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Coronary microvascular and endothelial function regulation: Crossroads of psychoneuroendocrine immunitary signals and quantum physics [Part A]

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Abstract

Nowadays the heart can be considered as a psycho-neuro-endocrine-immunitary structure that constantly interacts with other organs through a dynamic dialogue made of neurotpeptides, hormones and cytokines. The exploration of microvascular function is important as predictive tool and as prognosis of cardiovascular risk and progression of heart failure. This review describes the present knowledge on whether neurotramitters, hormones and cytokines influence microvascular/endothelial function and its genetic and epigenetic background. The review, describing the rich network of connections acting every moment of our lives linking endothelial function to the psychophysical environment, leads then to the description of an endothelial cell functioning, with the look of quantum physics. All this allows to describe some actual scientific methodological and epistemiological problems that remain to be resolved in order to fully understand endothelial function regulation, and future research, prevention and treatment directions. In the end, we describe the "Integrative Medicine" approach (and its beneficial influences on endothelial function regulation) that has emerged as a potential solution to the crisis in the healthcare system of western countries. It provides care that is patient-centered and healing-oriented, stressing the use of treatments originating from both conventional and alternative medicine.

Abstract [Part A]

In this first part we discuss the factors that regulate endothelial/microvascular coronary function. This represents the barometer of cardiovascular functioning and its regulation intervenes in almost all heart diseases. In particular, endothelial cells are affected by psycho-neurological, endocrine and immune stimuli that, influencing each other, constitute an integrated network (PNEI). This system responds to the environment and its organization is transgenerationally transmitted through epigenetic mechanisms.

Introduction

According to the 2010 Heart Disease and Stroke Statistics update of the American Heart Association, about 20 million persons in the United States have coronary heart disease (CHD), precisely 8.5 million with myocardial infarction and 10.2 million with angina pectoris [1]. The lifetime risk of developing CHD for men and women aged 40 years is respectively 50 percent and 30 percent. For those reaching 70 years, the lifetime risk is 35 percent in men and 24 percent in women [2]. Over 4 million annual deaths are due to cardiovascular disease according to a 2014 World Health Organization study, using data from 49 countries in Europe and northern Asia [3]. Mortality from CHD is expected to increase in developing countries (including China, India, sub-Saharan Africa, Latin America and the Middle East), from an estimated 9 million in 1990 to a projected 19 million by 2020 [4].

Hypertension, dyslipidemia, diabetes mellitus and cigarette smoking represent well established risk factors for cardiovascular disease (CVD), but understanding how other factors, such as stress [5], contribute to this burden is essential in order to develop new strategies to combat and/or prevent it.

An important indication is offered by the study and the understanding of cardiac microvascular function and the factors that regulate it.

In order to understand the logic of the factors that regulate endothelial function we will have to do an overview of many concepts that do not strictly belong, yet for the moment, to the "world of cardiology". Unfortunately, the fragmentation and specialization of knowledge prevents sometimes a vision that would allow to understand the phenomena that we observe in daily clinical practice. In this review we will try to make a journey to discover the main factors regulating the coronary microcirculation and endothelial function in general, deeper and deeper, reaching the structure of matter. A path that will lead us then again to the surface to suggest new avenues of research and treatment of cardiovascular diseases on the basis of the connections drawn. In this perspective we will present some difficulties in the Scientific Method related to the correct observation of biological

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phenomena from the point of view of the human network connections, that can greatly affect the clinical work. Finally, we will present several examples of what can be done to modulate endothelial function for the prevention of the cardiovascular burden. The paper is focused on the main topic of the regulation of endothelial function as a key to understanding several cardiovascular disorders in order to be able to prevent their onset or severity. From this point of view we won't go into the details of individual molecular actions of all the presented actors (to this end, please consult the corresponding bibliography).

Coronary flow physiology, coronary microvascular function and coronary flow reserve

The myocardium is a strictly aerobic and oxygen-dependent tissue. 40% of the myocellular volume is occupied by mitochondria and their work is based on the assumption of free fatty acids, glucose or lactate [6]. The myocardial oxygen needs, or "oxygen consumption", is an accurate indicator of overall cardiac metabolism and depends on: heart rate, contractility and parietal tension (in turn dependent on the endoventricular pressure, the mean radius of the cavity and the wall thickness). The heart receives blood through the coronary circulation for 70% of its needs during the diastolic phase and for 30% in systole. Increasing the heart rate (greater energy demand) the duration of diastole decreases but the contribution of myocardial oxygen and energy substrates is ensured by the increased speed of coronary blood flow (up to 5 times greater) and the coronary vasodilation induced by adenosine releasing. Increasing the metabolic demands of the heart, adenosine (as a paracrine agent) induces vasodilation especially at the level of the coronary resistance vessels, which together form the microcirculation [7]. In basal conditions the heart consumes about 6.5-10 ml/min/100 g tissue of oxygen and such an expenditure serves in 3-5% for the electrical activity, in 20% for the maintenance of cellular integrity, in 72 -75% for contractile activity [8]. Given the high baseline myocardial oxygen extraction (about 70%), the only compensation mechanism in case of increased oxygen requirements is represented by a proportional increase in the coronary flow, determined by a coronary vasodilation of the arteriolar district (resistance vessels) [9]. The maximum capacity of vasodilation secondary to a metabolic stimulus is defined Coronary Flow Reserve (CFR).

The ability to maintain the coronary flow relatively constant despite changes in perfusion pressure is defined "coronary autoregulation". Through this mechanism, decreases in perfusion pressure are compensated by decreases of the resistance, conversely increases of perfusion pressure are offset by increments of resistance; so that the flow remains constant [10]. The phenomenon of self-regulation, based on a multiplicity of mechanisms, hereinafter analyzed, is predominant in the microcirculation, in such a way as to have the greatest possible impact on coronary resistances [11].

As depicted in Figure 1, the coronary arterial system can be schematically divided into three compartments, each characterized by different structure and function. The first compartment is represented by proximal epicardial arteries with a vessel diameter ranging from 500 μm up to 2-5 mm. The epicardial arteries have a main capacitance function and offer only 10% of the resistance to coronary flow. The intermediate compartment is represented by prearteriole, the diameter of which ranges approximately between 100 μm and 500 μm. Their function is to maintain the pressure distal to the origin of the arterioles within a certain range in the case of coronary perfusion pressure changing or a change in coronary flow. They are responsible for 25% of the total coronary resistance. The distal compartment is represented by arterioles, with a diameter of less than 100 μm, offering 55% of the total resistance to coronary flow. Together, prearterioles and arterioles offer the most resistances to the coronary flow and go to constitute the so-called "coronary microcirculation"[12]. In rest conditions, the coronary perfusion pressure is maintained along the epicardial arteries, then slowly fall along prearterioles and finally take a quick descent into the most distal compartment, *i.e.,* within the microcirculation. When there is a change in coronary flow, the epicardial arteries and proximal arterioles have an inherent tendency to maintain a certain level of shear-stress through endothelium-dependent vasodilation. When there is an increase in aortic pressure, the distal prearterioles undergo myogenic vasoconstriction in order to maintain a constant pressure at the origin of the arterioles, the most distal compartment. The latter plays a key role in the metabolic regulation of coronary flow. The arterioles, in fact, have a high resting tone and dilate in response to the release of the metabolites by the myocardium when there is an increase in oxygen consumption. Following this expansion, both the resistances along the coronary arterial system, both the pressure in the distal prearterioles decrease. Moreover, the dilatation of pre-distal arterioles and arterioles induces an increase of the shear-stress which in turn determines a flow-dependent vasodilatation in proximal prearterioles and in epicardial capacity arteries [13].

The coronary circulation is regulated by four main factors (Figure 1): 1) anatomical (left ventricular wall thickness and the presence of collateral circulation), 2) mechanical (systemic flow, vascular resistance, systolic compression, myogenic reflection and blood viscosity or hemolysis and platelet aggregation), 3) neuro-immune (through alpha and beta2 receptors, vagal action) and 4) endocrine-metabolic (pO2, pH, K+, adenosine, prostaglandins, tromboxane, hyperlipemia and nitric oxide (NO)) [13]. Among the anatomical factors we must remember that the coronary vessels are distributed in myocardial in a fractal way [14]. We can distinguish epicardial conductance vessels (they are in the surface and have a large caliber) and resistance vessels represented by arterioles, by intramyocardial vessels and capillaries [15]. The coronary resistance are regulated precisely by extrinsic factors (compression by the ventricular muscle) and intrinsic factors (such as neuro-hormonal, metabolic and myogenic factors) [16]. Coronary flow takes places especially in diastole because in systole intramural branches are virtually occluded by ventricular contraction. It follows that the tachycardia predisposes to the development of ischemia, as it shortens the diastolic time. Subendocardial layers are generally more exposed to ischemia mainly because more exposed to intracavitary pressure and tributaries of a terminal circulation.

The increased metabolic demand of the myocardium determines the hydrolysis of ATP and the resulting release of adenosine in the interstitium [17]. Adenosine induces vasodilation (counteracting the input of the calcium ion within the smooth muscle cells), especially at the level of resistance vessels, with a consequent increase in the coronary flow proportional to the increase of metabolic demands[8]. Other factors such as prostaglandins, hydrogen ions, potassium ions, the carbon dioxide and nitric oxide, are produced locally with vasodilating action [18].

The coronary arteries are innervated by the autonomic nervous system (the sympathetic system, through the action of noradrenaline on alpha-receptors, causes vasoconstriction, while acetylcholine, amine of vagal-parasympathetic system, causes vasodilatation) which ensures the normal vascular tone. It should be emphasized that the metabolic

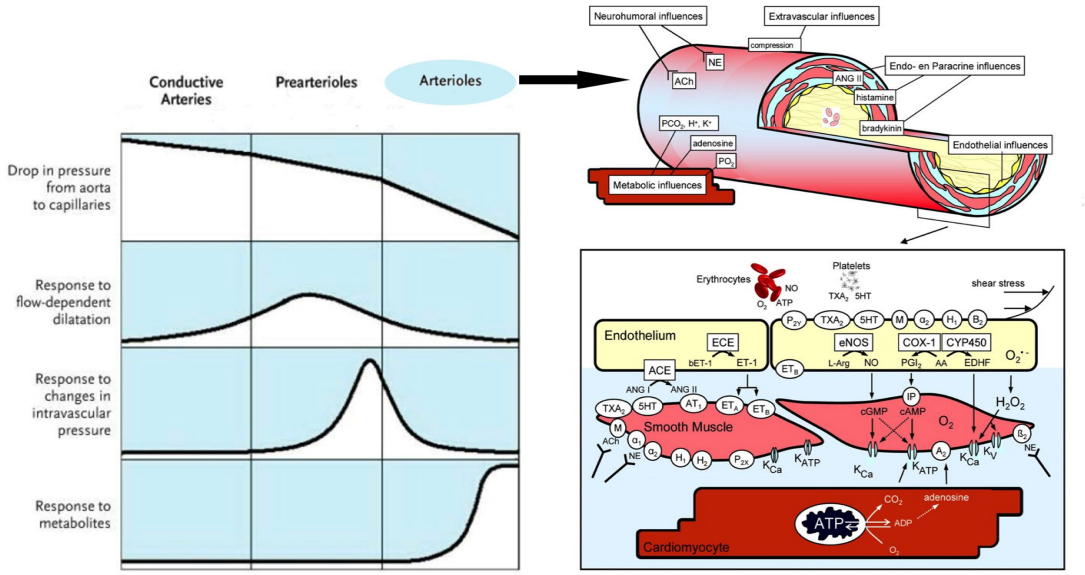

Figure 1. Functional anatomy of the coronary circulation (modified from [6,443]**). Schematic drawing of the coronary flow regulation in the three compartements of the coronary arterial system. In particular is depicted a coronary arteriole and the various influences that the determine "microcirculatory function".**

In the prearterioles and in the arterioles is present a endothelium-dependent vasoreactivity that transforms stimuli related to the flow in vasomotor responses. Vasodilation induced flow (FID, Flow-Induced vasodilatation) is an important physiologic mechanism which aims to adjust the coronary tone. The FID has been demonstrated in many different species, and thus is not only present in the human, although it varies the endothelial factor that mediates this response. The principal molecules responsible of this mechanism are nitric oxide (NO), prostacyclins (PGI2) and the EDHF (endothelium-derived hyperpolarizing factor) [444]. The increase of the shear stress on endothelial cells, due to an increase of the speed flow, results in a stimulation of endothelial nitric oxide synthase (eNOS) and the resulting release of NO, which determines the relaxation of smooth muscle cells. So, increasing the flow, vasodilation occurs maintaining constant intra-coronary pressure [10]. The release of NO and EDRF (endothelium-derived relaxing factor) can be also consequent to a stimulation of the endothelial cells of the vessels with larger caliber by many factors such as neuronal noradrenaline, adrenaline and acetylcholine. As explained in the main text, coronary microvascular function depends on four main factors. **1)*neurological control*** : sympathetic and parasympathetic (vagal) systems innervate the coronary resistance vessels, changing their tone through a direct action on vascular smooth muscle cells (VSMC), or by stimulating endothelial NO releasing [445]. Both endothelial cells and VSMC express adrenergic receptors. For example, during stress or exercise, the release of norepinephrine from sympathetic nerve endings in the coronary vessels and the release of catecholamines from the adrenal glands cause a constriction of VSMC mediated by α-adrenergic receptors that normally was offset by the release of vasodilatory substances (mainly NO) from endothelial cells. This interaction between the forces that cause vasoconstriction (mainly dependent on VSMC) and vasodilation (mainly based on the endothelium) adapts the diameter of the vessel on the flow, optimizing the resistences [10]. The effects of sympathetic system are complex and are connected to the activation of both β1 and β2 receptors (which mediate small arterioles vasodilatation) and α1 receptors (which determine pre-arteriolar vasoconstriction) [10]. The latter is necessary to optimize the coronary flow during exercise or stress conditions, making pre-arteriolar vessels less vulnerable to the compressive forces and tachicardia [446]. The parasympathetic action, mediated by acetylcholine, results in two simultaneous and opposite effects: the vasoconstriction of epicardial vessels and the release of vasodilating endothelial factors. **2)** ***Myogenic control:*** the VSMC possess stretch receptors that are able to sense changes in intraluminal pressure. When it increases, vasoconstriction occurs and, on the contrary, when the pressure decreases, there is a vasodilatation. ***3) Metabolic control:*** despite the increase in knowledge in this field, there is still no full consensus about the specific mediators of metabolic coronary vasodilation. The resistance in the coronary microcirculation is determined by integration of physical factors (eg. pressure and flow), vasodilating molecules (adenosine, pO2 and H+), and neuro-humoral factors. All these elements and mechanisms contribute to forming muscle tone of vascular smooth muscle, which could eventually be controlled by opening and closing the ATP-sensitive potassium channels (KATP) [445]. It is thought that metabolic control is the most important mechanism by which increases in metabolic activity and oxygen consumption result in increases in coronary flow. The accumulation of vasoactive peptides may be subsequent to an increased metabolism, but also to a reduced perfusion pressure and the consequent reduced wash-out [11]. There is considerable redundancy in the mechanisms of local control of coronary flow; accordingly, eliminating a single mechanism in experimental conditions or in early pathological conditions, this does not necessarily affect the coronary flow balance at normal pressures or at rest. However, the lack of an important vasomotor mechanism can be discovered through cardiac stress tests, evaluating the flow regulation under reduced perfusion pressures distally to a coronary stenosis at rest or during exercise [445]. ***Interaction of microvascular control mechanisms:***the control mechanisms described above interact with each other in order to increase blood flow and to ensure the oxygen supply in response to the increased demands of the myocardium. For example, a sudden increase in oxygen consumption in the course of stress or physical exercise increases the production of metabolites which mediate vasodilation of small caliber arterioles and, therefore, decreases the pressure upstream. The decreased pressure causes the medium caliber arterial myogenic vasodilation. The result is the decline in downstream resistance which increases flow in small arteries and those of great caliber upstream. This increased flow results in a endothelium-dependent vasodilation. This upstream vasodilation allows the transmission of the pressure in the downstream segments counteracting myogenic vasodilation. Furthermore, the increase of the flow allows the wash-out of the vasoactive metabolites, attenuating the metabolic vasodilation [11]. **PO2, oxygen tension; TxA2, thromboxane A2 (receptor); 5HT, serotonin or 5-hydroxytryptamine (receptor); P2X and P2Y, purinergic receptor subtypes 2X and 2Y that mediate ATP-induced vasoconstriction and vasodilation, respectively; ACh,acetylcholine; M, muscarinic receptor; H1 and H2, histamine receptors type 1 and 2; B2, bradykinin receptor subtype 2; ANG I and ANG II, angiotensin I and II; AT1, angiotensin II receptor subtype 1; ET, endothelin; ETA and ETB , endothelin receptor subtypes A and B; A2, adenosine receptor subtype 2; ß2, ß2-adrenergic receptor; α1 and α2, -adrenergic receptors; NO, nitric oxide; eNOS, endothelial NO synthase; PGI2, prostacyclin; IP, prostacyclin receptor; COX-1, cyclooxygenase-1; EDHF, endothelium-derived hyperpolarizing factor; CYP450, cytochrome P450 2C9; KCa, calcium-sensitive K+ channel; KATP, ATP-sensitive K+ channel; KV , voltage-sensitive K+ channel; AA, arachidonic acid; L-Arg, L-arginine; O--, 2 superoxide. Receptors, enzymes, and channels are indicated by an oval or rectangle, respectively.**

factors are dominant on the nervous ones [19]. The stimulation of the stellate ganglion (sympathetic station) induces vasodilation (mediated by beta receptors), but at the same time increases the heart rate and muscle contractility [16]. On the other hand, beta-receptors blockade determines the appearance of alpha mediated effects (vasoconstriction) [16].

A condition of myocardial ischemia is established by a mismatch between demand (oxygen consumption increased) and supply of oxygen and nutrients through the coronary flow. The most obvious case is the presence of an atherosclerotic stenosis of an epicardial branch that determines a downstream pressure drop proportional to the reduction of vasal caliber. The pressure gradient created stimulates

the dilation of resistance vessels, in order to maintain adequate flow in basal conditions (in this situation, the coronary tree undertakes its reserve to maintain a proper metabolic balance). In case of increase of metabolic demands the circle is no longer able to cope with the demands with onset of ischemia. This mechanism can occur even in the absence of angiographically critical epicardial atherosclerotic lesions or even free of epicardial coronary lesions [20]. This is the case of the so called microcirculatory dysfunction, at the base of anginal symptoms with release of troponin and myocardial damage typical of many cardiac, endocrine, psycho-neurological and immunitary conditions, as we will see.

The discovery of NO as a crucial endothelium-derived molecule for vascular relaxation and the recognition of the endothelium as more than a passive interface between blood and the vessel wall, led to substantial progress in the field of vascular research [21]. The integrity of the endothelial cells (ECs) is critical for endothelial homeostatic responses. ECs are in a strategic anatomic position between the circulating blood and the vessel wall and regulate vascular function and structure releasing a variety of relaxing and contracting factors [22], by responding to mechanical forces and neurohormonal mediators. The endothelium-derived relaxing factors(EDRFs) (such as NO, prostacyclin and a still elusive factor that hyperpolarize vascular myocytes by opening voltage channels [23]), can also inhibit platelet adhesion and aggregation, leukocyte adhesion and migration and the proliferation of smooth muscle vascular cells [24]. Moreover, ECs produce vasoconstrictors such as angiotensin II, endothelin-1 (ET-1) and prostaglandin H2 (PGH2) that act also as growth promoters [24]. In normal ECs, NO is constitutively produced by endothelial-NO synthase (eNOS) through a 5-electron oxidation of the guanidine-nitrogen terminal of L-arginine [25]. Generally, NO biovailability indicates a functional and healthy vascular bed. Endothelial-derived NO regulates vasomotor tone (induces vasodilatation activating guanylyl cyclise on subjacent vascular SMCs [26]), blood fluidity and vascular cell growth. As described by Osto *et al.* [24]: "*the activity of endothelial NO depends on the balance between synthesis of NO and its breakdown by superoxide anion (O2-). Under physiological conditions, the production of this molecule is not affected by O2-. Hence, the endothelium-derived NO may exert its well-known vascular protective effects. However, excessive generation of O2- rapidly inactivates NO, leading to the formation of high concentrations of peroxynitrite (ONOO-), a very powerful oxidant. Peroxynitrite easily penetrates across phospholipid membranes and produces substrate nitration, thereby inactivating regulatory receptors and enzymes such as free radical scavengers. Increased production of reactive oxygen species (ROS) is regarded as major determinant of reduced levels of NO. The loss of NO due to enhanced oxidative stress in the vessel wall might be considered the central mediator of all different aspects related to endothelial dysfunction, critically contributing to plaque destabilization in traditional atherosclerosis. The loss of endothelium-derived NO permits increased activity of the pro-inflammatory transcription factor nuclear factor kappa B (NF-kB), resulting in expression of leukocyte adhesion molecules and production of chemokines and cytokines. These actions promote monocytes and vascular SMCs migration into the intima and formation of macrophage foam cells, characterizing the initial morphological changes of atherosclerosis. The activity of the endothelium, thus, extends far beyond the control of vascular tone and reactivity, and the release of vasodilating mediators is only one aspect of its homeostatic and protective roles*".

An impaired NO bioavailability, leading to endothelial dysfunction, is a key pathological condition which is associated with most, if not all, cardiovascular diseases and risk factors [27].

The description of all the methods available for clinical endothelial function assessment is away from the scope of this paper: Flammer *et. al.* well described [27] all these aspects, showing that it is possible to consider the endothelial function as a "barometer" of cardiovascular health useful to direct patient management and evaluation of therapeutic strategies.

Among other vascular beds, the endothelial function can be assessed also at the level of the coronary circulation by mean of the CFR [28]. From what we described so far is easy to understand that reduced CFR can result from the combination of different alterations such as impaired vasodilation, enhanced vasoconstrictor responsiveness, and/or structural remodeling of the coronary microvasculature. Thus, the functional status of the coronary microcirculation can be assessed by testing endothelium-dependent (using acetylcholine (Ach), bradykinin or substance-P administration) and endothelium-independent (through adenosine, dipyridamole, or papaverine vasodilatating trigger) vascular responses [12]. It is important to consider that rheological factors (such as heightened plasma viscosity and increased red blood cell aggregation) modify blood fluidity. A reduced fluidity may limit the microcirculatory flow due to the viscus resistance [29].

The CFR, defined as the maximal hyperemic flow divided by resting flow, represents the ability of the coronary flow to increase above its basal value when the coronary vascular bed is maximally dilated and is commonly measured by echocardiography and by other techniques (coronary angiograms and fractional flow reserve, positron emission tomography, and magnetic resonance imaging), each one with distinct advantages and limitations [30]. CFRis a global parameter of coronary flow, which is early altered in the presence of a coronary microvascular dysfunction/disease or epicardial coronary artery stenosis. It is possible to study coronary flow in all main coronaries by transthoracic-Doppler echocardiography; however, normally the left anterior descending artery is the coronary of choice. CFR is defined as the ratio of maximal hyperemic to basal diastolic coronary velocity and maximal hyperemic flow is obtained during adenosine infusion. Buus *et al.* demonstrated in healthy subjects that adenosine-induced myocardial hyperemia is partly dependent on an intact endogenous NO production suggesting that adenosine-mediated vasodilation is partly endothelium dependent [31]. Thus, as we and others confirmed [7,32,33], a decrease in myocardial perfusion reserve may be caused by endothelial dysfunction. We want to stress that the distinction between "endothelium dependent" and "endothelium independent" regulation of coronary function is probably too simplistic and mechanistic. The categorization is based on histological studies and patterns [31], the results of which were then transferred *in vivo*, not taking into account those paracrine, molecular or even electromagnetic influences weaving intercellular dialogue [34].

CFR represents simple but at the same time very important tool to investigate the physiology and pathophysiology of heart and systemic diseases [27]. It's a marker for cardiovascular risk estimation, and it is also helpful in evaluating therapeutic interventions and prognosis-risk stratification in cardiomyopathies [35], coronary artery disease, and heart transplantation [35,36]. Coronary microvascular dysfunction, defined as reduced coronary flow reserve and/or coronary endothelial dysfunction, is associated with a 2.5% annual major adverse event rate that includes death, nonfatal myocardial infarction, nonfatal stroke,

and congestive heart failure [37]. Early identification of microvascular coronary disease by echo-derived CFR or other coronary reactivity tests may be beneficial in prognosis evaluation and patient stratification for optimal medical therapy [38]. This is of paramount importance because many diseases, that is, endocrine, metabolic, and immune conditions, affect vascular and in particular coronary function. Finally, endothelial dysfunction has been detected in the coronary epicardial and resistance vasculature as well as in peripheral arteries, so that endothelial dysfunction can be regarded as a systemic condition [39]. On the other hand, the endothelial cells are evenly distributed in all organs and throughout the body even if they receive specific influences related to the district of belonging and its metabolic state.

Psycho-neuro-endocrine-immune system (PNEI), the stress response and epigenetics

PNEI

Besedovsky and Sorkin in 1977 first proposed the theory of psycho-neuro-endocrine-immune network (PNEI) as an integrated system having the purpose of regulating homeostasis and maintaining the health of the human organism (Figure 2) [40]. The balance of the system affects different pathophysiological conditions such as inflammation [41–43], aging [44], rheumatic disorders [45], cancer [46] and, as we will see, cardiovascular diseases. PNEI system regulates homeostasis of the body producing and secreting an extraordinary variety of

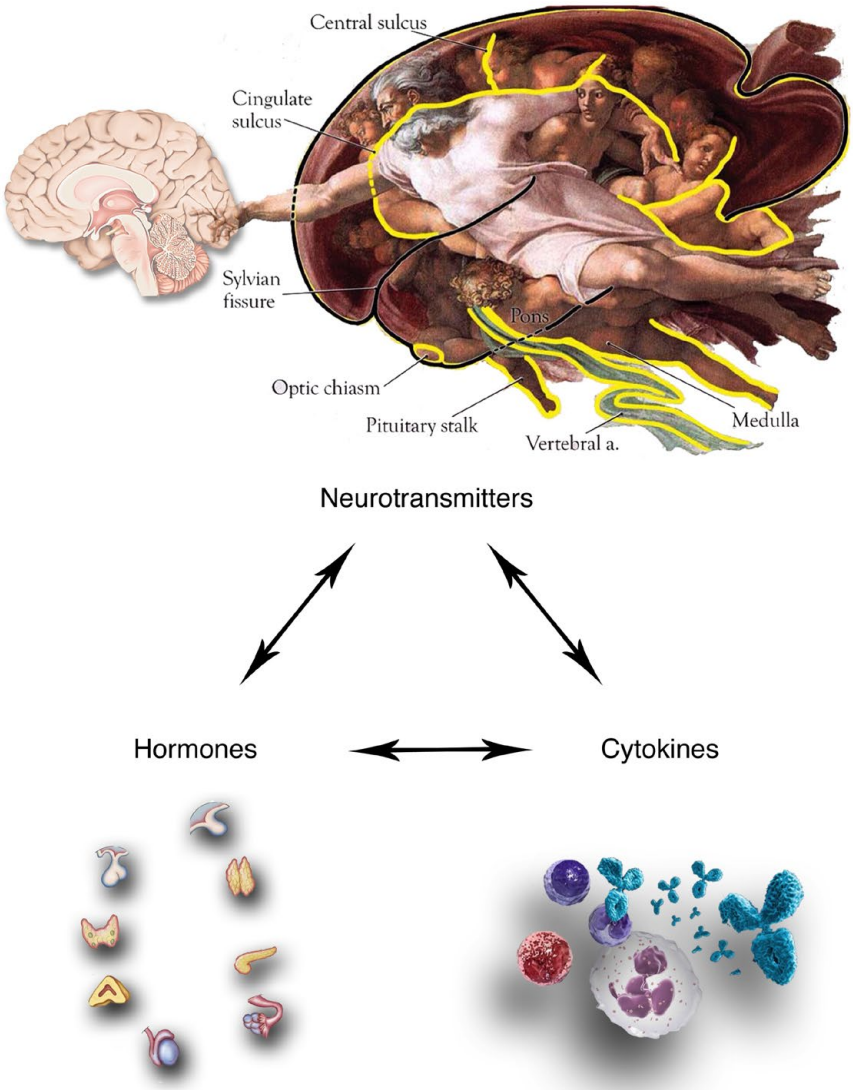

Figure 2. The concept of Psychoneuroendocrineimmunology. Psyche and biological systems are linked. Nowadays, a lot of studies [52,53] document this bi-directional connection and show how psychological states of mind modify the activity and the balance of biologic systems (such as nervous, endocrine, immune and metabolic systems) and how their functioning could influence the mental attitude. For example, depression causes sterile inflammation and a primitive inflammatory event may trigger depressive processes. Furthermore, immunosuppression could be induced by individual behavior and psychological processes (please consult the references cited in the text).“Emotions <=> thoughts <=> actions. As Michelangelo foretold in " Creation of Adam", all gods and demons that ever existed are within us as a possibilities, desires, and ways to escape. Within the dark red vault of our skull we see human and god-like forms reaching out, as thoughts escape into actions - with legs extending into our brainstem and a fist is pushing from our hypothalamus into the pituitary stalk. Above the pituitary we have thoughts, ideas, impulses, and neurotransmitters. Below we have hormones. Between is the realm of neuroendocrinology - the neurosecretory cells which turn emotions into the releasing factors for the pituitary hormones and the immune system that in turn will give their feedback on the brain”. Modified from [447].

cellular regulatory mediators known as peptides, neurotransmitters, neuropeptides, hormones, cytokines or growth factors [47]. These are the actors that mediate the connection between the psyche and biological systems. These factors influence each other, mediating cellular gene expression in response to environmental factors and a disruption in the network will affect the entire network itself [46–49]. The psyche and biological systems are linked and there are now many studies that document this bidirectional connection [50-52]. The studies show how psychological states of mind modify the activity and the balance of biologic systems (such as the nervous [53], endocrine [54], immune [55] and metabolic systems [56,57]) and how the way they function could influence mental attitude [52,58,59].

In Table 1 are reported the evidences and some mediators and mechanisms by which: 1) nerves talk to immune cells, 2) the immune system plays with the nervous system, 3) hormones and immune cells dialogue and 4) the brain produces hormones that in turn act on the brain. These connections are very complex and still under study by dedicated disciplines and scientific journal (such as neuroimmunoendocrinology [45], neuroimmunology [60], psychoneuroimmunology [61] or neuroendocrinology [62]). There is also an online database that tracks PNEI interactions with related genetic pattern expressions [46,47].

The stress response

Hans Selye's [56] experiments with rats led to the recognition of the "general adaptation syndrome" and described as the triad of enlarged adrenal glands, lymph node and thymic atrophy, and gastric erosions/ulcers [63].

All activities and functions in the life of any organism, and of course of human beings, try to maintain a complex and dynamic psycho-metabolic balance called "homeostasis", which is constantly challenged by internal or external adverse forces termed "stressors" (hot, cold, toxins, infections, wounds, fatigue, psychosocial factors etc.) [64]. As we recently described [65], "*stress occurs when homeostasis is threatened or perceived to be so [66]; homeostasis is re-established by various physiological and behavioral adaptive responses that constitute the so called "stress response*" [67]. Thus stress could be defined, according to the original Selye's definition, as the general and non-specific response to any request from the environment. Under favorable conditions, individuals can develop vegetative and pleasurable responses that enhance their emotional and intellectual growth and help the survival of their species, such as food intake and sex [68]. In contrast, activation of the stress response during threatening situations beyond the control of the individual can be associated with dysphoria and eventually emotional or somatic disease [69]. Tsigos and Chrousos reviewed the mechanisms underlying the stress response [69]. Briefly, *"the main components of the stress system are the corticotropin-releasing hormone (CRH) and locus ceruleus–norepinephrine (LC/NE)-autonomic systems and their peripheral effectors, the pituitary–adrenal axis, and the limbs of the autonomic system. An active stress system leads to behavioral and peripheral changes that improve the ability of the organism to adjust homeostasis and increase its chances for survival. The CRH and LC/NE systems stimulate arousal and attention, as well as the mesocorticolimbic dopaminergic system, which is involved in anticipatory and reward phenomena, and the hypothalamic beta-endorphin system, which suppresses pain sensation and, hence, increases analgesia. CRH inhibits appetite and activates thermogenesis via the catecholaminergic system. Moreover, reciprocal interactions exist between the amygdala and the hippocampus and the stress system, which stimulates these elements and is regulated by them. During stress CRH inhibits GnRH and through somatostatin, GH, TRH and TSH secretion, which in turn, suppress the reproductive, growth and thyroid functions. Interestingly, all these functions receive and depend on positive catecholaminergic input. The hormones at the end of the hypothalamic–pituitary–adrenal (HPA) axis, glucocorticoids have multiple roles. They simultaneously inhibit the CRH, LC/NE and b-endorphin systems and stimulate the mesocorticolimbic dopaminergic system and the CRH peptidergic central nucleus of the amygdala. In addition, they directly inhibit pituitary gonadotropin, GH and TSH secretion, render the target tissues of sex steroids and growth factors resistant to these substances and suppress the 50 deiodinase, which converts the relatively inactive tetraiodothyronine (T4) to triiodothyronine (T3), contributing further to the suppression of reproductive, growth and thyroid functions. They also have direct as well as insulin-mediated effects on adipose tissue, ultimately promoting visceral adiposity, insulin resistance, dyslipidemia and hypertension (metabolic syndrome X) and direct effects on the bone, causing "low turnover" osteoporosis. Central CRH, via glucocorticoids and catecholamines, inhibits the inflammatory reaction, while directly secreted by peripheral nerves CRH stimulates local inflammation [70] (immune CRH)"*[69].

The stress reaction is therefore an aspecific biological response to any form of danger, which can come from both outside with a biological (virus, bacteria, toxins) or physical (heat, cold, radiation) nature, or following psychological processes as anger or depression (perceived stress) [71]. In this last case, the platelets seem to play a fundamental role [72,73]. In fact, it was demonstrated their dysfunction linked to processes of mental depression or anger, resulting in hyperaggregability, increased oxidative stress and thrombotic risk [74]. Furthermore, platelets contain serotonin which has an important vasospastic action in the cardiovascular system [75] as well as being implicated in the pathogenesis of carcinoid syndrome [76]. The neurotransmitter serotonin is an evolutionary ancient molecule that as remarkable modulatory effects in almost all central nervous system integrative functions such as mood, anxiety, stress, aggression, feeding, cognition and sexual behavior [77]. The platelet secretion of serotonin seems to be essential in mediating the interaction between immune [78,79] and neurological system [80]. Moreover, Cocchi *et al.* [81] revealed that the viscosity of the platelet membrane is a general influencing factor for serotonin receptor uptake and it is involved in many pathologies that recognize serotonin changes; that is scleroderma, inflammatory bowel disease, neuroinflammation, multiple sclerosis and osteoporosis. Platelet membrane viscosity modifies in case of depression [82], and interestingly represent a novel risk factor for ischemic heart disease [83]. A condition of physical or psychological stress leads to increased oxidative stress [84,85], a known risk factor for endothelial health [86]. In this context, an important protective mechanism is the metabolism of bilirubin and its derivatives [87–89]. In fact they produce an antioxidant effect [89] and are able to inhibit platelet aggregation [91,92], explaining the greater level of cardiovascular security of hyperbilirubinemic patients with Gilbert's syndrome [93].

As demonstrated by Charmandari *et al.*, appropriate responsiveness of the stress system to stressors is a crucial prerequisite for a sense of well-being, adequate performance of tasks, and positive social interactions. By contrast, inappropriate responsiveness of the stress system may impair growth and development and may account for a number of endocrine, metabolic, autoimmune, and psychiatric disorders [94,95]. The development and severity of these conditions primarily depend

Table 1. Looking over the keyhole of individual scientific disciplines. Neuropeptides, cytokines and hormones and their reciprocal effects in the perspective of the PNEI network.

Immune mediators	Endocrinological effects	Neurologic and psychiatric effects	References
Interleukin-1 (IL-1)	• ↑ adrenocorticotropic hormone (ACTH) levels • ↑glucocorticoids levels (effect abrogated by the administration of corticotropin-releasing hormone (CRH) antagonists); • activates growth system • ↑ prolactin (PRL) secretion • Inhibits gonads function and thyroid's function • ↑βendorphin levels	• ↑blood flow through noradrenaline; • activates the stress axis; • ↑noradrenaline, dopamine, serotonin metabolism; • correlates with major depression	[379,397,401-407]
Interleukin-1β (IL-1 β)		important role in memory and learning	[408]
Interleukin-2 (IL-2)	• ↑ ACTH levels; • ↑glucocorticoids levels • IL-2 receptor gamma-chain messenger RNA (mRNA) is regulated by gonadotrophin-releasing hormone (GnRH) in vitro	analgesic effects through interaction of the analgesic domain of IL2 with the opioid receptor	[401-403,104,389,409 ,410]
Interferon beta (IFN-β)	• ↑ ACTH levels; • ↑glucocorticoids		[401-404]
Interferon gamma (IFN-ɣ)	• ↑ ACTH levels; • ↑glucocorticoids; • ↑melatonin release by the pineal gland; • upregulates glucocorticoid receptor expression by macrophages	acts on the glutamate receptor	[401-404,411-413]
Leukemia inhibitory factor (LIF)	• ↑ ACTH levels; • ↑glucocorticoids		
Tumor necrosis factor-alpha (TNF-α)	• ↑ ACTH levels; • ↑glucocorticoids	• ↑levels of tryptophan in brain; • ↑noradrenaline metabolism • correlates with major depression	[401-404,414,397]
Interleukin-6 (IL-6)	• ↑ ACTH levels; • ↑βendorphin levels; • blocks thyroid stimulating hormone (TSH) production; • hinders thyroxine (T4) to triiodothyronine (T3) conversion; • ↑CRH levels; • ↑arginine vasopressin (AVP) levels	• ↑levels of serotonin and tryptophan; • correlates with major depression	[397,399,401-403,407,414-416]
Interleukin-10 (IL-10)	• ↑corticotrophin-releasing factor (CRF) levels • ↑ACTH levels		[417]
Granulocyte Macrophage colony-stimulating factor (GM-CSF)	• ↑ melatonin release by the pineal gland; • ↑ACTH levels • ↑glucocorticoids		[411,412,418]
Granulocyte colony-stimulating factor (G-CSF)	stimulates release of melatonin by the pineal gland		[411,412]
Histamine		• ↑ release of substance P; • ↑release of calcitonin gene-related peptide • Inhibits IL-12, TNF and IFN-γ and enhances IL-10 production	[419,420]
Macrophage inhibitory factor (MIF)	• is pro-inflammatory by counteracting the antiinflammatory and immunosuppressive effects of glucocorticoid inhibition of T-cell proliferation and cytokine production; • anterior pituitary cells secrete large quantitaties of MIF when stimulated with (lipopolysaccharide) LPS *in vitro*	,	[420-423]
Prostaglandin E2 (PGE2)		Inhibits IL-2 production	[420]

Nervous mediators	Endocrinological effects	Psychiatric effects	Immunological effects	References
Endorphins and enkephalins	In acute stress βendorphins inhibit GnRH, follicle-stimulating hormone (FSH), luteinizing hormone (LH) release	analgesic role	• modulate the Th1/Th2 balance of the immune system, inhibiting the Th1 axis; • Inhibit immunoglobulin (Ig) production; • Enhances IFN-γ production and natural killer (NK) cell mediated cytotoxicity; • Inhibits T-cell proliferation; • enhances antigen-specific proliferation	[399,420,424]
substance P and calcitonin gene-related peptide			• Control vascularity of lymphoid tissue; • induces the release of histamine from mast cells • Increases T-cell adhesion and stimulates IL-2, IL-4 and IFN-γ production; • Enhances T-cell proliferation and IL-1, IL-6, TNF and IFN-γ production and macrophage action	[419,420]
norepinephrine			• Control vascularity of lymphoid tissue; • Determines a change in the level of gene expression for cytokines and antibodies	[379]
Acetylcholine (Ach) (Vagus nerve stimulation)			• Inhibits proinflammatory cytokine production by signaling through the α-7-nicotinic acetylcholine receptor subunit; • Stimulates T and NK cells and increases IFN-γ production	[420,425]
Catecholamines/ adrenalin		• high levels during pregnancy mark epigenetically the offspring's brain and function	• Inhibit Th1 immune responses and set a Th2 profile during chronic stress; • in acute stress enhance the production of antibodies and the proliferation of natural killer cells, B cells and T cells; activation of the pro-inflammatory gene NF-kappa B in monocytes; • Inhibits IL-1 and IL-2 production; • Enhance Ig production. • Decrease the number of T and NK cells in the peripheral circulation inhibit NK cells	[400,426,427]
Nerve Growth Factor (NGF)			• Low levels of NGF turn off mast-cell activity; • Enhances B-cell proliferation, IL-6 production, IL-2 receptor expression and Ig-G4 synthesis	[420,428]
Angiotensin 2			Enhances IFN-γ production	[420]
Cyclic adenosine monophosphate (cAMP)			• Enhances IL-4 and IL-5 production; • Inhibits IL-2 production	[420]
Neuropeptide Y			• Increases T-cell adhesion and stimulates IL-2, IL-4 and IFN-γ	[420]
Serotonin			• Inhibits T-cell proliferation and IFN-γ induced human leukocyte antigen (HLA) class II expression • Enhances NK cytotoxicity	[420]

Hormones	Neurological and psychiatric effects	Immunological effects	References
Cortisol and glucocorticoids	• Glucorticoid excess damages brain function impairing memory and cognitive performance • deficiency in stress axis activity is linked with chronic fatigue syndrome and seasonal affective disorder	• inhibit Th1 immune responses and set a Th2 profile during chronic stress; • in acute stress enhance the production of antibodies and the proliferation of natural killer cells, B cells and T cells • role in the regulation of antigen-specific T-cell development; • Inhibits IFN-γ, IL-2, IL-6 and TNF-α; • Enhances IL-4 and transforming growth factor beta (TGF-β) production; • Enhances immune cell expression of IL-1, IL-2, IL-6 and IFN-γ receptors;	[399,405,420,430-432]
dehydroepiandrosterone sulfate(DHEAS)	• plays an anti-depressive and anxiolytic role in the brain; • increases memory capacities that counteract glutamate action	• enhances Th1immune responses; • Enhances IFN-γ production and T-cell proliferation; • Imparts a Th1 bias	[44,420,433]
Alpha-Melanocyte stimulating hormone(α-MSH)		• is an anti-inflammatory signal; • Suppresses delayed type hypersensitivity(DTH) and inhibits IL-1 and IL-2 production via inhibition of nuclear factor-Kb (NF-κB)	[420,434]
Prolactin (PRL)		• stimulates NK and T cells in a concentration-dependant manner in the presence of IL-2; • high concentrations inhibits NK cells and NK INFγ production; • Enhances T-cell proliferation, IFN-γ, IL-2 receptor expression and macrophage function	[420,435]
Growth hormone (GH) and Insulin-like Growth Factor-1 (IGF-1)		• Stimulate neutrophils and macrophages; • Activates macrophages and enhances H2O2 production; • Enhance peripheral blood mononuclear cell (PBMC) proliferation	[405,420]
Melatonin		• reduces tissue destruction during inflammatory reactions hunting toxic free radicals; prevents NF-kappa B translocation into the nucleus and its binding to DNA, thereby reducing the up-regulation of a variety of pro-inflammatory cytokines; inhibits production of adhesion molecules; enhances IFN- ɣ production; • Enhances IL-1, Il-2, IL-6 • Imparts a Th1bias	[420,436-439]
Corticotropin-releasing hormone (CRH)	• Chronic high levels lead to: depression, anxiety, obsessive-compulsive disorders, such as anorexia and panic; • high levels during pregnancy mark epigenetically the offspring's brain and function	• Activates macrophages; • Inhibits IL-1 and IL-6 production	[187,420,426,427]
oxytocin and vasopressin	Correlate with affectivity and sociality	• Enhances IFN-γ production; • Enhances IFN-γ production	[121,420]
Vitamin D		• decreases the production of Th1 cytokines (TNFα and INFγ); • Inhibits IL-2 and IFN-γ; • Enhances IL-4 production	[399,420,440]
Adrenocorticotropic hormone (ACTH)		• Inhibits IFN-γ production and Ig production and blocks macrophage activation by IFN-γ • ↑IL-18 mRNA in cells of zona reticularis and fascicolata	[420,441]

Gonadotropin-releasing hormone(Gn-RH)		Increases interleukin-2 receptor (IL-2R) expression, T- and B-cell proliferation and serum Ig	[420]
Inhibin		Inhibits IFN-γ production	[420]
Luteinizing hormone(LH)		Enhances IL-2 stimulated T-cell proliferation	[420]
Oestrogen		Enhances T-cell proliferation and activity IFN-γ gene promoter	[420]
Progesterone		• Enhances IL-4 production and CD30 expression; • imparts a Th2 bias	[420,442]
Somatostatin		Inhibits T-cell proliferation and IFN-γ production	[420]
Testosterone		Enhances IL-10 production	[420]
Thyroid stimulating hormone (TSH)		Enhances IL-2, GM-CSF and Ig production	[420]
Thyroxine		Activates T cells	[420]
Vasoactive Intestinal Polypeptide(VIP)		• Inhibits T-cell proliferation and IL-12; • Enhances IL-5 and cAMP production	[420]

on the genetic vulnerability of the individual, the exposure to adverse environmental factors, and the timing of the stressful events, given that prenatal life, infancy, childhood, and adolescence are critical periods characterized by increased vulnerability to stressors [94,96]. A hyper- or hypoactive stress system associated with abnormalities of the systemic anti-inflammatory feedback and/or hyperactivity of the local pro-inflammatory factors play a relevant role in the pathogenesis of chronic inflammation and immune-related diseases, such as atherosclerosis, hypertension, ischaemic heart diseases (also through coronary mast cells stimulation [97]) or heart failure [65,95].

Genetics and epigenetics: from the "central dogma of DNA" to epigenetic genome regulation

The old linear correlation between DNA sequences and single proteins [98] has been overwhelmed by the evidence of alternative splicing mechanisms, prion action and epigenetic regulation of DNA expression [99,100]. Tollefsbol *et al.* well described the science of Epigenetics: *"The term epigenetics is defined as the causal interaction between genes and their products that allow for phenotypic expression. Methylation of a particular DNA region silences DNA expression while the deacetylation process produces opposite consequences. Chromatin could be compacted or rolled out by modifying histone tails through methylation, acetylation, phosphorilation, ubiquitination or proline isomerization. Non-coding RNA plays a regulatory role as well. Epigenetics is not only intricately associated with metabolism but also functions in stem cell behavior, X chromosome inactivation, tissue regeneration, genomic imprinting, the transfer of information through generations, neurological memory processes and even the aging of organisms. Epigenetics has also played a role in evolution and has served as a molecular driver of mutations. Moreover, the changing environment is currently re-shaping the evolution of many organisms through plastic epigenetic processes. Epidemiological factors such as diet, environmental exposure, microbial infections and drugs are also influencing daily life through epigenetics. Diseases that have been associated with epigenetic processes range from schizophrenia to cancer and the list of these diseases is rapidly growing longer. Fortunately, the field of epigenetic therapy is also expanding, which provides hope for a future with many new treatments for the numerous diseases arising from epigenetic defects"*[101].

Epigenetically, DNA genes are active every single second of our life, responding to thoughts and reacting dynamically and reciprocally to environmental activation and deactivation. This process starts during pregnancy.

Stress during pregnancy: Environmental conditions during pregnancy could produce epigenetic changes that persist during life [102]. Even individual's birth month has a significant impact on the diseases they develop during their lifetime [103]. Plasticity in developmental programming has evolved in order to provide the best chances of survival and reproductive success to the organism in changing environments. Maternal stress during pregnancy is related to spontaneous preterm birth, low birth weight, congenital malformations [104] and spontaneous abortion [105] due to increased levels of CRH, inflammation and catecholamines that hinder implantation, stabilization and embryo growth [106]. Maternal behavior [107], with its hyperactive stress system and its neuroendocrine balance, epigenetically marks the offspring's brain and function [108] and thus, from what we have seen so far, conditions offspring behavior and thoughts. Furthermore, stress has an impact on health by modulating the rate of cellular aging. Psychological stress (perceived stress and chronic stress) is significantly associated with higher oxidative stress, lower telomerase activity and shorter telomere length, which are known determinants of cell senescence and longevity. If stress occurs in pregnancy, newborn telomeres are shorter as well [109]. Maternal behavior after labor could also epigenetically determine a biological mechanism in the child [110] which is then potentially reversible in adulthood. Hence, epigenetics in early life leaves marks that can be detected in adulthood [111].

Cellular DNA epigenetic marking is stable but reversible: There is evidence that epigenetic differences arise during the lifetime of monozygotic twins [112,113]. Cellular DNA epigenetic marking is stable but reversible. From this point of view the paramount importance of research is clear, not only in pharmacological therapy (which could modify an epigenomic DNA mark) but also, as we will see, in behavioral therapies, nutrition, physical activity and stress-reduction techniques, which could play a remarkable role in health and be very cost-effective [114-117].

The brain is the central organ for stress and adaptation to stress because it perceives and determines what is threatening, as well as the behavioral and physiological responses to the stressor. Memorizing is a physiologic stress event involving hippocampal neurons. Acetylation and methylation/demethylation mechanisms play an

important role during the process. A stable methylating process leads to maintaining the mnemonic track [118]. Chronic social defeat stress significantly decreases subsequent social interactions and provokes other depression-like behaviors by inducing histone H3 deacetylation, a chromatin mark of transcriptional activation, in the hippocampus and amygdala [119]. Social defeat stress induces methylation of the BDNF gene, bringing on a depressant effect [120] and a CRH increase caused by stress axis activation. An opposite effect in the brain reward circuit happens during internal exposure leading to early gene expression modifications in oxytocin and vasopressin (substances related to affectivity and sociality) neurons [121]. Human beings could change their epigenetic depressive states by learning anti-stress mind techniques such as meditation, yoga or tai chi that have effects on genetic expression [122,123]. Thus, chronic stress leads to an epigenetic stable brain marking that alters stress axis function, thoughts and behavior and balance of the neuroendocrine system.

What is worrying is that the same configuration is then transmitted to the offspring.

Transgenerational epigenetic transmission: Crews *et al.* demonstrated how environmental contamination by endocrine-disrupting chemicals (EDC) can have epigenetic effects (through DNA methylation) on the germ line and promote disease across subsequent generations. In natural populations, both sexes may encounter both affected and unaffected individuals during the breeding season and lowered attractiveness could compromise reproductive success. Crews *et al.* described mate preference in male and female rats whose progenitors had been treated with the antiandrogenic fungicide vinclozolin. This sex-specific effect demonstrates that females three generations removed from the exposure discriminate and prefer males who do not have a history of exposure, whereas similarly epigenetically imprinted males do not exhibit such a preference. The observations suggest that the consequences of EDCs are not just transgenerational but can be "transpopulational", because in many mammalian species, males are the dispersing sex. This result indicates that epigenetic transgenerational inheritance of EDC action represents an unappreciated force in sexual selection. These observations provide direct experimental evidence for a role of epigenetics as a determinant factor in evolution [124]. The majority of environmental toxicants do not have the capacity to modulate DNA sequence, but can alter the epigenome. If an environmental toxicant (such as an endocrine disruptor) modifies the epigenome of a somatic cell, this may promote disease in the exposed individual, but it will not be transmitted to the next generation. But if the toxicant modifies the epigenome of the germ line permanently, then the resulting disease can become transgenerationally transmitted to subsequent progeny [125].

Furthermore, paternal experience across a lifespan can induce germ cell epigenetic reprogramming and impact the offspring's hypothalamic-pituitary-adrenal (HPA) stress axis regulation through specific non-coding microRNAs. It may therefore offer novel insight into factors influencing neuropsychiatric disease risk [126].

Epigenetic modifications are transmissible, but there is also a mechanism that deletes epigenetic signs and that is more powerful in male than in female gametes [127]. Some studies documented a link between nutrition in grandfathers and the risk of diabetes and cardiovascular mortality in their grandchildren [128]. Moreover, male starving some days before fecundation leads to a decrease in levels of IGF-1 and glucocorticoids in the offspring and if a weekly stress condition happens before fecundation, children and grandchildren show stress axis suppression when in contact with stress stimuli [129].

Another example derives from a study by Rehan *et al.* Asthma is a major public health hazard worldwide. Its transgenerational inheritance has been inferred from epidemiological studies. Rehan's data, for the first time, demonstrated the transgenerational transmission of the asthma phenotype to third generation offspring following perinatal nicotine exposure [130].

Circulating micro-RNAs (miRNA): epigenetic elements of PNEI communication: In recent years, increasing evidence suggests that genetic and epigenetic factors could be involved in disease onset and comorbidity [131-133]. Following the discovery of circulating microRNAs (miRNAs) in Caenorhabditis Elegans more than a decade ago [134], research has majorly evolved in order to gain insight of how the miRNA gene network can have an impact on health and disease in humans. Studies in animal models demonstrate that miRNA genes are essential for life [135], whereas changes in miRNA expression profiles in humans are found in several diseases, such as cancer as well as neurological and cardiovascular disorders [136-139]. The miRNA gene family comprises a class of highly conserved small (~19-23 nt) non protein-coding RNAs that function in the cell to regulate gene expression at the post-transcriptional level [140,141]. Circulating miRNAs are protected by encapsulation in membrane-bound vesicles such as exosomes, but the majority of circulating miRNAs in human plasma and serum cofractionate with Argonaute2 (Ago2) protein, rather than with vesicles [141]. Changes in miRNA expression occurring in the PNEI network and in particular within the heart [142] impact on cardiovascular characteristics by modulating organ function, accentuating cellular stress, and impinging on heart cell survival [143].

The circulating-miRNAs acting on a myriad of genes and protein targets, build a complex network of interactions that are still largely unknown [141]. There are numerous studies that reveal the simple association between some of these elements and several diseases, but the precise mechanism of their action is still unknown [139]. Many different algorithms exist for the bioinformatic prediction of miRNA targets and all generally predict hundreds of targets for each miRNA [144]. As described by Mendell *et al.* [145], "*these highly complex target networks pose a significant challenge to the mechanistic dissection of miRNA-mediated phenotypes. The prevailing model posits that miRNAs function by fine-tuning the expression of numerous targets. While each target is regulated subtly (typically less than a 2-fold change in individual target protein abundance results from gain or loss of miRNA function), the additive effect of coordinated regulation of a large suite of transcripts is believed to result in strong phenotypic outputs [145]. On the other hand, some miRNA-mediated functions might be driven by the strong regulation of one or a few targets*" [134,146].

Figure 3 shows the main mechanisms of action of some circulating miRNAs mediating stress signalling within the cardiovascular system. Table 2 shows how a single circulating miRNA acts, even simultaneously, on different target genes, in different diseases and in the various districts composing the PNEI system. (The data are taken from the "miRandola database", available online [141]). Interestingly, more circulating miRNAs are involved in a specific disease, governing differently a same gene expression.

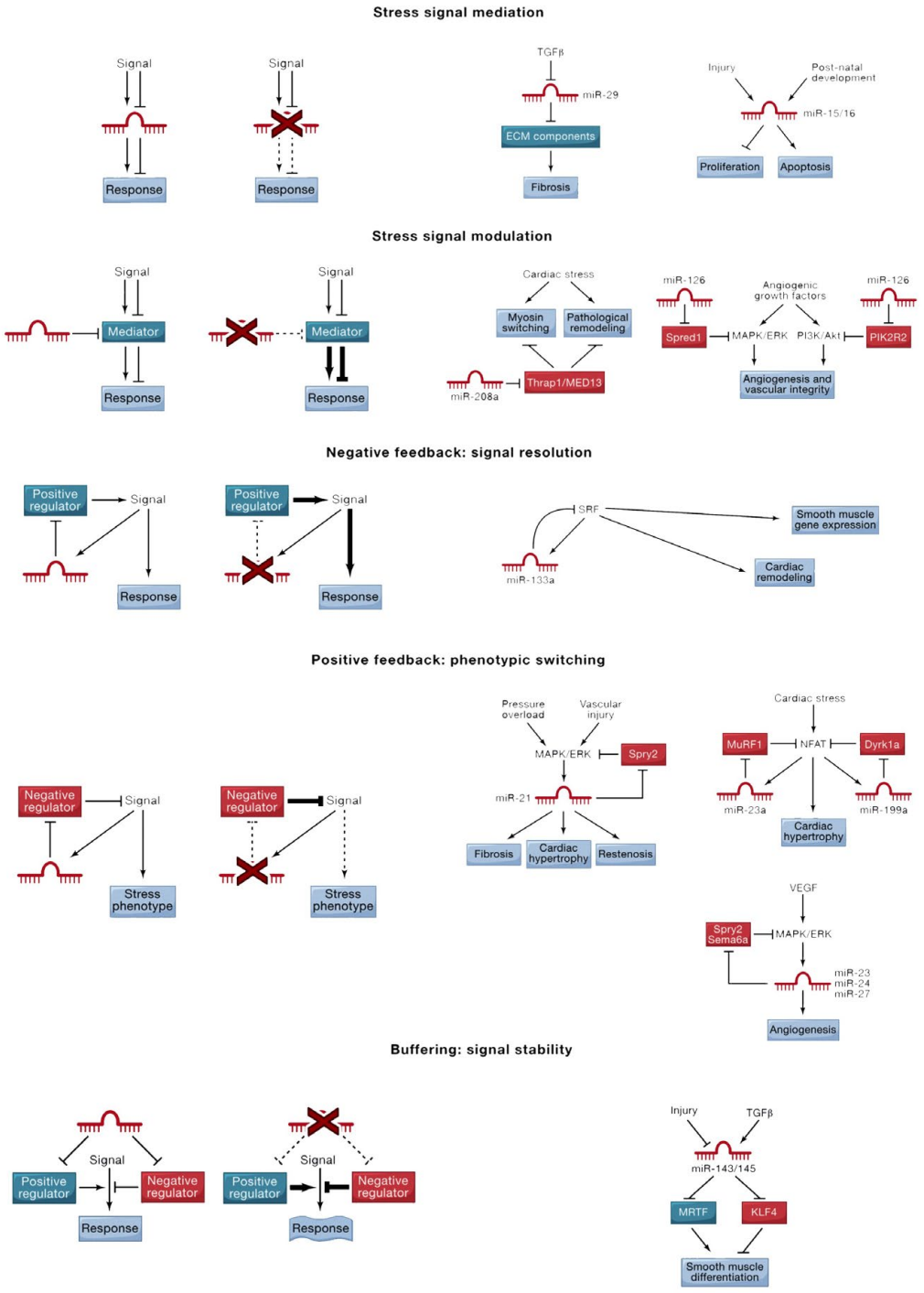

Figure 3. Potential Mechanisms through which miRNAs regulate stress signaling pathways. Observing, on the left is reported the general mechanism, on the right its application in the cardiovascular system. A miRNA can perform a *stress signal mediation* function in which it acts as a critical intermediate in a signaling pathway. miR-29 and miR-15 family members act as mediators of stress signaling pathways that regulate fibrosis and cardiomyocyte proliferation and survival, respectively. A miRNA may act as a *stress signal modulator* in which it titrates a signaling intermediate. miR-208a and miR-126 titrate regulators of cardiac remodeling and angiogenesis and thereby function as stress signal modulators. A miRNA may participate in a *negative (or positive) feedback loop* that serves to dampen or amplify a signal, respectively. miR-133a directly targets its activator SRF and in this manner restrains excessive SRF activity in adult cardiomyocytes, which can lead to heart failure. miR-21, miR-199a, and the miR-23a/27a/24-2 cluster participate in positive feedback loops, which serve to stably activate signaling pathways that lead to pathologic cardiac remodeling and angiogenesis. Lastly, a miRNA may target both activation of the pathway and thereby the stable switching of the cellular state under the stress condition, which can be important for restoring homeostasis but can also contribute to disease (*Buffering: Signal Stability*). Given the multiplicity of miRNA targets within complex biological pathways, a miRNA may function to buffer pathway activity by simultaneously dampening expression of both positive and negative regulators. In this capacity, the miRNA would prevent stochastic fluctuations in signaling. Under normal conditions or in controlled laboratory environments, this type of buffering may not be critical to maintain normal function. However, in stress states, pathways may need to be transiently activated to a high level thus increasing the requirement for buffering to avoid run-away pathway activation or a failure to achieve the appropriate level of activation. There are documented examples in which gain- and loss-of function of a specific miRNA result in similar phenotypes, which may reflect the perturbation of a buffering function. The miR-143/145 cluster targets both positive and negative regulators of smooth muscle differentiation. Through this buffering activity, these miRNAs maintain the characteristic phenotypic plasticity of this cell type, allowing smooth muscle cells to proliferate in response to injury.

Table 2. Circulating miRNA, diseases in the districts composing the PNEI system and their actions on different target genes (data from miRandola databse [140]).

miRNA	PSYCHIATRIC DISEASES	NEUROLOGIC DISEASES	CARDIOVASCULAR DISEASES	ENDOCRINOLOGICAL DISEASES	IMMUNOLOGICAL DISEASES	TARGET GENES
1	depression	ischemic stroke	atrial fibrillation	diabetes mellitus type 1	clozapine induced agranulocytosis	BDNF
	autism	Parkinson's disease	Brugada syndrome	Graves' disease	Kawasaki disease	KCNE1
	personality disorders	morphology and cognitive function	generalized atherosclerosis	polycystic ovarian syndrome	acute promyelocytic leukemia	FLT3
10a	bulimia nervosa	epilepsy	coronary atherosclerosis	Graves' disease	follicular lymphoma	BDNF
	schizoaffective disorder	Huntington's disease	left ventricular hypertrophy	hyperaldosteronism	drug -induced agranulocytosis	FABP2
	nicotine dependence	glioblastoma multiforme	cardiac arrhythmias and sudden death	polycystic ovarian syndrome	ANCA associated vasculitis	PTEN
16	obsessive compulsive disorder	neurofibromatosis 1	hypertension	gestational diabetes	leukemia	ATXN1
	Schizophrenia	dementia	coronary artery disease	Graves' disease	sarcoidosis	ADIPOQ
	smoking behavior	myotonic dystrophy	abdominal aortic aneurysm	polycystic ovarian syndrome	psoriasis	APOA5
21	alcohol abuse	cerebral vascular malformations	congenital heart abnormalities	hyperandrogenism	leukemia	BMPR2
	obsessive compulsive disorder	leukoencephalopathy	hypertension and myocardial infarction	hypoparathyroidism	lymphoma	PPARA
	schizophrenia	epilepsy	pulmonary hypertension	early menopause	agammaglobulinemia	TLR4
24	autism	meningioma	coronary atherosclerosis	Cushing's syndrome	acute leukemia	CDKN2A
	anxiety disorder	ALS/amyotrophic lateral sclerosis	hypertension	hyperparathyroidism	non-Hodgkin's lymphoma	MTHFR
	bipolar disorder	Alzheimer's disease	left ventricular hypertrophy	pituitary carcinoma	Behcet's Disease	APOA5
29a	major depression	ischemic stroke	carotid and coronary atherosclerosis	autoimmune thyroid disease	leukemia	BACE1
	autism	myasthenia gravis	abdominal aortic aneurysm	diabetes mellitus type 1 and 2	graft versus host disease	DNMT3B
	drug abuse	meningioma	mitral valve prolapse	male infertility	severe combined immunodeficiency	PPARGC1A
34a	anxiety disorder	impaired memory	coronary atherosclerosis	diabetes mellitus type 1 and 2	Hodgkin's disease	VEGFA
	autism	tardive dyskinesia	dilated cardiomyopathy	pheochromocytoma	leukemia	BCL2
	sleep disturbances	frontotemporal dementia	ischemic heart disease	thyroid cancer	Behcet's Disease	HTR2C
92a	affective psychoses	neuropathy	myocardial infarction	premature ovarian failure	atopy	EN2
	autism spectrum disorder	anaplastic astrocytoma	Cardiomyopathy	polycystic ovary syndrome	systemic sclerosis	PAFAH1B1
	anorexia nervosa	ALS/amyotrophic lateral sclerosis	coronary atherosclerosis	Graves' disease and Hashimoto's thryoiditis	agranulocytosis	GCLM
122	anorexia nervosa	epilepsy	hypertension	diabetes mellitus type 1 and 2	primary biliary cirrhosis	GYS1
	nicotine dependence	migraine with aura	acute coronary syndrome	Graves' disease	pemphigus	NTRK2
	post traumatic stress disorder	brain aneurysm	atrial fibrillation	hyperandrogenism	Common Variable Immune Deficiency	IL1RN
125 b	schizophrenia	multiple sclerosis	acute coronary syndrome	multiple endocrine neoplasia (MEN)	sarcoidosis	ERBB3
	alcoholism	myotonic dystrophy	congenital heart abnormalities	polycystic ovarian syndrome	severe combined immunodeficiency	IL1RN
	personality disorders	Parkinson's disease	cardiac arrhythmias	autoimmune thyroid disease	Hodgkin's disease	CYP1A1
126	Schizophrenia	Alzheimer's disease	hypertension	diabetes mellitus type 2	Hodgkin's disease	BCL2
	bipolar disorder	multiple sclerosis	myocardial infarction	hyperandrogenism	follicular lymphoma	VCAM1
	depression	Huntington's disease	coronary atherosclerosis	polycystic ovarian syndrome	LES	IRS1
129-5p	major depression	impaired memory	hypertension	autoimmune diabetes	follicular lymphoma	CAMTA1
	drug abuse	neurofibromatosis 1	complications related to heart transplant	autoimmune thyroid disease	LES	ACSL4

	schizophrenia	epilepsy	aortic valve sclerosis	hyperandrogenism	Behcet's Disease	BCL6
133a	ADHD	Alzheimer's disease	atrial fibrillation	diabetes mellitus type 2	non-Hodgkin's lymphoma	KCNH2
	Schizophrenia	multiple sclerosis	long QT syndrome	hypothyroidism	atopy	CASP9
	alcohol abuse	epilepsy	hypertension myocardial infarction	polycystic ovarian syndrome	sarcoidosis	DLG5
133b	bipolar disorder	ALS/amyotrophic lateral sclerosis	coronary atherosclerosis	premature ovarian failure	non-Hodgkin's lymphoma	ADCYAP1
	anorexia nervosa	multiple sclerosis	acute coronary syndrome	Graves' disease	ANCA associated vasculitis	LPL
	autism	impaired memory	aortic dissection	Addison's disease	acute myeloid leukemia	DRD4
138	major depression	Parkinson's disease	atrial fibrillation	premature pubarche	multiple myeloma	MINK1
	smoking behavior	ischemic stroke	coronary atherosclerosis	Graves' disease	non-Hodgkin's lymphoma	PHOX2B
	schizophrenia	neuropathy	congenital heart abnormalities	hyperaldosteronism	allergic rhinitis	RXRA
139-5p	autism	Becker and Duchenne muscular dystrophy	coronary atherosclerosis	early menopause	Hodgkin's disease	HMGCR
	mental retardation	myotonic dystrophy	long QT syndrome	primary hyperparathyroidism	leukemia	ATXN1
	personality disorders	polyneuropathy	congenital heart abnormalities	premature pubarche	inflammatory bowel diseases	PMP22
142-5p	mental retardation	Parkinson's disease	myocardial infarction	pinealoma	myeloid leukemia	DIO2
	psychosis	Creutzfeldt-Jakob disease	hypertension	polycystic ovarian syndrome	immunodeficiency	SLC18A2
	anxiety disorder	multiple sclerosis	long QT syndrome	pheochromocytoma	Chron's disease	CALCRL
143	anorexia nervosa	Alzheimer's disease	heart failure	Addison's disease	acute myeloid leukemia M4	FGF1
	anxiety disorder	meningioma	hypertension	male infertility	follicular lymphoma	PTGS2
	ADHD	cerebro vascular ischemia	aortic stenosis	diabetes mellitus type 1	sarcoidosis	CBFB
144	mental retardation	spinocerebellar ataxia	myocardial infarction	diabetes mellitus type 1 and 2	inflammatory bowel diseases	ABCA1
	alcoholism	cerebro vascular ischemia	left ventricular hypertrophy	premature ovarian failure	LES	FMR1
	schizophrenia	Alzheimer's disease	heart failure	Hashimoto's thyroiditis	porpora di Scholein Henoch	GABRA1
145	antisocial personality disorder	ALS/amyotrophic lateral sclerosis	coronary artery disease	hyperandrogenism	leukemia	IRS1
	anorexia nervosa	Alzheimer's disease	hypertension	polycystic ovarian syndrome	Sjogren's syndrome	NEDD4L
	bipolar disorder	agenesis of the corpus callosum	atrial fibrillation	Addison's disease	autoimmune hepatitis	GJA5
146b-5p	depression	cerebro vascular ischemia	carotid and coronary atherosclerosis	polycystic ovarian syndrome	agranulocytosis	CCL5
	ADHD	Hirschsprung's disease	acute coronary syndrome	Addison's disease	Wegener's granulomatosis	RET
	aggressive behavior	Alzheimer's disease	cardiac arrhythmias	diabetes mellitus type 1 and 2	non-Hodgkin's lymphoma	PDE11A
150	Alcoholism	epilepsy	aortic stiffness	acromegaly	primary biliary cirrhosis	GABRG2
	obsessive compulsive disorder	subarachnoid bleeding	heart failure	hyperaldosteronism	granulomatosi di Wegener	CACNA1G
	ADHD	Huntington's disease	myocardial infarction	hyperglycemia	non-Hodgkin's lymphoma	IL1A
155	schizophrenia	epilepsy	coronary and generalized atherosclerosis	autoimmune thyroid disease	ANCA associated vasculitis	AGTR1
	eating disorders	ischemic stroke	heart failure	hypoparathyroidism and hyperparathyroidism	chronic myeloid leukemia	CTLA4
	anxiety disorder	leukoencephalopathy	hypertension	polycystic ovarian syndrome	MGUS and myeloma	KRAS
181b	ADHD	dementia	aortic valve sclerosis	pancreatic endocrine tumors	graft-versus-host disease	ESR1

	drug abuse	essential tremor	heart failure	diabetes mellitus type 1 and 2	non-Hodgkin's lymphoma	TNF
	depression	trigeminal neuralgia	hypertension	hypothyroidism	Sjogren's syndrome	PPARA
192	mental retardation	charcot marie tooth disease	atrial fibrillation	acromegaly	LES	MECP2
	affective psychoses	epilepsy	complications related to heart transplant	Addison's disease	graft-versus-host disease	OPRM1
	alcol craving	Creutzfeldt-Jakob disease	hypertension	hyperandrogenism	inflammatory bowel diseases	SSTR2
193b	autism	meningioma	mitral valve prolapse	diabetes mellitus type 1 and 2	ANCA associated vasculitis	PTEN
	anxiety disorder	frontotemporal dementia	hypertensive cardiomyopathy	hypothyroidism	acute promyelocytic leukemia	PLAU
	bipolar disorder	narcolepsy	hypertrophic cardiomyopathy	polycystic ovarian syndrome	anti-phospholipid syndrome	TFAP2B
195	psychosis	ataxia	acute coronary syndrome	hyperparathyroidism	follicular lymphoma	ADRB2
	anxiety disorder	cerebrovascular diseases	heart failure	hypothyroidism	Hodgkin's disease	SLC6A4
	sindrome premestruale	Huntington's disease	long QT syndrome	pheochromocytoma	psoriasis	ANK2
203	bipolar disorder	ataxia	cardiac arrhythmias	diabetes mellitus type 1 and 2	ANCA associated vasculitis	FMR1
	personality disorders	myasthenia gravis	acute coronary syndrome	Graves' disease	LES	EDN1
	mental retardation	Guillain-Barre's sindrome	isolated idiopathic dilated cardiomyopathy	premature pubarche	non-Hodgkin's lymphoma	CD1D
208 (a, b)	bipolar disorder	Alzheimer's disease	generalized atherosclerosis	Addison's disease	graft-versus-host disease	HTR2C
	depression	ALS/amyotrophic lateral sclerosis	heart failure	diabetes mellitus type 2	LES	FLT3
	personality disorders	meningioma	acute coronary syndrome	polycystic ovarian syndrome	multiple myeloma	VDR
222	psychosis	Multiple sclerosis	Abdominal aortic aneurysm	Male infertility	psoriasis	ESR1
	schizophrenia	spinocerebellar ataxia	aortic valve stenosis	hypothyroidism	ANCA associated vasculitis	CD4
	alcoholism	cerebral hemorrhage	Brugada syndrome	pancreatic endocrine tumors	ankylosing spondylitis	KIR3DL1
223	mental retardation	ischemic stroke	myocardial infarction	Addison's disease	Behcet's Disease	MECP2
	alcoholism	ALS/amyotrophic lateral sclerosis	coronary atherosclerosis	Graves' disease	acute leukemia	ITGB1
	bipolar disorder	frontotemporal dementia	calcific aortic valve stenosis	diabetes mellitus type 1 and 2	anti-phospholipid syndrome	CIITA
331-3p	ADHD	Alzheimer's disease	coronary atherosclerosis	Graves' disease	atopy	TNF
	major depression	cerebral hemorrhage	heart failure	early menarche	graft-versus-host disease	LEP
	alcoholism	narcolepsy	acute coronary syndrome	diabetes mellitus type 1 and 2	Behcet's Disease	UCP3
340	bulimia nervosa	ALS/amyotrophic lateral sclerosis	acute coronary syndrome	Graves' disease	acute myeloid leukemia	ITGB3
	anxiety disorder	cerebral hemorrhage	atrial fibrillation	hyperandrogenism	atopy	MLL
	ADHD	dystonia	hypertension	hyperparathyroidism	inflammatory bowel diseases	CLOCK
376a	eating disorders	multiple sclerosis	abdominal aortic aneurysm	hypothyroidism	acute myeloid leukemia	HTR2C
	drug abuse	neural tube defects	myocardial infarction	polycystic ovarian syndrome	Behcet's Disease	MBL2
	obsessive compulsive disorder	ischemic stroke	long QT syndrome	pheochromocytoma	sclerosing cholangitis	CFTR
484	Alagille's sindrome	headache	hypertension	male infertility	Kawasaki disease	JAG1
	personality disorders	cerebral amyloid angiopathy	heart failure	hyperandrogenism	acute mieloblastic leukemia	GPX1

	delirium tremens	multiple sclerosis	congenital heart abnormalities	polycystic ovarian syndrome	psoriasis	SLC6A3
499-3p	alcohol abuse	Alzheimer's disease	acute coronary syndrome	diabetes mellitus type 2	inflammatory bowel diseases	ADIPOQ
	antisocial personality disorders	ischemic stroke	congenital heart abnormalities	endometrial cancer	Hodgkin's disease	MAOA
	bipolar disorder	cognitive function	hypertension	premature ovarian failure	non-Hodgkin's lymphoma	SNAP25
499-5p	psychosis	Tourette's sindrome	myocardial infarction	Graves' disease	Hodgkin's disease	HTR2C
	Schizophrenia	ischemic stroke	heart failure	pheochromocytoma	Kawasaki disease	BCL2
	depression	ALS/amyotrophic lateral sclerosis	aortic stenosis	diabetes mellitus type 1 and 2	leukemia	VHL
608	anorexia nervosa	cerebrovascular diseases	coronary atherosclerosis	Addison's disease	sclerosing cholangitis	HLA-DQA1
	antisocial personality disorder	epilepsy	atrial fibrillation	congenital adrenal hyperplasia	Chron's disease	HTR1D
	autism	glioblastoma multiforme	hypertensive cardiomyopathy	gestational diabetes	Henoch-Schönlein purpura	PAX2
625	anxiety disorder	impaired cognitive function	coronary atherosclerosis	hyperaldosteronism	acute myeloid leukemia	ADIPOQ
	eating disorders	primary dystonia	cardiac arrhythmias	Kallmann syndrome	anti-phospholipid syndrome	EDN1
	obsessive compulsive disorder	HIV-leukoencephalopathy	congenital heart abnormalities	Addison's disease	psoriatic arthritis	TBP
1207-5p	anxiety disorder	ALS/amyotrophic lateral sclerosis	abdominal aortic aneurysm	Addison's disease	ANCA associated vasculitis	FCGR2B
	bipolar disorder	ataxia	acute coronary syndrome	Hashimoto's thyroiditis	drug -induced agranulocytosis	ELN
	hallucinations	charcot marie tooth disease	atrial fibrillation	hyperaldosteronism	Henoch-Schönlein purpura	VEGFA

The heart as well as being included in the PNEI network is itself a PNEI organ

The PNEI network that constitutes the human body is responsible for the process of human adaptation to the environment and its status, its mode of activation has important consequences on both the psychological and the biological level, not only of the individual but also of future generations, through epigenetic marking mechanisms.

The heart and the cardiovascular system belong to this network.

The brain-heart symphony

Neurologic and cardiovascular diseases: two sides of the same coin?: Over the past years, there is increasing evidence about the brain-heart interaction with major potential implications for treatment of neurological and cardiovascular diseases [147,148]. A number of experimental data provide evidence that intensity of the cardiovascular responses to stress is regulated by neuropeptides. Vasopressin, angiotensin II and interleukin-1beta (IL-1 beta) appear to be responsible for exaggeration of the cardiovascular responses to stress whereas oxytocin seems to act in the opposite way [149].

Cerebrovascular accidents and transient ischemic attacks are frequently caused by cardiac arrhythmias (such as atrial fibrillation) and/or congestive heart failure. On the other hand, cerebrovascular dysfunction may lead to electrocardiographic disorders and cardiac rhythm disturbances. Subarachnoid bleeding may lead to dramatic electrocardiographic changes and even ventricular fibrillation, possibly due to QT-interval prolongation [150,151]. Even mental stress alone can induce cardiac electrical instability, arrhythmias [152] and elecrocardiographic T waves' changes at lower heart rates than observed with exercise [153]. Furthermore, psychosocial stress is associated with detectable plasma levels of troponin in healthy subjects, independently of the presence of coronary atherosclerosis [154].

During a cardiac arrest the brain isn't hypoactive and presents an high-frequency coherent activity [155]. Panic disorders and emotional distress such as the Takotsubo syndrome may give rise to fatal arrhythmias, ensuing transient left ventricular dysfunction with troponin release from myocytes and symptoms similar to those of myocardial infarction [156-158]. Amyotrophic lateral sclerosis and several central nervous system disorders can produce a 'pseudo-infarction' pattern on the electrocardiogram, with ST elevation followed by biphasic T and inverted T without any detectable myocardial abnormality [159].

Researches in patients with long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia revealed that the abnormal ion channel characteristics of these people may not be the only explanation for sudden death and that differences in autonomic patterning are critical [160]. This could be interpreted that the mutation creates the substrate of the arrhythmia, but the autonomic nervous system is a modulating factor that leads to the fatal triggers in situations of heightened adrenergic drive, specifically anger and exercise or unexpected acoustic stimuli during rest or sleep [160]. Moreover, patients with long QT syndrome have abnormal electroencephalograms [161].

Diabetic autonomic neuropathy being a common complication of diabetes mellitus is related to an increased risk of cardiovascular mortality [162]. Spinal cord stimulation imparts cardioprotection under conditions of neuronally dependent cardiac stress [163] and mitigates transient ischemia-induced myocardial infarction [164]. Moreover, an intra- and extra-cardiac neuronal remodeling happens after a myocardial infarction [165]. Coronary artery bypass surgery has major effects on neurocognitive functioning [166,167]. Furthermore,

chronic vascular and congenital heart disease patients present a peculiar neuroncognitive decline [168]. Exercise stimuli may prevent or slow down the cognitive decline in elderly patients with heart failure [169,170]. It has been demonstrated the strict connection between cerebral activity and cardiorespiratory synchronization [171] and baroreflex control of heart rate [172]. Parkinson's disease could lead to autonomic failure with cardiac and extracardiac sympathetic denervation and orthostatic hypotension [173]. "Cathecolamine autotoxicity" plays an important role both in Parkinson and in cardiovascular diseases [9,174,175].

It has recently been proposed that heart failure is a risk factor for Alzheimer's disease [176]. Decreased cerebral blood flow and neurohormonal activation due to heart failure may contribute to the dysfunction of the neurovascular unit and cause an energy crisis in neurons. This leads to the impaired clearance of amyloid beta and hyper phosphorylation of tau protein, resulting in the formation of amyloid beta plaques and neurofibrillary tangles [176]. Heart failure seems to relate with dementia being vascular dementia the most common dementia disorder [177]. Lee *et al.* have identified a common network of genes (and metabolic pathways) that was altered in Alzheimer's disease coinciding with myocardial infarction [131].

Both Parkinson's and Alzheimer's disease are linked to dementia and depression [178-185]. Depression is an important risk of cardiovascular events. It causes and in the meantime is worsened by immune dysregulation [186-190] that in turn is related to atherosclerosis, endothelial dysfunction, coronary artery disease [191] and calcification [192], myocardial infarction[193] and heart failure [194,195]. A recent study by Batty *et al.* confirmed that psychological distress represents a risk of peripheral vascular disease, abdominal aortic aneurysm, and heart failure [196,197]. Finally, the heart seems to play a surprising processing and decoding data role during intuition [198], a process by which information normally outside the range of conscious awareness is perceived by the psychophysiological systems [199].

In all aforementioned neurological and cardiovascular diseases, endothelial dysfunction is present [200,201].

The brain-heart connection: The brain-heart connection represents a growing research field that is revolutionizing many of our past knowledge. Conventionally, the heart and brain are believed to be connected in a hierarchical way with the brain in the role of conductor (prefrontal cortex, mainly the right side) and the heart in the role of executor [202]. While intimate connection between the brain and the heart was enunciated by Claude Bernard over 150 years ago, only recently it has been proposed a model of neurovisceral integration able to explain the linkage between the cognitive-affective processing system and the autonomic nervous system [203]. A relationship is present between vagal tone and event-related potentials [204,205].

Biological systems are complex at multiple levels of temporal and spatial scales and consist of interconnected feedback loops. The Fourier-based spectral analysis averages the signals, so it cannot sufficiently display the nonlinear and non-stationary properties of complex biological systems [206]. Many complex and interesting phenomena in nature are due to nonlinear phenomena. The theory of nonlinear dynamical systems, also called 'chaos theory', has now progressed to a stage, where it becomes possible to study self-organization and pattern formation in the complex neuronal networks of the brain both in healthy conditions and in diseases [207,208]. A broad body of experimental work has demonstrated that apparently spontaneous brain activity is not random, being the so-called brain "resting-state networks" or "default mode network" closely related to the underlying anatomical and functional connectivity [209].

From this point of view, the hierarchical brain-heart interaction model should be reconsidered. Many regulatory processes and signals between the brain and the heart incorporate interactive feedforward and feedback mechanisms. Probably we should consider the whole as an integrated and synergistic system. The heart begins to beat before the brain is formed. A transplanted heart is not connected to the host nervous system but can immediately satisfy the physiological demands of its new host [210-212] .

Entropy measurement techniques, which compute the regularity patterns of a time series, provide quantitative connotations that facilitate comparisons and correlations between two systems and between individual subjects [213-215]. Starting from these considerations, Pei-Feng Lin *et al.* demonstrated close correlations between the signal complexity of cerebral and cardiac electrical activity [206]. This demonstration will open the way for further research aimed at clarifying the relationship between electromagnetic connection between the brain-heart axis and the entire body. Tofani *et al.* revealed that electromagnetic energy could be the key link between the world of atoms and the world of genetics and cells [216,217]. This could be therapeutically important since scientific evidence is emerging about the effects of electromagnetic energy in the treatment of cancers [218] and wound healing [219] .

J. Andrew Armour described the presence of a cardiac neuronal system [220] (Figure 4) in which the intrinsic cardiac ganglia and intrathoracic extracardiac ganglia can process information independently of the brain [221].

Taggart *et al.* recently reviewed the anatomical and functional relationships that link anger, emotions, arrhythmias and sudden death. Briefly, the sympathetic and parasympathetic activity is not only reciprocal with a simple see-saw effect where sympathetic stimulation is proarrythmic while enhanced parasympathetic tone is protective. A co-activation also occurs [160]. Furthermore, it seems that the heart is reached by autonomic input with different spatial and temporal patterns (the so-called "brain–heart laterality hypothesis" by Lane and Jennings [160,222]) (Figure 5) and that emotional processing in the cortex is conveyed ipsilaterally through the brainstem to the autonomic nerves which in turn are distributed asymmetrically in the ventricular myocardium [223-225]. In particular left sided neural signals reach the postero-inferor heart walls and the left ventricle and the right sided neural innervation the anterior wall and right ventricle, albeit with substantial overlap [160,222,226,227,228–230]. Moreover, Beau *et al.* showed an heterogeneous myocardial transmural distribution of beta-adrenergic receptor subtypes [231]. Sympathetic and parasympathetic inputs to the heart are modulated by different reflexes rising from mechano- or chemo-receptors within the myocardium, blood vessels and lungs that send their signals not only to the brain vasomotor center but also involve higher brain centers of the medulla oblungata, in a dynamic interplay [160,232-236].

Different emotions are associated with different patterns of autonomic activity and different brain cortical representations [237-239]. Clinical studies have identified anger as the most common emotion precipitating ventricular arrhythmia [240,241]. Several studies have demonstrated specific patterns of autonomic activity for

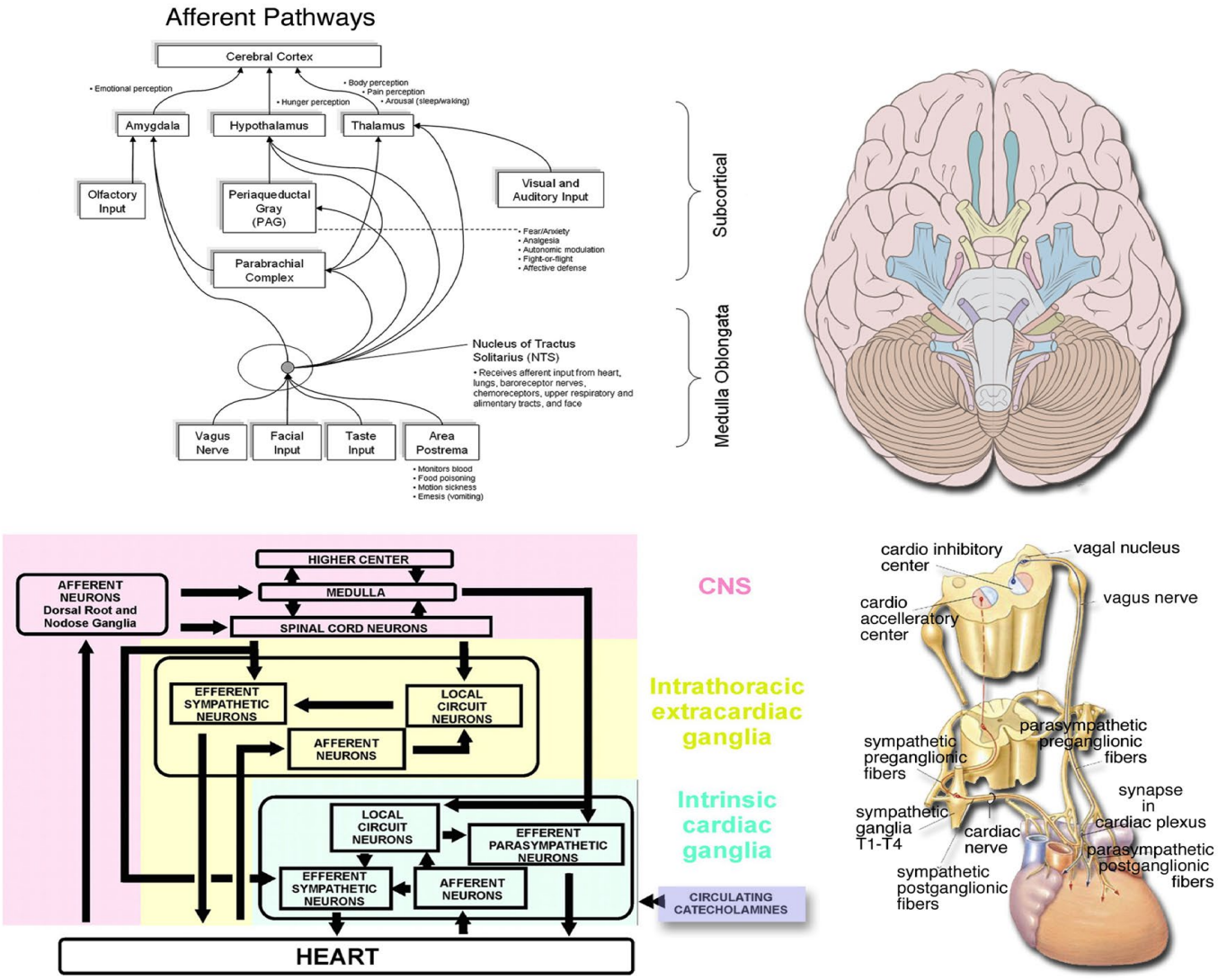

Figure 4. Neural control system of the heart, a hierarchy of three neuronal centers residing in central command, intrathoracic ganglia, and intrinsic cardiac ganglia: the dr. Armour's discovery [448]. The cardiac neuronal hierarchy can be represented as a massively parallel and, for the most part, stochastic control system such that stable cardiac control occurs in the absence of obvious cause and effect. This hierarchy displays robust external behavior while matching cardiac output to whole body blood flow demands. "The little brain on the heart" transduces centripetal and centrifugal inputs in the coordination of regional cardiac electrical and mechanical indices [448]. The regional cardiac mechano-sensory and chemosensory milieu is transduced by afferent neuronal somata located not only in nodose and dorsal root ganglia but also in intrathoracic intrinsic and extrinsic cardiac ganglia. This information engenders intrathoracic, as well as central (medullary and spinal cord) reflexes. The lower right-hand box indicates that circulating catecholamines influence cardiomyocytes not only directly but also indirectly via intrinsic cardiac adrenergic neurons [449]. While the main priority in central command is blood demand, the priority at the intrathoracic and cardiac levels is heart rate. As a result of this breakdown, heart rate becomes less predictable and therefore less reliable as a diagnostic guide as to the traumatic state of the heart, which it is commonly used as such following an ischemic event. On the basis of these results dr.Armour proposed that under the singular conditions of myocardial ischemia a determination of neural control indexes in addition to cardiovascular indexes has the potential of enhancing clinical outcome [450]. As shown in the top left part of the figure, cardiovascular afferents have connections to numerous brain centers involved in emotion and stress perception including the thalamus, hypothalamus, and amygdala.Ample evidence implicates anger together with other emotions and mental stress in playing a significant role in myocardial ischemia, arrhythmias and sudden death [157]. The mechanisms involved embrace neuroscience, physiology of the autonomic nervous system and cardiac electrophysiology which are usually investigated and reported by investigators from different disciplines. Growing evidence favors specific cortical representation of emotions in concert with autonomic reflexes and the molecular physiology of the myocardium. Feedback mechanisms from heart to brain probably play a significant modulatory role, particularly in pathological conditions. Such a highly interdependent schema could be regarded as a control system underlining the importance of an interdisciplinary approach to this field [160]. This is of paramount importance because standard drug therapy may not protect our patients from mental stress induced ischemia and its consequences [451]. Modified from [255,449]

anger and other emotions in response to emotional facial expressions [242,243], film clips [244], and to the recall of previous emotional experiences [239,245]. Rainville *et al.,* using Fourier analysis of the ECG R-R tachogram (or "heart frequence-Heart Rate Variability" (HRV)), demonstrated that anger recall was associated with an increase in heart rate but no change in HRV, suggesting relative dominance of sympathetic activity [239]. In contrast fear, happiness, and sadness were associated with an increase in heart rate but a decrease in HRV (parasympathetic activity) suggesting an overall decrease in parasympathetic activity, or increase in sympathetic/parasympathetic ratio [160,239].

Asymmetric autonomic neural traffic to the heart in response to emotion could be generated by several cortical upstream mechanisms.

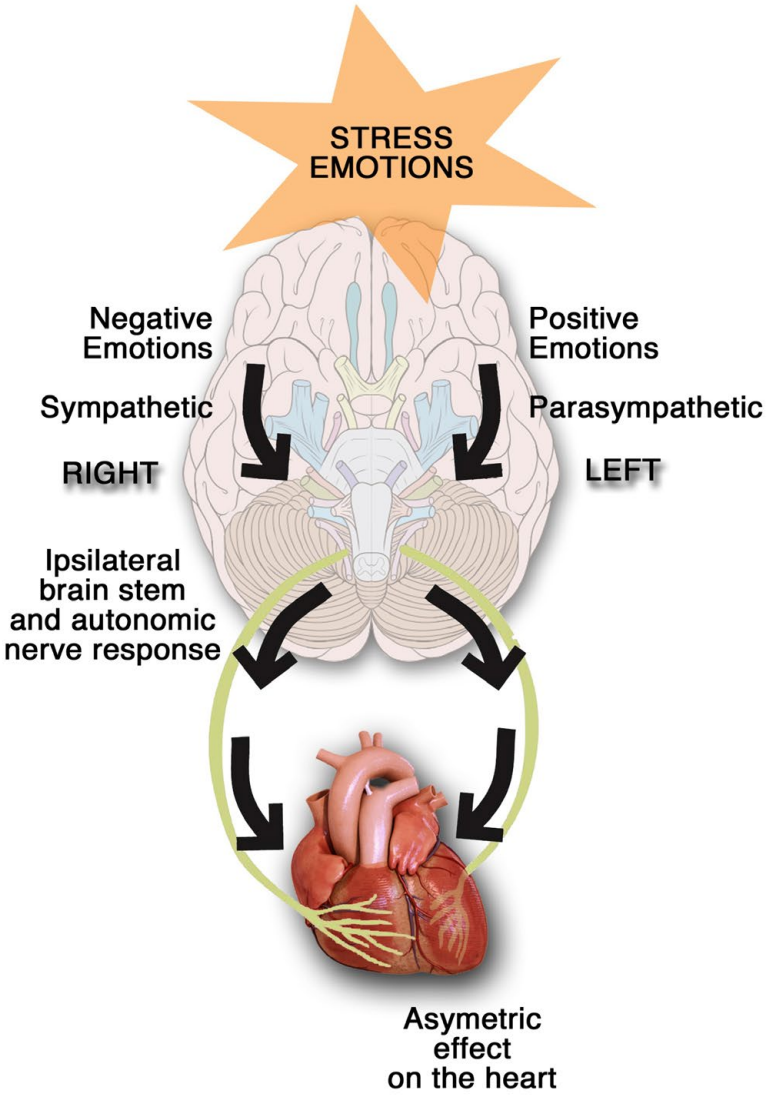

Figure 5. Brain–heart laterality theory [160]. Autonomic nerve traffic from the brain to the heart is mainly ipsilateral between the brainstem and heart. There is also some degree of lateralization of the distribution of the right and left autonomic nerves on the heart. These considerations form the basis for the laterality hypothesis whereby central neural processes may be represented asymmetrically on the heart and thereby induce inhomogeneous repolarization and be proarrhythmic. Modified from [160].

Considerable evidence suggests that the left and right halves of the human forebrain are associated differentially with specific emotions: positive emotions are associated to the left and negative emotions to the right hemisphere with specific neural pathways used for particular emotions [246]. As depicted in Figure 5, a similar lateralization is apparent for the cortical control of cardiac activity which may be related directly to predominantly sympathetic effects arising from the right hemisphere and predominantly parasympathetic effects arising from the left hemisphere [247–250].

On the other hand, cognitions and emotions can be influenced by bodily physiology [232]. Garfinkel *et al*. demonstrated that the cerebral processing of fear stimuli is selectively gated by their timing in relation to individual heartbeats, being amygdala responses greater to fearful stimuli presented at systole than that if presented in diastole [251]. The signals from the heart to the brain are then filtered by central limbic structures modulating the level of the signal to the cortex [252].

According to all these data, researches by McCraty *et al*. at the HeartMath Institute described that the communication pathways between the heart and brain occur through the generation and transmission of rhythms and patterns of activity that are related to cognitive and emotional function and self-regulatory capacity[253]. They showed that self-induced positive emotions increase the coherence in bodily processes, which is reflected in the pattern of the heart's rhythm [254,255]. It seems that heart beats form a rhythmic information code, that is perceived by the brain as a Morse code [256,257]. Aftanas *et al.* described a relationship between brain (alpha and theta waves) and heart oscillations (individual rate and blood pressure variability) [258,259]. The shift in the heart rhythm in turn plays an important role in facilitating higher cognitive functions, creating emotional stability and facilitating states of calm [260]. Over time, this establishes a new

inner-baseline reference, a type of implicit memory that organizes perception, feelings, and behavior [198,199,261]. Without establishing a new baseline reference, people are at risk of getting "stuck" in familiar, yet unhealthy emotional and behavioral patterns and living their lives through the automatic filters of past familiar or traumatic experience [255]. Many studies confirm that cardiac timing influences memory and impacts cognitive functions [262]. Furthermore, physiological fluctuations in cardiovascular afferent information influence specific emotional judgments, mediated through regions including the periaqueductal gray matter, and shape evoked autonomic responses through engagement of orbitofrontal cortex [263].

Many cell types secrete small vesicles called exosomes, that are derived from multivesicular bodies and that can also form from endocytic-like lipid raft domains of the plasma membrane [264]. Secretory exosomes contain a characteristic composition of proteins, and a recent report indicates that mast cell exosomes harbor a variety of mRNAs and microRNAs as well [265]. Exosomes express cell recognition molecules on their surface that facilitate their selective targeting and uptake into recipient cells [264]. Smalheiser *et al.* described that cells within the central nervous system communicate transferring vesicles containing RNAs and proteins among themselves and with endothelial cells within the brain [266]. Then, neural exosomes may pass into the bloodstream reaching endothelial cells and immunitary cells [266].

As we already described, circulating miRNAs are protected by encapsulation in membrane-bound vesicles such as exosomes, but the majority of circulating miRNAs in human plasma and serum cofractionate with Argonaute2 (Ago2) protein, rather than with vesicles [141]. Changes in miRNA expression occurring in the brain and heart could have an impact on coexisting neurological and cardiovascular characteristics by modulating organ function, accentuating cellular stress, and impinging on neuronal and/or heart cell survival [143].

Finally, the brain and the heart dialogue also through the immune system. As a matter of fact, the brain and the immune system are the two major adaptive systems of the body and are nowadays considered as a single neuroimmunitary system [267-270]. Dysregulation of the autonomic system enhances the inflammatory response of the innate and adaptive immune systems leading to the initiation or acceleration of pathological processes and worsening increasing of cardiovascular risks [271]. In turns, the heart cells talk to immunitary cells directly [272-274] and, being connected to the nervous system, probably through brain mediation. The heart releases hormones such as the natriuretic peptides (Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP) and Cardiac Natriuretic Peptide (CNP)) and endogenous cardiac steroids that act as neurotransmitters or neuromodulators in the brain [275]. The same compounds are able to modulate lymphocyte reactions [276]. Finally, it is interesting to notice how brain, the immune system and the heart share similar mnemonic properties. We can remember past events or concepts through our brains; there is the memory of past infections in "memory lymphocytes" circulating in the blood, and finally there is an electrical memory within the heart as described by Ozgen and colleagues [277,278] and as is commonly found in clinical cardiologic practice in case of "T memory waves" after cardiac pacemaker stimulation. Figure 6 depicts the brain-heart dialogue.

The connection between the heart, the endocrine and immune systems

It 's already well known that the cardiovascular system is influenced by the activity of many hormones [9,65,76] and of the immune system. Considering the cardiovascular system, we can find traces of the immune action in every disease, being involved in atherosclerosis [279] and myocardial ischemia/infarction [280,281], in heart valve calcification and stenosis progression [282] or heart valve endocarditis, in heart failure [283], aortic aneurysms [284], pericarditis, myocarditis and autoimmune heart pathologies [285] and even in congenital affections [286]. Furthermore, complement, a primordial sentinel of the innate immune response, engages in multiple inflammatory cascades and complement proteins have been implicated in tissue and organ regeneration including the cardiovascular system [287].

The heart as a primary PNEI organ

The heart, in addition to receiving all these PNEI influences, is itself a PNEI organ.

We have already seen how is actively involved in the psycho-neurological processes.

The heart also acts as a gland: secreting atrial, brain and C-type natriuretic peptides (ANP [288], BNP and CNP [289]), mediates important cognitive functions in the brain [275,290] and regulates the immune system activity [276]. Moreover, anger and stress could cause an excess consumption of natriuretic peptides in nervous and cardiovascular system which inhibit their compensatory self-repair action on atherosclerotic process, leading to fibrosis and lipid peroxidation and heart failure, as demonstrated in animals [291]. A failing heart also secretes adrenomedullin (ADM) which has a coronary vasodilatatory effect [292] and is involved in the cardiorenal signalling [293-295]. From epicardial adipose tissue are also produced and released the endocannaboinoids with a protective action on cardiac metabolism, atherosclerosis and possible ischemic injury [296]. Finally, the heart interacts bidirectionally with the immune system through numerous signals: ANP, BNP, cytokines, toll-like receptors 2 and 4 (TLR-2, TLR-4 [297-299]) etc.

Endothelial cells in the PNEI network

The coronary circulation endothelium is part of the endoderm, the largest endocrine organ in our body [300,301]. From this point of view it is easy to understand how it receives signals from neurotransmitters, hormones and cytokines, and in this way its function is regulated by the PNEI network [302]. This observation suggests that the PNEI-system equilbrium could be used as an ideal marker of endothelial health and therefore cardiovascular health [303]. For example, in order to explain the dynamics related to the onset of obesity and endothelial dysfunction, Yuan *et al.* observed the changes of vascular endothelial function and PNEI network molecules in case of hyper-alimentation diet in combination with restricting movement. Confort-based lifestyle, inducing changes of common PNEI chemical signal molecules, lead to vascular endothelial dysfunction [304].

We recently reviewed [65] the hormonal influences that act on the coronary endothelium, influencing its function and that can be studied through the evaluation of the CFR. In summary, on endothelial cells acts a real neuro-endocrine-immune symphony in which the melody is played by the vitamin D [305], parathyroid hormone (PTH) [32], renin-angiotensin-aldosterone system (RAAS) [195,306] axis in concert with

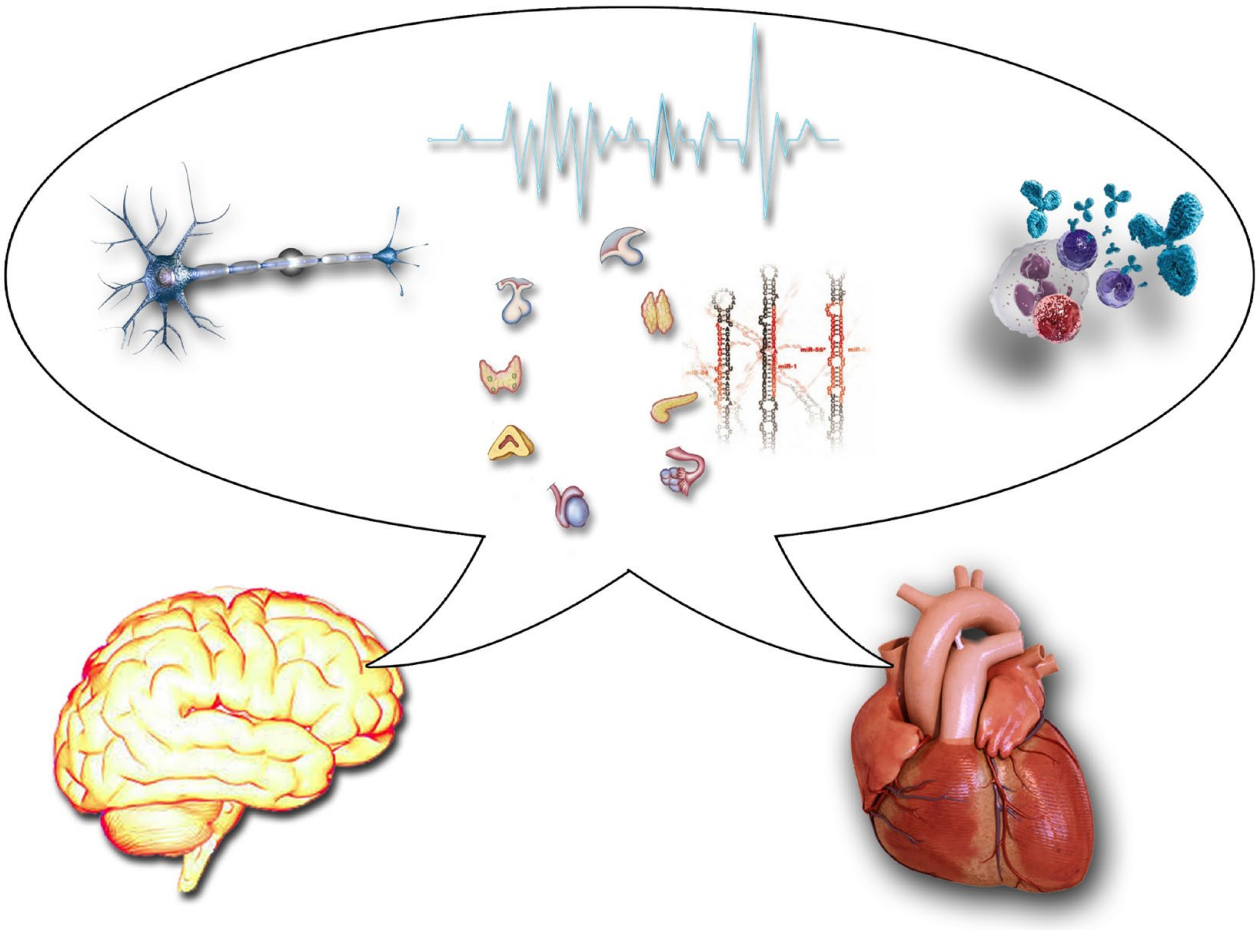

Figure 6. The brain-heart dialogue There is a dynamic, bidirectional communication between the heart and brain continuously influencing each ones functions [168,195,452]. The cardiovascular system communicates with the brain in four major ways: neurologically (through the direct transmission of nerve impulses), biochemically (via hormones, neurotransmitters, cytokines [453] and miRNAs [454]), biophysically (through pressure waves [172], baroreflexes [455,456], breathing patterns [233,457] and heart rhythms [198,199,252–255,261]) and energetically (through electromagnetic field interactions[206]). Based on relatively recent scientific discoveries, it seems that the heart is capable of mediating cognitive processes [206,251,458] and also possesses an intrinsic neurological activity [221] enough to be considered a "little pumping brain" or a part of the neurological system. On the other hand more and more clinical evidences are emerging about connections that bind neurological affections and the cardiovascular ones and vice versa [173,177,459]. The heart is also affected by the psychological balance of the human organism. In fact there are many demonstrations of how our emotions can trigger different types of cardiovascular events: the best known case is the Tako-tsubo syndrome or "stress cardiomyopathy" [460,461], but also arrhythmias and electrocardiographic changes [157,222,462,463], release of troponin in healthy subjects undergoing psychological stress [154] and myocardial infarction in case of outburst of anger [160,464,465].

thyroid and TSH hormones [307–310], GH and insulin like growth factor 1 (IGF-1) [311-313], cortisol and adreno-corticotropic hormone (ACTH) [314,315], sex hormones [316], insulin and glucagon like protein-1 (GLP-1) [317–320], adipokines [195,321-323], oxytocin and vasopressin [324–329], prolactin [330–333], melatonin [334–337], bilirubin, heme catabolic pathway, and gamma-glutamyltransferase [338–341].

Rounding out the orchestra is the immune system [62,342], with the familiar example of inflammation as a key process involved in the pathogenesis of atherosclerosis [323,343–348], the already discussed action of platelets and the autonomic balance, where the prevalence of the sympathetic system on the parasympathetic, is a determining factor for endothelial dysfunction [195].

From the point of neuro-endocrine-immune system view, we have shown how the fat in itself is not a cardiovascular risk factor, but it will become in the presence of inflammation (in turn linked to the presence of one or more stress factors) [322,323]. Peri-coronary adipose tissue, in the absence of stress, instead produces adipokines with vasoprotective effect (increased production of adiponectin compared to pro-inflammatory cytokines) [349,350]. Adipose tissue mediates important effects in the cardiovascular system and details of which are yet unknown. In particular, the endocannabinoid system is an interesting field of both pathophysiological and clinical research [351]. As explained by Hiley *et al.* "*endocannabinoids, such as anandamide and 2-arachidonoylglycerol, are synthesized from membrane phospholipids in the heart and other cardiovascular tissues. They activate several epigenetic mechanisms [352] through cannabinoid CB1 and CB2 receptors, transient receptor potential V1 (TRPV1), peroxisome proliferator-activated receptors, and perhaps a novel vascular G-protein-*

coupled receptor. Inactivation is by cellular uptake and fatty acid amide hydrolase. Endocannabinoids relax coronary and other arteries and decrease cardiac work but seem not to be involved in tonic regulation of cardiovascular function. They act as a stress response system, which is activated, for example, in myocardial infarction and circulatory shock [353,354]. Endocannabinoids are largely protective [355,356]; they decrease tissue damage and arrhythmia[357,358] in myocardial infarction [359] and may reduce progression of atherosclerosis (CB2 receptor stimulation inhibits lesion progression), and fatty acid amide hydrolase knockout mice (which have enhanced endocannabinoid levels) show decreased cardiac dysfunction with age compared with wild types. However, endocannabinoids may mediate doxorubicin-induced cardiac dysfunction. Their signaling pathways are not fully elucidated but they can lead to changed expression of a variety of genes, including those involved in inflammatory responses [360-363]. There is potential for therapeutic targeting of endocannabinoids and their receptors, but their apparent involvement in both protective and deleterious actions on the heart means that careful risk assessment is needed before any treatment can be introduced [364,365]" [296]. As a PNEI mediator, the endocannabinoid anandamide is a lipid transmitter synthesized and released "on demand" by neurons in the brain and is also generated by macrophages where its endotoxin (LPS)-induced synthesis has been implicated in the hypotension of septic shock and advanced liver cirrhosis [366]. Endocannabinoid signaling processes are present in diverse organisms and in organisms 500 million years divergent in evolution and their relaxing action on vascular tone [354,367] is coupled to NO [368].

As briefly described in the introductory paragraphs, NO generated from L-arginine by NO synthase (NOS) has a pivotal role in regulating blood flow. In most vascular beds, the continuous generation of NO reduces basal vasomotor tone and increases blood flow. As such, local NOS inhibition, eg, with the non–isoform-selective inhibitor NG-monomethyl-L-arginine (L-NMMA), reduces resting blood flow both in animal studies and in humans [369]. These effects have generally been attributed to NO generated by endothelial NOS (eNOS) expressed in the endothelium of blood vessels. NO derived from eNOS also mediates increases in blood flow elicited by agonists such as acetylcholine and substance P, and the impairment of such responses (known as endothelial dysfunction) predicts the development of atherosclerosis [16,370].

Recent data from animal studies indicate that NO generated by local neuronal NOS (nNOS) can influence vascular tone, raising the possibility that different NOS isoforms may subserve distinct effects on the regulation of blood flow [371]. These results were confirmed in humans, indicating that basal microvascular tone in healthy subjects *in vivo* is regulated by local nNOS-derived NO, whereas acetylcholine-stimulated vasodilatation is eNOS mediated [372,373].

We can also consider the NO as PNEI molecule mediating multiple interactions between neuroendocrine and neuroimmune systems [16,268,270,374–380] in physiological and pathological processes [200]. It plays an important role in creating and regulating the dialogue between the actors involved in our adaptation to the environment [381]. NO participates in signal transduction pathways that result in the release of corticosterone from the adrenal gland and nNOS modulates learning and memory and is involved in development of neuropsychiatric diseases, including depression [382]. Nitric oxide generated in response to stress exposure is associated with depression-like and anxiety-like behaviours [74].

Especially noteworthy is the endothelial interaction with the immune system through TLR-2 and TLR-4. In particular the TLR4/NFκB/p38 signaling pathway may lead to endothelial and NO impairment (through the decreased eNOS phosphorylation) [383]. This process can also occur in the course of mental stress [268] and may be associated with coronary and atrial thrombogenesis [384,385]. Moreover, systemic TLR2 and TLR4 response and expression decrease after percutaneous coronary interventions and TLR response is positively associated with coronary flow reserve, percentage diameter stenosis and presence of multivessel disease [386]. Toll-like receptors 2 and 4 modulate autonomic control of heart rate and energy metabolism [297].

We know that cigarette smoking and alcohol abuse are important cardiovascular risk factors [9]. What we have just described about the PNEI influences on endothelial function and on the dialogue between endothelium and immune system through TLR allows us to understand why. TLR-4 is an innate immune regulator of neuroimmune and neuroendocrine interactions in stress responses and could be activated either by exogenous pathogenic mechanisms, or as a result of endogenous stress signals [268]. As described by Vetreno *et al.,* adolescence is a critical developmental stage of life during which the prefrontal cortex matures, and binge drinking and alcohol abuse are common. Recent studies have found that ethanol increases neuroinflammation through Toll-like receptors signaling, leading to persistent upregulation of innate immune danger signaling in the adult prefrontal cortex that correlates with adult neurocognitive dysfunction [387,388]. Furthermore, cigarette smoke induces TLR-4 expression and its inflammatory pathway in many districts [389]. A vast body of research attests to the adverse effects of alcohol [390,391] and chronic smoking [392,393] on cardiac, pulmonary, and vascular function as well as the increased risk for various forms of cancer [394]. Alcohol assumption and cigarette smoking are often associated and the common final inflammatory TLR-4 pathway with NO production impairment [395], could further explain their deleterious effects. Furthermore, the interactive pharmacological effects of nicotine and low doses of alcohol play an important role in motivating contemporaneous use and suggest roles for cross-reinforcement and cross-tolerance in the development and maintenance of alcohol and nicotine use and dependence [396]. Finally, we have to consider that both alcohol consuming and cigarette smoking are common behaviors in depressed or anxious people. Nowadays, we know that inflammation and cell-mediated immune activation are key factors in depression [187,397]. From all these data we can understand how alcohol and cigarette smoking, albeit giving a temporary relief, enslave the patient in harmful behaviors and thoughts. From this point of view, we have to appreciate legislations banning smoking in indoor public places and workplaces to protect the population from secondhand smoke exposure. Several studies have reported reductions in hospitalizations for acute coronary events following the enactment of smoke-free laws [398].

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