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Editorial

The inevitable link between heart and behavior New insights from biomedical research and implications for clinical practice[☆]

The idea that actions and reactions may be governed by “the heart or the head” indicates that the importance of each in the control of human behavior is well recognised. This dichotomy does not, of course, imply that the influences of each are independent: the activity of the heart is necessary for neural activity and behavior, while emotional and behavioral states and traits dramatically influence cardiovascular function. The evidence for this close functional association is compelling. Thus, the new frontier of research and clinical practice in cardiology, embracing recent and sophisticated developments in genetics and molecular biology, is incomplete without the integration of neurocardiology and behavioral cardiology. Likewise, neurocardiology and behavioral cardiology will only move forward in the context of cutting edge molecular and cellular cardiology. To reach this goal, it is necessary to integrate in a systematic manner the knowledge and techniques of modern cardiovascular research with those in the fields of ethology, psychology and psychiatry. We believe that this integrated approach is the only one that will allow investigators to address a number of questions of high clinical relevance. What is the impact of different acute and chronic stress conditions on cardiocirculatory function? Do subjects of different socioeconomic status really exhibit different cardiovascular vulnerability? How far does cardiovascular health depend on different strategies of coping with the everyday social environment? Do psychological traits like dominance, aggression or hostility significantly increase the risk of atherosclerosis, hypertension or sudden cardiac death? Which are the biological substrates linking psychological disorders such as depression, and cardiovascular pathologies such as atherosclerosis? Can behavioral interventions be as effective as conventional pharmacologic therapies with fewer undesirable side effects? To what extent does perinatal environment influence adult cardiovascular function and stress sensitivity?

This special issue gathers the expertise of leading scientists who, although belonging to different research disciplines, share a common interest in the complex integration among brain activity, behavior, and cardiovascular function. It includes original contributions, based on both human and animal studies, presented at an international conference entitled “The inevitable link between heart and behavior: new insights from biomedical research and implications for clinical practice”, held at the Ettore Majorana Center for Scientific Culture in Erice (Sicily, Italy, 27 September–2 October 2007). The lectures and discussions followed the pedagogical style espoused by the International School of Ethology

chaired by Danilo Mainardi and the present review articles provide a snapshot of current investigation on some key issues in this area.

This issue begins with Drs. Steptoe and Brydon considering the role of emotional events in the triggering of cardiac events. They review the evidence that psychological factors may contribute not only to the evolution of coronary atherosclerosis and long-term risk of coronary heart disease, but also to the triggering of acute cardiac events in patients with advanced atherosclerosis.

Heart rate variability (HRV) is used as a tool to investigate the link between heart and behavior by Dr. Montano and colleagues. These investigators review the evidence that the interaction of sympathetic and vagal outflows can be explored by assessing cardiovascular rhythmicity with appropriate spectral methodologies. They also contend that the nonlinear dynamics inherent in sympatho-vagal balance may provide crucial diagnostic, therapeutic and prognostic information that other analytic approaches can not.

Next, Drs. Thayer and Lane review and elaborate the model of neurovisceral integration first enunciated by Claude Bernard over 150 years ago. They review recent neuroanatomical studies that implicate inhibitory GABAergic pathways from the prefrontal cortex to the amygdala and from the amygdala to brainstem nuclei that modulate heart rate and HRV. They summarize the role of vagal tone as reflected in HRV in the regulation of physiological, affective, and cognitive processes, the role of low HRV in pathology, and consider the heritability of HRV.

Dr. Paton focuses on central neural mechanisms to address causes of essential hypertension. It has long been thought that sympathetic nervous system (SNS) activation is a key contributor to hypertension. The nucleus tractus solitarius is a brainstem structure involved in sympathetic activation which also plays a critical role in the modulation of arterial pressure. Dr. Paton posits that inflammation of the brainstem microvasculature may increase vascular resistance in the brainstem. Together increased vascular resistance and inflammatory processes may promote the release of pathological paracrine signaling molecules affecting central neural cardiovascular control resulting in neurogenic hypertension.

Drs. Nalivaiko and Sgoifo broaden the discussion of nervous system involvement in stress responses that increase cardiovascular disease risk by reviewing current thinking about the role of serotonin receptors in stress-induced changes in cardiovascular function. The traditional views of central serotonin (5-HT)1A, 5-HT2A, and 5-HT3 receptor systems as inhibitory or excitatory to cardiovascular function are considered in light of new observations.

Dr. Hautala and associates take into consideration the marked heterogeneity in training-induced changes in aerobic fitness which are observed in healthy human subjects even with highly

[☆] Dedicated to the memory of Alberto Malliani

standardized training programs. They consider the role of the autonomic nervous system (ANS) in the heterogeneity of responses to physical training, and make the case that assessment of ANS functioning may aid in tracking individual improvement in aerobic fitness in response to physical training programs.

Dr. Davy and coauthors continue the discussion of the role of the SNS in cardiovascular disease. They consider the essential role of the SNS in the regulation of metabolic and cardiovascular homeostasis. They present and discuss evidence for the importance of visceral fat as an important depot linking obesity with skeletal muscle SNS activation. They also consider the influence of weight change on SNS behavior and the potential mechanisms and consequences of region specific SNS activation in obesity.

The issue of circulating lipid concentrations in psychiatric disease is reviewed by Dr. Troisi. He questions whether a negative impact on mental health is an inevitable downside of cholesterol-lowering interventions for coronary heart disease. Dr. Troisi suggests that there are some subgroups of vulnerable individuals who may be susceptible to adverse psychological and behavioral outcomes associated with low cholesterol levels, and discusses the need to be able to identify such individuals.

Dr. Shively and her colleagues make the case that while coronary heart disease is the leading killer of women, little is known about stress effects on the cardiovascular system that are specific to women. They review the effects of low social status on depression and coronary artery atherosclerosis risk in female primates, and demonstrate that certain stress responses, like the propensity to develop depression and the suppression of ovarian function, are cardiovascular risk factors specific to females and should be considered in studies of women.

Dr. Newton focuses on the role of the personality trait of dominance in modulating cardiovascular responses to challenge. She summarizes the literature on connections between dominance/submissiveness and cardiovascular morbidity and mortality in human beings. She also considers the gender specificity of patterns in the relationship between dominance/submissiveness and cardiovascular function, particularly in cardiovascular reactivity.

Competition is a common human experience. Drs Salvador and Costa address the consequences of competition on health. They consider the hypothesis that the appraisal of the situation is more important than the situation itself in terms of health effects. Thus an understanding of the cognitive processes underlying the social stress response in human beings is needed. They propose that human competition should be studied from a social stress perspective and within an evolutionary framework.

Dr. Grippo considers the bidirectional association between mood disorders and cardiovascular diseases in human beings. She appraises the utility of experimental investigations with rodent models, particularly prairie voles (*Microtus ochrogaster*), and focuses the discussion on the analysis of behavioral, physiological and neural mechanisms underlying depressive disorders and cardiovascular dysfunction.

Dr. Stiedl and colleagues review their work on heart rate dynamics in mice exposed to novelty, and the expression of fear conditioned to an auditory cue as an affective challenge, to characterize baseline dynamics and conditioned adjustments by learned fear. They use non-linear analyses of neuroautonomic cardiac control and discuss the implications of an improved understanding of brain heart interactions for autonomic dysregulation in affective disorders.

Finally, Dr. Mastorci and colleagues take up the issue of epigenetic influences on stress sensitivity and cardiovascular regulation. They present original data demonstrating that prenatal stress does not induce changes of cardiac autonomic modulation at rest in the rat adult offspring. However, they underline that prenatally stressed rats – when further stimulated in adulthood – exhibit prolonged adrenocortical stress responsivity, disturbed circadian rhythmicity of heart rate and increased adrenal weight. They conclude that prenatal stress affects resilience and renders the animal more susceptible to pathophysiological outcomes when further insults occur during adulthood.

We are truly grateful to the authors for their excellent contributions and to the Director of the School of Ethology at the Ettore Majorana Center – Danilo Mainardi – for his enthusiastic help in the organization of the meeting. We also want to express our sincere gratitude to Verity Brown, editor of the journal, for her priceless support in this *small enterprise* and to the referees for their qualified and rigorous comments on the manuscripts. Finally, we wish to say that while it is far beyond the scope of this special issue to provide a complete overview of such a multifaceted topic, we hope that we have been able to suggest some possible answers to the questions posed above. Hopefully, the readers will enjoy the style and content of the reviews and find some stimulating ideas for their own future research on the inescapable and fascinating link between heart and behavior.

Certainly Prof. Alberto Malliani, who was initially invited to give the introductory lecture, would have enjoyed the spirit of the workshop and would have enriched the contents of this special issue with his scientific brilliance. This special issue of *Neuroscience and Biobehavioral Reviews* is dedicated to his memory.

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