac dynamics, with the ultimate goal of identifying all the links associated to a network that is formed with the ongoing changes in cardiac dynamics under different conditions [34].

Another related framework provides biomarkers related to large-scale brain-heart interaction by quantifying the intricate dynamics between global brain activity and cardiac dynamics [35] (Fig. 5c). This framework showcases how the study of brain-heart interactions can be approached in various conditions where global neural dynamics are not fully understood by solely examining the dynamics of specific brain regions. It delves into the variations in global network dynamics, focusing on parameters such as efficiency, clustering, modularity, and assortativity within brain connectivity matrices [146]. The aim of this framework is to provide a holistic quantification of global dynamics and their relationships with the fluctuations in cardiac sympathetic-vagal dynamics [35]. While the framework

primarily focuses on characterizing brain dynamics through changes in brain connectivity structure, it can also be extended to other metrics of global brain dynamics, such as the synergy-redundancy balance or global brain signals (e.g., EEG wideband power or fMRI global signal). Although the physiological meaning of these global parameters is debated [147], this approach could offer valuable insights into large-scale brain-body dynamics [148], especially in the context of ascending arousal signaling that can also modulate cognitive processing [149].

As a proof-of-concept, it was proposed to approach brain-other organs interactions through frameworks of multilayer networks [150] (Fig. 5d). The multilayer structure provides a comprehensive framework for understanding, for instance, complex interactions by incorporating detailed structural and functional information across multiple levels [151]. Multilayer network analysis offers a means to study the human brain's diverse functional layers, enabling the potential integration of brain-heart interactions. This framework may also allow the modeling of the interactions at different scales, from molecular to systemic mechanisms [14] at different layers. Multilayer analysis may contribute to transcend from brain-centered analyses, fostering a holistic understanding of brain-other organ interactions. Operationalizing multilayer definitions depends on the specific phenomena modeled, offering flexibility in adapting to various research contexts. For example, functional interactions between signals in different body regions can be conceptualized as a network layer (Fig. 5d), where the interactions from one layer (e.g. brain regions) can influence other ones (e.g. that estimated from multivariate skin or gut signals) [58]. The direct interaction observed between cardiac dynamics and the neocortex further illustrates these dynamics [21]. Similarly, cortical layers can receive information from lower-body regions via non-neural pathways, bypassing the middle layers [18]. In this view, network dynamics could better explain physiological interactions, as compared to traditional analyses focused on individual and isolated brain region activations [152]. By integrating empirical evidence from brain-heart interplay, multilayer frameworks hold promise as an integrative framework for advancing our understanding of complex systems, but more importantly, their relationships with cognition and behavior. For instance, to enlighten how physiology relates to the active inference of bodily states, potentially anticipating interoceptive sensations [153].

A summary of the approaches adopted across the different methodologies outlined in this review are presented in Table I.

## VIII. Methodological applicability

The applicability of methods for analyzing brain-heart interactions depends on various factors, with the most significant being the amount of available data, prior physiological knowledge, and underlying hypotheses regarding time, frequency, and regional dimensions. Below, we outline some of these factors that need to be considered, including aspects related to physiological causality analysis [106], which are not exclusive to brain-heart interactions.

### *A. Limited amount of data*

When data is scarce, visualizing brain-heart interactions graphically can be more valuable. Symbolic transformations of the data are ad-hoc methods commonly used in such instances. These approaches may prove suitable due to their robustness against noise and potential accounting for nonlinearities. They often prioritize pairwise comparisons over multivariate analyses.

Additionally, the analysis of HRV is limited by the length of the recording. Short-term recordings, typically one minute or less, may not capture the full range of HRV fluctuations of interest and are more susceptible to transient artifacts and anomalies [154]. Therefore, balancing the duration of recordings as a function of the expected physiological outcomes is necessary to achieve reliable and representative HRV measurements.

Instead, in large datasets containing rich information from multiple brain regions, model-free methods offer computationally tractable estimations and can facilitate an agnostic search for hierarchical dynamics. Within this framework, phase space methods provide a model-free approach to detect such dynamics, even in multivariate time series.

### *B. System agnostic analyses*

Without prior knowledge of the systems studied, coupling measures drawn from information theory offer versatility, as they are less likely to overlook nonlinear couplings. Information theory-based methods can be further extended to have notions of causality and multivariate interactions. However, these analyses have to be re-considered in cases of limited amount of data, given the computational resources needed, for instance, to estimate probability distributions.

### *C. Prior knowledge available*

With prior knowledge at hand, measures and models investigating causality are likely to offer a more informative framework. Some of these approaches are easily adaptable to the available data and can be applied directly or in transformed and multivariate analyses. The expected complexity of these methods should be balanced with the available data. For instance, if multiple auto-regressive processes need to be conducted, detecting only linear interactions may suffice for the analysis needs.

### *D. Region-agnostic analyses*

When the goal is to comprehend global neural dynamics without prior hypotheses regarding specific brain regions involved, network-based analyses may be suitable. This is particularly applicable in cases with uncertainty in the data due to population heterogeneity or neural damage preventing analysis in the same region for all subjects. Methods based on global network dynamics offer characterizations that are regions-specific independent, enabling comparisons of global dynamics across the dataset's heterogeneity. However, these approaches may necessitate control measures to ensure that the effects observed are not attributable to differences in the number of nodes or network densities.

## IX. Methodological challenges

### *A. Improving specificity of the brain regions involved in brain-heart interactions*

Current data-driven methods for inferring and analyzing complex networks involve constructing a model from observed time series, where nodes represent units in the system and edges/hyperedges signify functional pairwise/higher-order dependencies between these units. However, most models are constructed from scalp-recorded EEG signals, often overlooking subcortical dynamics. This is a common shortcoming of most of the methodologies reviewed in this work, which should be overcame by future research targeting the specific cortical sources and their connectivity underlying the sensor/electrode level interactions [155]. This challenge can be approached by adapting the methodologies for assessing coupling and causality from heart and brain time series (Sections IV and V), currently developed using scalp EEG signals, to source-reconstructed signals [82] and adaptations for fMRI recordings. The cortical signals would likely refer to the regions previously identified as those belonging to the central autonomic network (Section III). These efforts will include modeling the relationships between electrophysiological activity and metabolic activity by accounting for the different confounding factors that appear when measuring various signals with different generative natures.

### *B. Improving the estimation of the directionality of the interactions between the brain and heartbeat dynamics*

On the one hand, distinguishing genuine interactions from mere correlations between brain and cardiac signals posits an utmost challenge. This requires emphasizing the need for methodologies capable of uncovering true causation and functional relationships. In this line, methods accounting for the physiological priors, such as generative modeling [33], [51], [52], could diminish the quantification of spurious correlations.

On the other hand, deciphering physiological dynamics may highly rely on understanding which system influences the other in specific conditions. While time-resolved estimations enable the observation of dynamic interactions within closed-loop physiological circuits, those works rely on pairwise measures to assess functional dependencies as those described in Section IV. However, these measures may not fully capture the interactions within complex systems that often exhibit collective behaviors at different hierarchical levels, involving more than two network nodes. To address this limitation, methods may explore multivariate approaches like conditional causality measures [78] or follow the approaches eliciting higher-order interactions among multivariate time series reviewed in Section VI. In this direction, the incorporation of strategies to uncover hierarchies of the interactions would enhance the causality estimation [139].

### *C. Achieving high time-resolution in the multiscale and time-resolved estimation of brain-heart interactions*

Given that physiological dynamics at the brain and heart level occur at different time scales, unfolding the complex interplay between brain and cardiac activities at a higher sampling rate posits different challenges based on the brain recording modality. Solutions include optimizing time-frequency analyses by incorporating state-of-the-art solutions for better time resolution, such as Wavelet transforms and smoothed Wigner-Ville distributions [156], [157]. In this line, development in time-resolved estimations may provide sufficient information for real-time applications, such as brain-computer interfaces and neurofeedback. Another crucial point is the different scales of oscillations, typically observed between brain and heart rhythms, requiring multi-scale and cross-scale markers allowing the exploration of new modes of brain-heart interaction.

### *D. Overlooking the complex network nature of brain-heart interactions*

While existing information-theoretic measures provide valuable insights, a limitation is their characterization of system dynamics with a single value, overlooking the rich oscillatory content inherent in complex network time series. For instance, brain-heart interactions involve rhythms in different frequency bands with varying physiological significance. While such information is disregarded by approaches targeting heartbeat-evoked responses (Section II), it is accounted for in several pairwise interaction measures using time series that map the amplitude of selected brain rhythms over time (Sections IV and V). However, the most complete account of the variety of brain rhythms requires developing an approach that connects spectral representation with higher-order interactions. In response, some emerging frameworks such as those discussed in Section VI account for the time- and frequency-domain analysis of higher-order interactions in multivariate stochastic processes mapping network system activity [56]. Upon these frameworks, multivariate decompositions may provide a better understanding of complex network dynamics, particularly in capturing the diverse nature of higher-order interactions across different bodily rhythms.

### *E. Overlooking the hierarchy of neural oscillations*

While multiple nodes may interact dynamically over time, a characterization of the hierarchical architecture of network dynamics remains challenging. In this line, identifying the leading nodes of a complex system may be relevant for targeted treatments using neuromodulation, pharmacologically or brain stimulation techniques. Network science techniques can be employed to further describe these interactions, exploring the level of brain network controllability from visceral or peripheral bodily inputs, studying the nodes in charge of network integration and segregation with respect to peripheral bodily signals, and employing various approaches to estimate causality and directionality of those measures among multiple-node signals.

### *F. Uncovering hidden brain-heart coupling patterns with interpretable artificial intelligence*

A challenge in signal processing for assessing causality is identifying parallel, nonlinear patterns that traditional methods often overlook, especially those based on pairwise correlations. To address the potential limitations of coupling measures in capturing complex interactions, deep learning-enhanced algorithms have been proposed [158], [159], [160], [161]. These algorithms help to analyze, for instance, directed functional connectivity patterns distinguishing two

experimental conditions. Such tools employing explainable artificial intelligence [162] serve to optimally decompose the output prediction of a neural network on a specific input by backpropagating the contributions of all neurons in the artificial neural network to every feature used [163]. These post-hoc analyses can be employed to identify and distinguish the different information inflow and outflow patterns.

### G. Methodology translation to other bodily rhythms

One advantage of studying cardiac dynamics is the well-established physiological basis, as cardiac function modeling has a long research history. This knowledge should allow the development of ad-hoc models incorporating physiological priors, which is more challenging for other bodily rhythms, like those originating in the respiration and gut dynamics.

Methodologies for quantifying simple pairwise interactions can be readily adapted to other bodily signals, such as skin conductance, eye movements, or blood pressure. However, for slower bodily signals, like breathing or gut rhythms, specific brain signal processing techniques are necessary. For example, phase-amplitude coupling has been used to study brain-gut interactions, capturing the slow changes in brain activity within the alpha band [164]. These techniques could mitigate spurious correlations when measuring the coupling between relatively slow signals with much faster signals (e.g., respiration vs EEG).

## X. Translational perspectives

### A. Mental health and neuromodulation treatments

The relationship between mental health and the bodily state has been paramount. Recognizing dysfunctions in interoception has become increasingly important in understanding various mental health conditions, including anxiety disorders, mood disorders, eating disorders, addictive disorders, and somatic symptom disorders [165]. Our understanding of the complex relationship between mental health and interoception has primarily been informed by behavioral evidence [166], yet a physiological explanation of affective states and associated disorders remains elusive [167].

Research into clinical and subclinical depression has predominantly centered on examining the brain dynamics of individuals exhibiting depressed mood symptoms. However, systematic analyses show that brain imaging-based biomarkers cannot identify depression at the individual level [168]. Moreover, evidence has shown that depression extends beyond a brain-exclusive disorder; it is intricately linked to cardiovascular conditions [169]. For instance, mood disorders are linked to an increased risk and more unfavorable prognosis of coronary heart disease [170]. Conversely, individuals with cardiac pathologies exhibit a higher prevalence of depression and depressive symptoms when compared to the general population [171], [172]. Recent research on brain-heart interactions suggests that depressed mood is associated with an intensified control over slow HRV changes [130] or reduced control over fast ones [173]. Similarly, some of those dynamics have been shown in anxiety as well [174]. These preliminary results suggest that research into brain-heart interactions holds immense promise for advancing the development of improved biomarkers crucial for the detection, prevention, and stratification of mental health conditions.

Beyond diagnosis and disorders' characterization, some treatments for depression include the use of transcranial magnetic stimulation (TMS), which uses magnetic fields to stimulate brain regions. However, the physiological mechanisms are not fully understood. From a systems perspective, TMS is believed to induce neuroplastic changes in the brain, promoting the formation of new neural connections, but also to modulate the excitability of neural circuits in the prefrontal cortex, which may contribute to restoring more balanced and healthy neural functioning [96]. However, several factors have been found or hypothesized to alter TMS effectiveness in treating depression; for instance, the specific TMS treatment protocol (location, frequency, intensity, and duration of sessions) can impact its effectiveness or the inter-subject variability in their pathology phenotype and their TMS responses. Recent work introduces the concept of a brain-heart network, which intersects with the functional nodes of the previously described depression network [96]. Neuromodulation studies using TMS typically trigger key nodes within this network, specifically the dorsolateral prefrontal cortex and the anterior cingulate cortex, which have a subsequent impact on cardiac dynamics. This evidence emphasizes the significance of incorporating brain-heart interplay measurements in human depression treatments, especially those involving neuromodulation. Developments on this can target the heterogeneity of the outcomes using neuromodulation, allowing the potential development of personalized therapies for depression. In this line, Neuro-Cardiac-Guided TMS treatment has emerged motivated by this brain-heart network [175], which enhances the precision of the TMS location. While a thorough delineation of the physiological dynamics is still pending. The frameworks of brain-heart interplay present a compelling approach to tackle the difficulties of neuromodulation in depression, which may provide biomarkers capable of stratifying patients based on their anticipated outcomes.

### B. Neurodegeneration, stroke, and rehabilitation engineering

Autonomic dysfunction under neurodegeneration can involve various bodily systems, including those generating the cardiovascular dynamics [176], [177]. Further research in different neurodegenerative conditions has suggested a disruption in the awareness of one's heartbeats, as measured from cardiac interoception tasks [178], [179], [180], [181], [182], suggesting a disruption in the communication between the brain and the heart. However, only recently brain-heart interactions have been assessed in these conditions, for instance, to characterize autonomic dysfunctions [183], orthostatic hypotension [184], or dopaminergic therapy effects on motor symptoms [34], [35]. On the other hand, brain damage caused by stroke can lead to extensive changes in the nervous system as well. Abundant evidence exists on the brain-heart effects caused by stroke, from molecular to systemic changes [14].

One of the main challenges in these conditions is the recovery of sensorimotor functions. Recently, brain-heart interactions have shown a close relationship with different aspects of responsiveness, decision-making, and motor functions [65], [66], [67], [185]. In particular, this knowledge can be embedded in brain-computer interfaces (BCIs), as they

hold promise in restoring lost sensorimotor abilities after suffering brain damage from conditions such as Parkinson's disease, stroke, and multiple sclerosis [186]. However, their effectiveness varies because BCIs typically require customization for each patient [187], [188]. For this, developing objective markers for monitoring task performance, learning, and progress remains one of the main challenges in BCIs [187], [188]. The study of brain-heart interactions in motor imagery and BCIs has emerged only recently [189], [190]. These studies show that biomarkers based on brain-heart interactions hold promise in identifying distinct couplings concerning cognitive and sensorimotor synergies. Therefore, the understanding of the specific contributions of cardiac dynamics can further enlighten the rehabilitation of sensorimotor abilities, by either facilitating the relearning of movements and enhancing functional recovery, for instance, by enabling patients to control on-screen commands, robotic exoskeletons, or prosthetic limbs [191].

Neural damage resulting from neurodegeneration or stroke often extends beyond specific brain regions, impacting various parts of the nervous system. In contrast to being solely localized to one area, this widespread pathology underscores the importance of exploring brain-heart interactions. Such investigations offer valuable frameworks for comprehending the physiopathology of these diseases and designing rehabilitation strategies, particularly those leveraging BCIs.

### *C. Severe brain damage, consciousness, and neuroprognostication*

In clinical practice, standard consciousness assessment after severe brain damage relies on characterizing bedside responsiveness [192]. Therefore, the presence of consciousness is often associated with the detection of non-reflex behavior. However, the challenge arises from the patients' high heterogeneity in their clinical phenotype, which may be translated into different sensorimotor impairments and fluctuations in vigilance, leading to a high rate of misdiagnosis [193], [194]. The research of an accurate consciousness diagnosis based on behavior and the exploration of neuroimaging and electrophysiology techniques to reduce the misdiagnosis rate has been part of extensive consciousness research [195]. One of the explored approaches is based on the variability of the neural responses to heartbeats at the bedside, indicative of the relationship between the presence of consciousness and a healthier brain-heart connection [71]. These responses to heartbeats were found to complement other EEG-based markers of consciousness [196] and to be more complex and more segregated through the scalp as a function of the level of consciousness [41]. Further evidence revealed that cardiac inputs in the brain seem to participate in the conscious processing of ongoing exteroceptive information, which also appears as a signature of consciousness in these patients [197], [198].

Exploring brain-heart interactions can provide valuable insights into the physiological condition following severe brain damage. This approach holds promise for identifying biomarkers that could aid in addressing the ongoing challenges faced in the clinical practice of these patients. For instance, prognostication remains challenging due to our limited understanding of the multisystem physiological implications caused by severe brain damage. In this direction, patients with severe post-cardiac arrest brain injury were found to display bidirectional brain-heart interactions that scale with the severity of the brain injury and with patients' neurological outcomes at 3 months [131].

Thus, the field of research focusing on brain-heart interactions offers a promising avenue for unraveling the complexities of physiology following severe brain damage. By investigating this relationship, diagnostic and prognostic biomarkers can be identified to provide valuable insights into the clinical phenotype of these patients. Ultimately, such advancements have the potential to revolutionize the way we understand and manage critical care monitoring, offering personalized approaches tailored to their specific needs and conditions.

## XI. Conclusion

There is an abundance of coupling measures that can be exploited for the analysis of brain-heart interplay, each with its own set of advantages and drawbacks. Beyond an overview of the methods, we aimed to provide some conclusive remarks and guidance on when to explore specific frames providing coupling measures, based on the study objective and the data available. In doing this, we highlighted the key methodological challenges in current approaches to measuring and modeling brain-heart interactions. Addressing these challenges will undoubtedly enhance our understanding of the physiological mechanisms underlying various neural functions, including interactions between the brain and other organs. Our outlines also offer insights into a research agenda for advancing methods for accurately estimating brain-heart interactions.

The ongoing evidence is uncovering non-linear, complex, and bidirectional communications between brain and heart dynamics. Further developments in these methodologies will contribute to a better understanding of the physiological dynamics involved in regulation mechanisms, predicting coding, and cognitive functions.

Finally, we highlighted some significant advancements in understanding the physiopathology of diseases and their connections with brain-heart interactions. These advancements prompt new research avenues where brain-heart interactions play a crucial role in understanding diseases, transforming them into diagnostic tools. Additionally, they offer insights into prognostic tools, treatment evaluation, and the design of personalized and targeted interventions.

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