Through their dynamical interplay, the brain and the heart ensure fundamental homeostasis and mediate a number of physiological functions as well as their disease-related aberrations. Although a vast number of ad hoc analytical and computational tools have been recently applied to the non-invasive characterization of brain and heart dynamic functioning, little attention has been devoted to combining information to unveil the interactions between these two physiological systems. This theme issue collects contributions from leading experts dealing with the development of advanced analytical and computational tools in the field of biomedical signal and image processing. It includes perspectives on recent advances in 7 T magnetic resonance imaging as well as electroencephalogram, electrocardiogram and cerebrovascular flow processing, with the specific aim of elucidating methods to uncover novel biological and physiological correlates of brain–heart physiology and physiopathology.
Over the past few years, there has been increasing evidence for the potential clinical implications of dysfunctional brain–heart interactions. For instance, cerebrovascular accidents and transient ischaemic attacks (transient episodes of neurological dysfunction caused by the loss of blood flow) are frequently caused by cardiac arrhythmias [1], and atrial fibrillation may also result in cognitive disorders [2], even in the absence of manifest stroke [3–6]. On the other hand, brain disorders, including stroke, epilepsy and others thought to be secondary to environmental stress (e.g. panic disorders and emotional distress), may lead to cardiovascular disorders and have been shown to result in cardiac arrhythmias both experimentally and clinically [7]. A recent article in Scientific American (‘A new idea for treating Alzheimer’s’) [8] begins with the following sentence: ‘If it’s good for the heart, it could also be good for the neurons, astrocytes and oligodendrocytes, cells that make up the main items on the brain’s parts list’, suggesting that Alzheimer’s disease may be a candidate for combined brain–heart therapeutic approaches. Furthermore, a wide variety of changes in the electrocardiogram, mainly referring to arrhythmias and repolarization, is often observed in the context of neurological disease [9].

In this context, a significant part of the current knowledge on brain–heart interaction as applied to the medical field refers to ‘neurocardiology’ (see [9] also for a historical review). While this discipline is inherently multidimensional, it may be conceptualized as divided into three major categories: the heart’s effects on the brain (e.g. cardiac source embolic stroke), the brain’s effects on the heart (e.g. neurogenic heart disease) and neurocardiac syndromes (e.g. Friedreich’s ataxia [10,11]).

Modern neuroimaging data, including positron emission tomography and functional magnetic resonance imaging (fMRI), have revealed that a network consisting of the insular cortex, anterior cingulate gyrus and amygdala plays a crucial role in the regulation of the central autonomic nervous system (ANS) [12]. More specifically, insular cortex damage has been associated with cardiac arrhythmia, disruption of physiological diurnal blood pressure variations (e.g. a non-dipper or riser pattern), myocardial injury and breathing-related sleep disorders, as well as higher plasma levels of brain natriuretic peptide, catecholamines and glucose [12,13]. Moreover, the paraventricular nucleus of the hypothalamus was seen to be one of the most important central sites involved in regulating sympathetic tone and is, in part, responsible for the evident dysregulation of the sympathetic nervous system in heart failure [1].

Despite the above-mentioned observations, current clinical practice in evaluating patients suffering from conditions that involve the central nervous system often does not take into account the concomitant autonomic/cardiovascular effects. This could possibly be due to a preferential emphasis, in current medical training programmes, on expertise in single physiological systems at the expense of interdisciplinary skills. Similar considerations result from examining the current scientific literature, and while increased funding from the principal western agencies (European Commission in Europe and National Institutes of Health in the USA) has been granted for the study of the brain (the European ‘Human Brain Project’ and the American ‘Human Connectome Project’), the heart as a physiological subsystem is not explicitly taken into account in these projects.

Another prominent reason why poor attention is devoted to the interaction between brain and heart is the current lack of data analysis methodologies able to reliably handle such information. It is not straightforward to obtain estimates of the bidirectional control effected through the brain–heart axis and, therefore, most experimental investigations of brain and cardiovascular dynamics are simply based on simultaneous observation. Given that recent advances in data collection techniques (such as high-resolution electroencephalogram (EEG) and ultra-high field 7T MRI [14]) are providing access to a wealth of currently underexploited information, the development of novel, evidence-based, ad hoc methodologies for biomedical signal and image processing is expected to greatly advance the understanding of the pathophysiology of brain–heart interactions. In this context, purposeful mathematical modelling is a key player, which can greatly aid in quantitatively characterizing complex heart–brain interactions, hence allowing an improved understanding of physiological and clinical measurements related to both domains [15]. In particular, novel methodological advancements have succeeded in combining...
imaging techniques with physiological measurements in order to map the central autonomic network dynamics initiating peripheral autonomic control mechanisms [16–20].

To this extent, this theme issue is focused on the application of advanced signal and image processing algorithms to characterize brain–heart interactions. The proposed contributions include several novel key elements concerning the brain–heart axis, from both experimental and theoretical points of view.

In detail, this theme issue includes both extensive reviews (which critically report on the current knowledge about brain–heart physiology) and original research articles (which present novel analysis methods targeted to extracting physiologically relevant information about brain–heart interactions).

Specifically, Silvani et al. [21] illustrate the functional and anatomical links between the brain and the heart, as well as their possible disease-related alterations. Perspectives on the potential clinical implications of advanced signal and image processing methods that are able to quantify these links are also included. Chang et al. [22] critically discuss the recent improvements and trade-offs in brain imaging at high and ultra-high field strengths (7 T MRI), also in the context of distinguishing non-neural physiological effects from neural signals of interest that reflect cardiorespiratory function. Recently developed data analysis methods to uncover novel heart–brain interactions are also covered. Rossi et al. [23] review current brain stimulation techniques and the mechanisms underlying their neuromodulatory action on brain networks, including the function of brainstem centres controlling vital functions as well as acute and long-term effects on brain sympathetic outflow controlling heart function and blood pressure. Rossi et al. also provide a critical perspective on how brain neuromodulation may enhance our understanding of the cortical/subcortical mechanisms of autonomic cardiovascular regulation, and discuss how such techniques may open a therapeutic window in patients with otherwise intractable autonomic dysfunctions.

These reviews are complemented by 12 research articles providing original perspectives on brain–heart interactions. The latter are studied by measuring electrical activity (EEG) and haemodynamic activity (cerebral blood flow and fMRI) while employing novel multivariate modelling methodologies to analyse experimental brain–heart-related findings in healthy subjects as well as in patients with mental or neurological disorders.

In detail, five research articles describe novel methodologies for uncovering brain–heart information using EEG signals in conjunction with peripheral signals related to ANS activity.

Faes et al. [24] introduce a framework to study the network formed by the autonomic component of heart-rate variability and the amplitude of the different EEG waves during healthy and pathological sleep using multivariate linear models, whereas Lin et al. [25] propose a generalized time-delay approach to quantifying dynamical interactions between physiologically relevant brain rhythms and heart rate in healthy subjects during night-time sleep.

Furthermore, Stankovski et al. [26] study cross-frequency coupling functions between neuronal, cardiac and respiratory oscillations, revealing how these relationships are altered by anaesthesia, and Valenza et al. [27] describe brain–heart dynamics during visual emotion elicitation in healthy subjects, considering linear and nonlinear coupling measures between instantaneous heart-rate estimates and EEG oscillations. Finally, Schulz et al. [28] study brain–heart interactions in paranoid schizophrenic patients, as compared with age–gender-matched healthy subjects, using high-resolution joint symbolic dynamics to analyse EEG signals.

In view of the crucial role that haemodynamics plays in brain–heart information exchange, Marmarelis et al. [29] combine information gathered from heart-rate variability, arterial blood pressure and cerebral blood flow velocity in healthy subjects through the concept of principal dynamic modes, whereas Bari et al. [30] investigate cardiovascular and cerebrovascular control systems through joint symbolic analysis, selectively conditioned on respiration, in subjects experiencing recurrent syncope episodes when compared with healthy individuals.

Five further research articles describe novel methodologies for combining MRI data with cardiovascular dynamics. Specifically, Bianciardi et al. [31] perform an initial validation of a
novel MRI indicator of cerebrovascular compliance measured at ultra-high field (7 T), which might prove useful to investigate brain–heart interactions in cerebrovascular disease and other disorders. Duggento et al. [32] demonstrate that ultra-high field functional imaging coupled with physiological signal acquisition and Granger causality analysis is able to quantify directed brain–brain and brain–heart interactions reflecting central modulation of autonomic outflow. Moreover, Sclocco et al. [33] combine high spatial resolution fMRI and high temporal resolution HRV estimates to characterize brainstem nuclei, suggesting that nociceptive afference induces pain-processing brainstem nuclei to function in concert with known premotor autonomic nuclei in order to affect cardiovagal response to pain. Finally, Wu & Marinazzo [34] show how the resting-state haemodynamic response function is significantly modulated in the brainstem and surrounding cortical areas, whereas Nikolaou et al. [35] examine the relation between dynamic functional connectivity patterns and the time-varying properties of simultaneously recorded autonomic signs (end-tidal CO2 and HR/HRV) using resting-state fMRI measurements in healthy subjects.

The common thread and underlying outcome in this theme issue is that, while the brain and heart have distinct biochemical and neural dynamics (which can be quantified in health and disease through a wide range of techniques), the dynamics of these two systems obey specific rules of information exchange whereby cognition, emotions and homeostasis can be jointly analysed and understood on a whole-body level.

We are confident that physicians of the future could benefit from a working knowledge of integrated physiological systems, which in turn will provide them with a broader perspective when evaluating and treating patients. One may envisage that future treatments of mental and neurodegenerative diseases will involve greater attention to the cardiovascular system, and vice versa. Moreover, the overwhelming growth of invasive, minimally invasive and non-invasive techniques to stimulate the brain with therapeutic purposes (e.g. in Parkinsonian patients [36–39], and patients with tremor or dystonia [40], depression [41–43], obsessive-compulsive disorders [44], severe epilepsy [45–48], migraine and chronic pain [49]) leads to the necessity of evaluating the impact of these stimulation practices on autonomic and heart functions.

References


