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STRESS AND ITS IMPACT ON HEALTH: A SYSTEMATIC REVIEW ON ADVERSE CARDIOVASCULAR OUTCOMES

L'IMPATTO DELLO STRESS SULLA SALUTE: UNA REVISIONE SISTEMATICA SUGLI ESITI CARDIOVASCOLARI AVVERSI

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Abstract

The impact of stress on the human body is often underestimated in today's society. Stressful circumstances, when experienced daily over the long term, can inflict gradual harm on the body's organs. However, the stress response is a complex phenomenon with both positive and negative aspects. It allows humans and animals to effectively deal with challenging situations, thanks to fine biological mechanisms created during evolutionary history. Yet, this adaptive response turns detrimental when faced with chronic stress, a relentless succession of unpredictable and uncontrollable circumstances. Homo sapiens seems uniquely affected by these severe repercussions, setting them apart from other species that employ stress adaptively in response to immediate threats. Humans, unfortunately, often engage these mechanisms unnecessarily, reaching an allostatic overload. The systematic review comprehensively explores the concept of stress from historical, conceptual, and biological perspectives, analyzing numerous experimental studies to elucidate the factors influencing stress responses. The primary aim is to emphasize the adverse health consequences of stress, with a specific focus on its impact on the cardiovascular system. Understanding these dynamics is crucial in a world where stress has become an omnipresent force that demands attention and proactive management to safeguard human health and well-being.

Index

INTRODUCTION

The often underrated impact of stress on the body can lead to severe consequences. In today's fast-paced society, people prioritize performance and speed, which, unfortunately, can gradually harm the body's organs when experienced daily over the long term. However, it's important to note that the stress response isn't always detrimental. Human biological mechanisms, honed over evolutionary history, serve to deal with life's destabilizing situations effectively. So, the stress response has a dual nature, with both positive and negative aspects. The adaptive side prepares the body for challenging situations, while the negative side kicks in when faced with a succession of difficult, unpredictable, and uncontrollable circumstances, known as chronic stress. This chronic stress is what's commonly referred to as a "stressor" and has detrimental effects on the body.

R. M. Sapolsky's well-known question "Why zebras don't get ulcers?" [1] gains particular relevance and fascination when it is considered that, among all species, Homo sapiens appears to be the only one experiencing such severe repercussions. Animals, in facts, use stress in an adaptive way, activating all those mechanisms functional to coping with a stressful situation, such as a threat from a predator. Conversely, humans often engage the same mechanisms in contexts where they are unnecessary, resulting in what is termed "allostatic overload" of the body.

In this systematic review, it will be explored the concept of stress from historical, conceptual, and biological perspectives. Subsequently, several experimental studies in the scientific literature that have investigated and continue to investigate the possible factors that influence the response to stress will be analysed.

[1] Sapolsky, R. M. (1994). Why zebras don't get ulcers.

The primary objective of this thesis is to highlight the adverse health effects of stress, particularly those related to the cardiovascular system.

The penultimate chapter is related to the laboratory experience that I was able to conduct in person at the Department of Psychology of the University of Limerick, during my curricular internship period abroad.

The concluding chapter go through the recent development in the area of research concerning cardiovascular reactivity to stress (CVR), which highlights that adverse consequences can arise not only when CVR is excessively high but also when it becomes too low. Studies exploring "blunted reactivity" now form the cutting edge of stress response research, challenging the conventional notion that low reactivity is always adaptive. These findings indeed suggest that a mid-range level of CVR may be considered optimal and adaptative.

CHAPTER 1

Stress and its adaptative role

1.1 A brief overview

Hearing the term "stress," it may seem simple to provide a definition. Effectively, this term has a common usage in our society and, nowadays, the awareness that stress can have severe consequences on the human body is quite widespread. However, within the current scientific community, defining the term "stress" in a systematic way is not that easy for a number of reasons: it can be used as a noun but even as a verb, it can refer to an internal state but also to an external situation, and sometimes it can be confused with the term "stressor." The uncertainty that surrounds the word "stress" as a noun is revealed in the countless meanings of the Oxford English Dictionary. For the purposes of this document, the most pertinent are the two following:

"Mental or emotional strain placed on or experienced by a person as a result of adverse or demanding circumstances, esp. the pressures of or problems in one's life; a state of feeling tense, anxious, or mentally and emotionally exhausted arising from this."[2]

"Disturbed physiological function occurring in an organism or cell in response to conditions, events, or factors that are deleterious or threatening; *esp.* a state occurring in humans and other vertebrates characterized by the release of hormones such as cortisol, epinephrine, and

[2] stress, n. : Oxford English Dictionary (oed.com)

norepinephrine, and by changes including increased heart and respiratory rate and elevated blood sugar. Also: the cause, or a causative agent, of such disturbed function."[3]

It would be more interesting to start exploring immediately all the evidence that has come out in this recent field of investigation, but there are several conceptual and historical issues that need to be clarified.

First, it may be useful to define that a "stressor" is an external or internal stimulus that generates feedback in the organism. In more specific terms, this reaction was called by Cannon the "fight or flight response." This physiologist, in the early 20th century, was the first to describe the response of the body to stress. He observed in animal models that, in front of threatening situations, the organism enters a state of heightened sympathetic activation, which allows it to survive. Mobilization of energy reserves, stimulation of the cardiovascular system, increment in muscle contraction force and bronchial dilatation are all consequences of the sympathetic activation and prepares the body to escape or to deal with the stressful threat.

The fight or flight response, as a survival instinct, has been conserved by nature in animals as well as in humans, but what recent research elucidates is the fact that these two ways of behaving are not ideal strategies in everyday human life. As McGonigal affirms: "You can't punch a past-due mortgage payment, and you can't make yourself disappear every time there's a conflict at home or at work"[4]. This point of view is called "mismatch theory" because the evolutionary baggage of the fight or flight response seems to collide with modern human's life. However, supporting this theory leads to ignoring two key facts: stressors can have several

[3] Ibid
[4] McGonigal, K. (2015). The upside of stress: why stress is good for you, and how to get good at it. https://ci.nii.ac.jp/ncid/BB28611158, p.46

properties; stress response has an adaptative value which allowed its parallel evolution with human society.

1.2 What makes a stimulus a "stressor"

Stressors can be physical, psychological, sociological, and even philosophical (for instance spirituality, use of time or find a purpose in life). All these forms of stressful stimuli can lead to the same reaction of the body: the activation of the sympathetic system. But this activation will not happen in all cases, and therefore, additional distinctions must be made.

Lazarus and Cohen in 1977 listed three types of stressors: major changes affecting many people, major changes affecting one or a few people and daily hassles. Even if the latter can appear less dramatic than major changes, it may be even more damaging for health. But it is not just the magnitude of the event that makes the difference in how the stimulus is perceived. It can even depend on others intrinsic properties of it, such as the duration and the degree of control and prediction.

The literature suggests that the physiological effects of stress may be quite different depending on whether the stressor is acute, chronic, or intermittent. Not all every day hassles are crucial and harmful for the body: they have more possibilities to become stressors if they are chronic. Weiss, in 1972, adds to the factors that make a stimulus a stressor the degree of control and prediction that people can exert on it. Obviously, these concepts should not be seen through an objective point of view but considering the internal representation of the stimulus.

To summarize, a stressor is an external or internal stimulus hard to control and predict that, if chronic, can seriously damage the organism to which it is directed. But what happens to the body if the stressor did not lead to defilement?

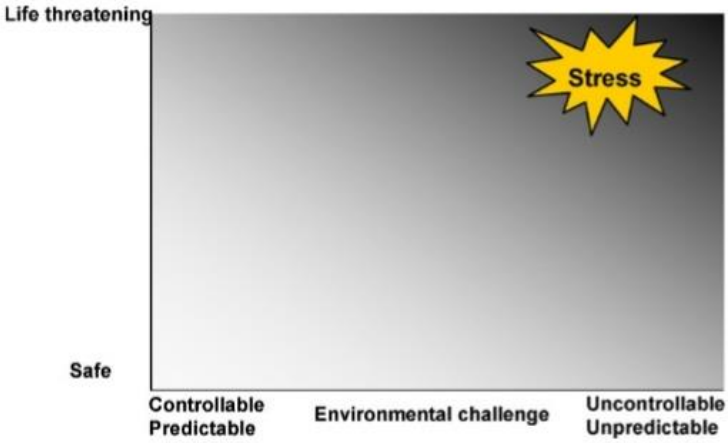

Figura 1 A graphical depiction of how the controllability and predictability of environmental challenges relate to their potential to become life-threatening.[5]

1.3 Stress is adaptative

Cannon is not the only one pioneer that, in the early 20th century, conducts the researcher's attention to stress. The work of Selye started to clarify the role of the endocrine mechanisms that exist behind the stress response. In 1936, he found a substantial enlargement of the adrenal glands cortex in experimental rats exerted to harmful physical stimuli. He called the reaction of the body to all kinds of noxious stimulus "General Adaptation Syndrome" and defined stress as a "response of the body to any demand made on it"[6]. Within this theoretical framework a stressor can be everything that happens to the body, in both a negative and a positive way. Stress

[5] Koolhaas, J. M., Bartolomucci, A., Buwalda, B., De Boer, S. F., Flügge, G., Korte, S. M., Meerlo, P., Murison, R., Olivier, B., Palanza, P., Richter-Levin, G., Sgoifo, A., Steimer, T., Stiedl, O., Van Dijk, G., Wöhr, M., & Fuchs, E. (2011b). Stress revisited: A critical evaluation of the stress concept. Neuroscience & Biobehavioral Reviews, 35(5), 1291–1301, p.1296

[6] Ibid, p.41

becomes the general body's response to life and that is why, by this point of view, not all stressful experiences will harm the organism. Selye distinguishes between two types of stress: the good one (eustress) and the bad one (distress). It can be difficult to dissociate these two sides of the coin, but Selye's contribute leads to abandon the bad reputation of stress to embrace its adaptative side. Thus, stress becomes a process that allows the mobilization of energies to the whole organism.

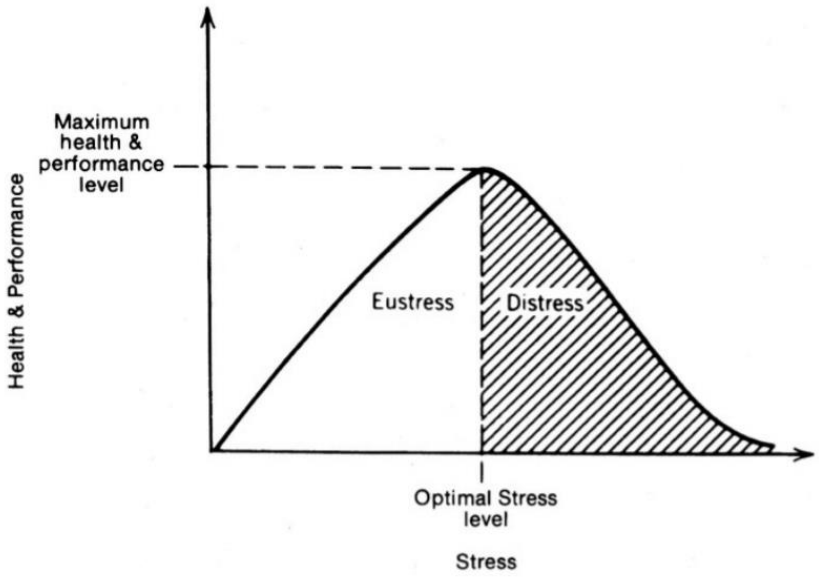

Figura 2 This graphic illustrates the connection between stress arousal and its impact on both health and performance. As stress levels rise, performance also increases, referred to as "eustress." At the optimal stress level, performance reaches its peak. However, if stress continues to escalate into the "distress" zone, performance rapidly deteriorates. Prolonged excessive stress levels can lead to a decline in health.[7]

McGonigal (2015) introduced the notion of "challenge response", which happens "when the stressful situation is less threatening" and stress "gives you energy and helps you perform under pressure". [8] The individual who experiences this state will feel focused and not fearful as in the fight or flight response. In this case, the stress

[7] Everly, G. S., & Lating, J. M. (2002). A Clinical guide to the treatment of the human stress response, p. 12
[8] Ibid, p.51

response gives access to mental and physical resources, and, in the long term, it will be protective for the body.

Parker's research team observed how early life stress can change, in a positive way, the developing of the brain. In the Laboratory of Developmental Psychology at Stanford University they studied, in squirrel monkeys, how a brief intermittent mother-infant separation can conduct to long-term effects. What they found out is that "intermittent separations represent a form of stress inoculation that enhances arousal regulation and resilience"[9].

In a previous study (1962), Levine and colleagues concluded that neonatal rats that were briefly separated from the nest showed in their adulthood increased exploration, improved learning and diminished HPA (Hypothalamic Pituitary Adrenal) axis activation. This may happen because when the little rats or monkeys returned to their mothers this latter implemented higher levels of maternal care. Furthermore, Parker and collaborators found out an enlargement of the ventromedial prefrontal cortical volumes in monkeys exposed to intermittent separations. These are interesting results since studies on human (Matsuo et al., 2009) highlighted that increased ventromedial prefrontal size predicts diminished impulsivity. Therefore, early life stress events may have a positive influence on neuronal plasticity and on how the reality is perceived and controlled.

Overall, stress in some situations can help to learn from experience, acting like a sort of vaccine for the brain.

[9] Lyons, D. M., Parker, K. J., & Schatzberg, A. F. (2010). Animal models of early life stress: Implications for understanding resilience. Developmental Psychobiology, 52(5), 402–410. https://doi.org/10.1002/dev.20429

1.4 A step backward

As already discussed, more attention has started to be given to stress in the 20th century but the link between emotional reactions and physiological responses is old as Hippocrates. Ancient Greeks conceived the state health considering four "humors": blood, yellow bile, black bile, and phlegm. In a more recent view, these can be compared to the hormones and neurotransmitters that are today studied in relation to health balance and behaviour. In the same way, for Greek thinkers, a loss of balance within the four humors could lead to pathology. Many Greek authors talked about the mental stress deriving from war and especially Gorgia described the long-term effects of the battlefield's dynamics from a psychological point of view.

Effectively, the consequences of war, especially World War II, were also crucial in creating awareness towards stress in the 20th century. In the landmark book entitled "Men Under Stress" (1945) Grinker and Spiegel discuss, in psychological terms, stress and its influence in soldiers' lives and even other several works of those years were focused on the impact of bombing, manipulation and concentration camps.

In this era, for the first time, society becomes truly conscious of the way in which stress, as a major event, can destroy a human's life. But it will take a few more decades for the diffusion among the population of the belief that even small daily hassles can be harmful.

1.5 New directions in stress conceptualization

The characteristics of stimuli called "stressors" have long been debated in the previous paragraphs. However, even individuals own some features that can change their way to perceive stress. They could be genetical, referred to early life experience

or arising from social history. Some of them, with their respective evidence, will be discussed in the next chapters but what is needed now is to realize their crucial role in the conceptualization of stress. This additional consideration is required to introduce the stress model of Lazarus. As this latter affirmed, psychological stress is "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her own resources and endangering his or her well-being."[10] In this model, the stress response emerges from an imbalance between the requirements of the environmental situation and the ability to cope with it. Thus, stressors disturb the balance of the organism, that in the medical field is called "homeostasis." The concept of homeostasis was involved in stress studies for a long time, but recently it has been implied in a critical evaluation. If the body is placed in front of a stressor, it is not passive as researchers of the early 20th used to think. The organisms constantly and dynamically transform themselves in relation to the surrounding stimuli since they need to adapt to them. Therefore, Sterling and Eyer (1988) proposed to abandon the concept of homeostasis in stress investigation to replace it with the term "allostasis".

Allostasis can be described as "the process of achieving stability through change in anticipation of physiological requirements"[11]. The use of the word homeostasis implied the employ of set-points: rigid physiological parameters in which what was conventionally considered a healthy body should stay in. The allostasis-vision appears instead more adequate to the reality of natural facts because individuals

[10] Lazarus, R. S., & Folkman, S. (2013). Stress: appraisal and coping. In Springer eBooks (pp. 1913–1915). https://doi.org/10.1007/978-1-4419-1005-9_215, p.19

[11] Koolhaas, J. M., Bartolomucci, A., Buwalda, B., De Boer, S. F., Flügge, G., Korte, S. M., Meerlo, P., Murison, R., Olivier, B., Palanza, P., Richter-Levin, G., Sgoifo, A., Steimer, T., Stiedl, O., Van Dijk, G., Wöhr, M., & Fuchs, E. (2011). Stress revisited: A critical evaluation of the stress concept. Neuroscience & Biobehavioral Reviews, 35(5), 1291–1301. https://doi.org/10.1016/j.neubiorev.2011.02.003, p.1297

continuously increase or decrease their vital functions in response to the environment. It consents a continuous readjustment of all parameters towards new set-points, permitting to the body to achieve stability through change.

Another advantage of allostasis is the possibility of anticipating the necessary adaptations when, on the contrary, homeostasis just corrects the physiological discrepancy right in the moment when it appears. Therefore, mechanisms of allostasis produce a reaction that corresponds to a specific prevision because natural selection, during the centuries, modelled the physiology and behaviour of species to make them adaptable to the most probable demands of their environment.

The response of the organism to his habitat is called “adaptative capacity.” This concept goes hand in hand with the notion of “regulatory range,” which can be a substitution of the term set-point. The regulatory range can be defined as a range of processes that regulate the body when there is no need of any substantial adaptive modifications. For example, the regulatory range for human body temperature is usually between 97°F (36.1°C) and 99°F (37.2°C). Consequently, it can be affirmed that the adaptative capacity should be optimized with the regulatory range and effectively, in normal situations, allostatic parameters can fluctuate considerably but always within regulatory ranges. If these fluctuations run chronically over the ranges, the body will enter in a state named “allostatic load” or, in the worst cases, “allostatic overload.”

The notion of allostatic load and allostatic overload equates the cumulative influence of chronic psychological stress: they represent the effects of all the stressors that last over time and exceed predictability and control. If the demand from the surrounding environment continues to be high for prolonged periods of time, the organism will

tend to produce anticipatory automatism of reaction. That is why, when the stressful event is terminated, this adaptative strategy can conduce to a slower return to "normal" parameters. How Sterling and Eyer asserted: "there continues to be allostatic regulation, but the average setpoint is much higher than normal."[12]

Koolhaas and colleagues in 2011 highlighted how this delayed recovery of the sympathetic activation may be helpful, more than the peak of response, to label a challenging situation as "stressor".

To conclude, it can be claimed that the same mechanisms that consent adaptation may also lead to pathology, and it may involve several areas of the organism: the cardiovascular system, the immune function, the gastrointestinal system, the metabolic function, and the central nervous system.

[12] Sterling, P. (1988). Allostasis : a new paradigm to explain arousal pathology. Handbook of Life Sress. https://ci.nii.ac.jp/naid/10019518960/

CHAPTER 2

The bad side of the coin

2.1 Models of target-organ pathogenesis

Since the damaging effects of everyday stress are known, several theories have been proposed with the purpose of investigating the factors that may link stress response mechanisms to any eventual target-organ disease. These perspectives on the stress-to-disease issue highlight different topics, but they all agree on the assumption that chronic stress, in terms of overstimulation of the organism, can provoke dysfunctions of the end-organs involved.

In his famous General Adaptation Syndrome, Selye discussed three phases of the stress response: the somatic shock, the resistance, and the exhaustion. The first one represents the initial alarm reaction of the organism. The second consists of the mobilization of resources to restore homeostasis (fight or flight response). Finally, is the exhaustion that Selye indicates as a probable cause of the target-organ damage.

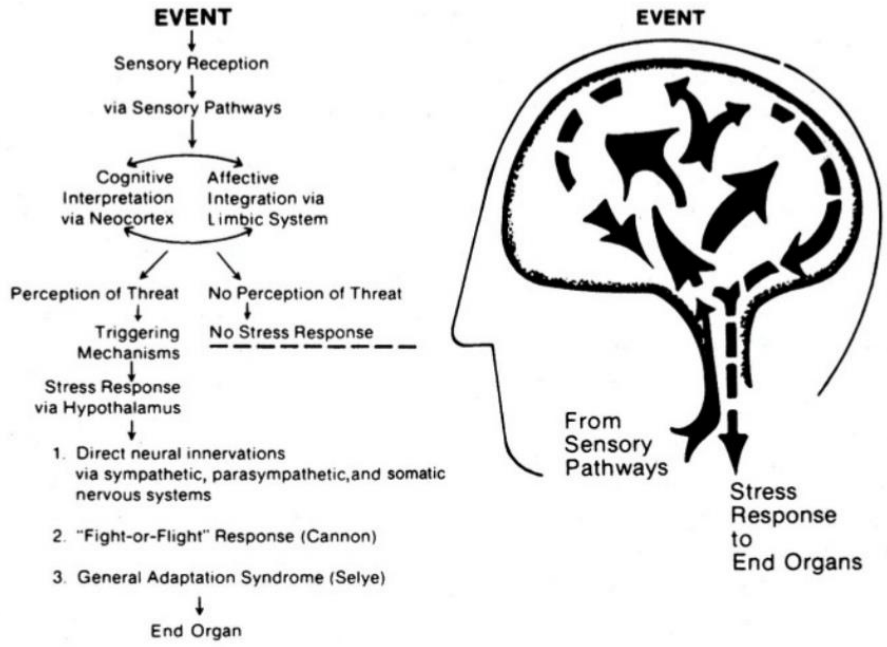

Figura 3 The stress response, considering Cannon and Selye's perspective.[13]

At the end of 1970, Schwartz presented his "dysregulation model" which is instead focused on the homeostasis phase. In this model, it is the disruption of the balance between different systems of the body that may lead the organs to pathology.

In 1972, Lachman proposed his "autonomic learning theory", according to which "the longer a given structure is involved in an ongoing emotional reaction pattern, the greater is the likelihood of it being involved in a psychosomatic disorder."[14] He believed that physiological reactions are learned patterns of emotional and autonomic responsiveness and their activity depend on both genetic and environmental factors.

Alternatively, Sternbach (1966) suggested a model that first considers "response stereotypy" or "predisposed response set" as a "tendency of an individual to exhibit characteristically similar patterns of psychophysiological reactivity to a variety of

[13] Everly, G. S., & Lating, J. M. (2002). A Clinical guide to the treatment of the human stress response, p.30

[14] Lachman, S. J. (1972). Psychosomatic Disorders: A Behavioristic Interpretation. https://ci.nii.ac.jp/ncid/BA13197477, pp. 69-70

stressful stimuli."[15] Even in this case, if the organ is involved in frequent activation of this response a disease can arise.

Finally, at Harvard University, Everly and Benson investigated the possible latent common denominator under the effects of chronic stress. They assumed, behind the stress response, a "limbic hypersensitivity phenomenon" (LHP) as the origin of the cascade of neurological, neuroendocrine, and endocrine mechanisms that can lead to somatic and psychiatric disorders called "disorders of arousal."

2.2 Biological pathways

An extremely prolonged stress response can affect a target-organ through three biological levels: the neural axes, the neuroendocrine axis, and the endocrine axes.

The neural component is the quicker that becomes activated in front of a stressor and is in turn constituted of three different axes: the sympathetic nervous system (SNS), the parasympathetic nervous system (PNS), and the neuromuscular nervous system (NNS). These systems allow the integration of the organism with its surrounding environment through neurons in three diverse ways: the SNS conducts the body to a state of excitation engaging resources during stressful situations, the PNS counteracts the SNS inhibiting the organism and preserving energies, and the NNS is essential for the motor output.

[15] Everly, G. S., & Lating, J. M. (2002). A Clinical guide to the treatment of the human stress response. In Springer eBooks. https://doi.org/10.1007/b100334, p.52

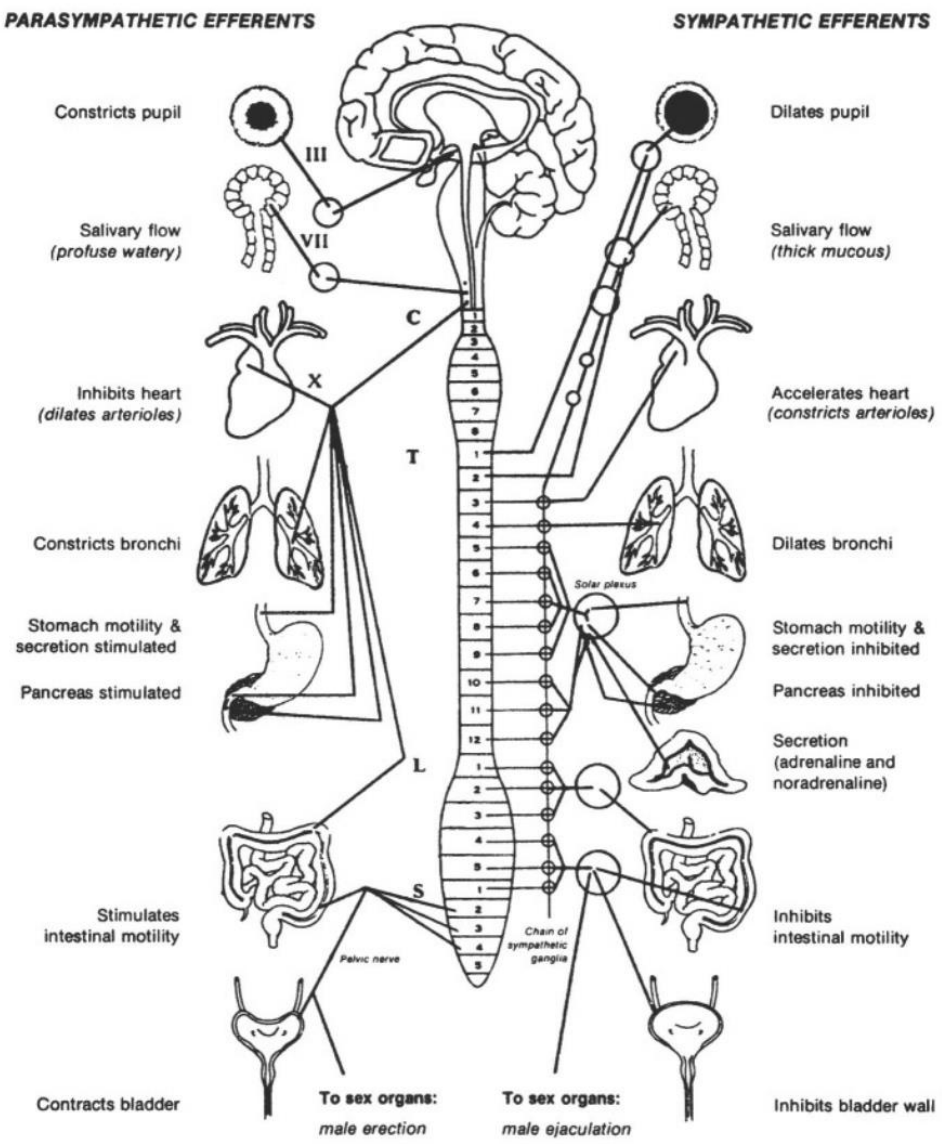

Figura 4 The two main division of the autonomic nervous system.[16]

When it is necessary to maintain a prolonged stress response, an additional physiological component must be added: the neuroendocrine axis. It is the organic substrate that operates behind the famous Cannon's "fight or flight response." This axis is called "sympathoadrenomedullary system" (SAM) and it is involved in the catecholaminogenesis. Adrenaline and noradrenaline are two kinds of

[16] Everly, G. S., & Lating, J. M. (2002). A Clinical guide to the treatment of the human stress response, p.22

catecholamines secreted by the adrenal medulla, a part of the adrenal gland. These types of monoamines can activate glucose and lipid metabolism, mobilizing the body's energies to increase the force of muscle contraction. In addition, they are responsible for the activation of the sympathetic nervous system.

Lastly, outcomes of endocrine axes represent the chronic somatic responses to stress. The most involved axis in threatening events is the hypothalamic–pituitary–adrenal (HPA). The outer part of adrenal gland or "adrenal cortex" releases corticosteroids, which are fat-soluble molecules that use cholesterol as a component. This allows them to pass across cell membranes and enter all the cells of the body to potentially influence every organ. Corticosteroids include glucocorticoids (GCs) such as cortisol, which have several functions for adaptation purposes: facilitation of catecholamine's action, stimulation of glucogenesis, suppression of the immune system and preparation for a subsequent stressor through appetite stimulation. The HPA activation is a slower system than the SAM but, on the other hand, it permits a more sustained response in stressful situations. Exaggerated exposures to GCs have toxic effects on the body but, fortunately, the HPA axis owns useful feedback mechanisms that can decrease the level of GCs through special receptors placed in the hippocampus.

Both cortisol and catecholamines are catabolic substances, which destroy other molecules to generate energy. Consequently, elevated levels of them may damage the organism, leading to a decrease of fat deposits, muscle mass and bone density.

Lovallo (2005), concerning the stress response, proposed a different view of the biological subdivision. He decided to use another kind of hierarchy to underline, for every level, the possible altered response tendencies. In Lovallo's model, the first

level is characterized by the interaction between the prefrontal cortex and the limbic system. It is indeed deputy to the integration of the emotional component and the cognitive processes, both necessary for the subjective mental representation of the threat. In this conceptualization, the hypothalamus and the brainstem are allocated in the second level and, finally, the third level is reserved for the peripheral tissues that determine the manifestation of the response.

To conclude, according to Lovallo's model, individual differences in the stress response may occur at any of the three levels, producing different pathological mechanisms.

2.3 The reactivity hypothesis

As has already been discussed, the stress response depends on both stressors and individual's characteristics. Subjective differences in responding to life's challenges may derive from genetic, developmental influences, and experience. The interactions between the factors that define a particular mode of react to the environment are well explained within the notion of "Reactivity Hypothesis." Every animal or human-being possesses its own reactivity and therefore some peculiarities in the cognitive-emotional component, in the neuroendocrine response, and in the peripheral organization of the body. The set of these features is usually measured through cardiovascular parameters.

In several studies researchers tried to understand how organisms respond to stress, observing cardiovascular reactions to acute psychological stress exposures. For decades different studies demonstrated that an exaggerated cardiovascular reactivity (CVR) may increase the risk of cardiovascular diseases, for example hypertension or

coronary heart disease. In 1974, Obrist collects in a single book entitled "Cardiovascular Psychophysiology" interesting evidence from different researchers that underlines the link between cardiovascular activity parameters and psychophysiological research. In this collection, Engel and Bleecker affirm that "hyperreactivity of the sympathetic nervous system may be a major factor in the elevation of blood pressures, as it is often associated with increased heart rate, high cardiac performance, and other related functions."[17] Thus, it is supposed that a prolonged high reactivity to stress may permanently change the structure and the functioning of the heart.

The association between the cardiovascular system and the stress axes is identifiable in the biologic role of catecholamines. Adrenaline and noradrenaline, secreted by the SAM axis, conduce to the sympathetic excitation of the body. The activation of the sympathetic system then causes the contraction of small arteries and veins, leading to a rise in the diastolic and systolic blood pressure.

The HPA axis also contributes through producing glucocorticoids, crucial substances for maintaining the circulatory system's normal response to catecholamines. For example, if glucocorticoid levels are low the response will decrease, the myocardial contraction force will weaken, and the blood pressure will be reduced. Consequentially, all these dysfunctional mechanisms may produce an endothelial injury, that can be an antecedent to arteriosclerosis and thrombotic disease. Furthermore, the release of hormones like vasopressin and oxytocin by the pituitary gland causes the contraction of the smooth muscles and the constriction of blood

[17] Engel B. T., Bleecker E. R. Application of Operant Conditioning Techniques to the Control of the Cardiac Arrhythmias in Obrist P. A. *Cardiovascular Psychophysiology*. Chicago: Aldine Publishing Company. 1974, p.452

vessel's walls. If this constriction is combined with the greater volume of blood, provoked by the effect of vasopressin on the kidneys, the result will be an increase of the blood pressure.

The cardiovascular system is therefore characterized by an elevated degree of flexibility, to consent continuous adjustments of the body in response to the surrounding environment. It can preserve the blood flow to vital organs during emergency situations and redistributes it to the tissues that need metabolic resources. This system exploits accurate mechanisms of regulation that indeed, in case of dysfunction, lead to "dysregulation diseases."

To summarize and clarify, mechanisms of regulation can be differentiated into local ones and remote ones. The local level includes all the homeostatic processes that are involved in the autoregulation of the blood flow. Instead, remote mechanisms are those neurogenic and neuroendocrine activities that also work for the stability of the homeostatic balance.

Gianaros (2008) investigated a specific homeostatic mechanism that constrains arterial pressure around a regulatory set-point, involving the amygdala. This part of the brain can adjust changes in blood pressure through a direct pathway that permits the control over the baroreflex, which regulates blood pressure as a response to the environment by calibrating heart rate, cardiac output, and vascular resistance. Gianaros's research team demonstrated that a greater MAP (mean arterial pressure) reactivity covaries with greater dorsal amygdala activation. This evidence suggests that the amygdala may be involved in the elaboration of behaviorally salient stimuli and in the control of visceromotor function, mediating atypical blood pressure reactions due to stressful situations. The present study is not the single Gianaros's

corroboration that explores the putative neural systems underlying elevated levels of CVR. In a previous work (2007) he had found interesting results concerning cingulate, prefrontal, insular and cerebellar areas of the brain, concluding that their activation may be considered as a functional neural phenotype of individuals that display an exaggerated cardiovascular reactivity to stress.

As a result, it is fundamental to specify that psychosocial events do not cause dysregulation diseases like hypertension by themselves. A stressful environment can obviously interact with other predispositions of the individual, such as genetic factors, coping strategies and personality traits. The next step is indeed to turn to the issue of the interaction that exists between external and personological factors, considering it as a probable cause of the onset of disease vulnerability.

CHAPTER 3

Biopsychosocial factors

3.1 Individual differences and cognitive appraisal

It became clear that an integrative approach is needed to investigate the regulation and implications of stress mechanisms. Social dimensions are crucial but their continuous co-action with the individual's dispositions should not be ignored. This clarification is the fundamental basis of the "Biopsychosocial model of challenge and threat" (BPS) proposed by Blascovich and Tomaka in 1996. According to the authors, it is the combination of two elements that determines to what extent an individual's experience is a threat or a challenge: personal resources and situational demands. A challenge is a positive experience that occurs when personal resources meet or exceed external demands. On the contrary, a threat arises when the demands outpace the resources, creating a potential source of maladaptive stress. Obviously, these categories must not be considered as dichotomic but as two parts of a single bipolar continuum.

The psychological component of the BPS model is linked to Lazarus's "Appraisal Theory." The main point of his thesis is that the cognitive appraisal of a stressful event can establish the consequent reaction of the individual to it and, as Lazarus asserted, "because cognitive appraisal rests on the individual's subjective interpretation of a transaction, it is phenomenological".[18] As a result, cognitive appraisal can be seen as a private mode of response that depends on the subjective representation of the environment.

[18] Lazarus R.S., Folkman S. Stress, appraisal and, coping. New York: Springer, 1984, p.46

Within the theoretical frame of BPS model both the perceptions of a challenge and threat should activate the SAM system, but it is believed that threat also results in a major involvement of the HPA axis. This exaggerated activation may than have a reverberation effect in all those physiological markers linked to the cardiovascular system: heart rate (HR), heart rate variability (HRV), blood pressure (BP), cardiac output (CO), total peripheral resistance (TPR), mean arterial pressure (MAP), vagal index (RMSSD), and ventricular contractility (VC). Specifically, HRV and RMSSD are recommended to understand the functioning of the autonomic nervous system and higher values in both parameters are recognized as features of a healthy organism.

In his work "Arousal and Physiological Toughness: Implications for Mental and Physical Health", Dienstbier (1989) furnished the methods to use biological and psychological markers to understand the concept of vulnerability and resilience. He introduced the term "toughness" to talk about individuals characterized by a fast onset and offset of the sympatho-adreno-medullary system activation. This mechanism may allow these individuals to appraise situations in a positive way because of their high personal resources compared to the external demands. It is clear that he is talking about the adaptative side of the stress response, which can be also called "resilience."

"In terms of the BPS, resilience to the potential stress of motivated performance should lead to evaluations of high resources and low demands, and thus challenge. In contrast,

vulnerability to this potential stress should lead to evaluations of low resources and high demands, and therefore threat."[19]

Resilience, as well as vulnerability, is a combination of genetic and environmental factors such as age, gender, and culture. These two kinds of reaction are widely studied in both animal and human models to improve the treatments and the prevention of physical and mental disorders.

Behavioral studies in rodents have demonstrated that environmental manipulations may produce even long-term consequences on stress vulnerability and resilience.

In a recent work Morais-Silva and colleagues (2019) corroborated the correlation between the development of mortality due to cardiovascular diseases and the onset of depression in a sample of Wistar rats. After the chronic exposure to the social defeat stress test, rodents were classified in resilient phenotype and vulnerable phenotype. The categorization was conducted observing alterations in the behavior during three other well-known stress tests: the social interaction test, the elevated plus maze, and the forced swim test. The interesting outcome was that susceptible animals showed harmful cardiovascular outcomes in both HRV and vagal tone (RMSSD). In addition, these physiological values were correlated with increased depressive-like behaviors, such as social avoidance or anhedonia. As a result, Morais-Silva's investigations suggest the importance of studying HRV and vagal tone to improve the prevention and the treatment of depression linked to stress autonomic activity.

[19] Seery M. D., Challenge or threat? Cardiovascular indexes of resilience and vulnerability to potential stress in humans. *Neuroscience and Biobehavioral Reviews* 2011; 1603-1610, p.1606

3.2 Personal factors

According to Lazarus, the perception of stress (or the "cognitive appraisal" of it) is not just a state of the organism but a process of transaction between the person and the environment. Considering stress as a simply external event may lead to ignoring all the individual differences that contribute to the reaction of the body. Varied factors have been investigated since this crucial assumption was made, but the scientific literature is rich in studies that concern two big areas of the psychology field: coping styles and personality traits.

3.2.1 Coping

One of the definitions of the verb "cope" in the Oxford English Dictionary is: "To manage, deal (competently) with, a situation or problem.[20]" It is one of the most common uses of the term since contemporary culture is quite obsessed with stress and how to cope with it.

Obrist conducted several research on the psychophysiology of coping, focusing on the interaction that exists between behavioral and cardiovascular processes. In 1975 and 1976 he underlined how the active type of coping can be an important sympathetic mediator of the cardiovascular system. Coping strategies can indeed be divided into two big groups: active coping and passive coping. The first one occurs when an individual tries to deal with a challenge, faces fears, participates in problem solving, and seeks social support. On the contrary, the second involves denial, avoidance of conflicts, suppression of emotions, and behavioral disengagement.

[20] cope, v.2 : Oxford English Dictionary (oed.com)

According to Obrist's investigation passive coping is regulated through vagal control, while active coping is related to the sympathetic system.

The habitual thought is that individuals can be categorized as good or bad copers, but the truth is that coping styles and strategies strongly depend on the context. In addition, the concept of coping is flexible even in the time domain: people continuously interact with external reality and, consequently, modify their behavior and beliefs through innate adaptation processes. As Aldwin pointed out: "Adaptative strategies are thus malleable – people can learn new skills, either in self or environmental management, that can allow to transcend difficult problems."[21]

Coping styles should not be seen as stable traits with a predictive value because this conceptualization may lead to underestimation of the nature of their complexity. It is important to consider that coping means both stability and change, through an approach that Lazarus and Folkman (1984) named "process-centered". How the researchers underlined, the definition of coping "must include efforts to manage stressful demands, regardless of outcome."[22] Coping is therefore a process that involves an effort and for this reason it must be distinguished from automatized adaptive behavior. Even if coping responses can indeed become automatized, not all adaptive processes should be recognized as coping mechanisms.

3.2.2 Personality

Appraisal and coping may in turn be influenced by personality. However, coping strategies and styles can also affect personality traits, within a mutual relationship.

[21] Aldwin, C. M. (2007). Stress, coping, and development: An integrative perspective, 2nd ed. The Guilford Press. https://psycnet.apa.org/record/2007-10765-000, p.93

[22] Lazarus, R. S., & Folkman, S. (1984). Stress, Appraisal, and Coping. New York, NY: Springer; New York Springer. https://ci.nii.ac.jp/naid/10015183136/, p.134

Personality is indeed a dynamic construct which is opposed to temperament. This latter term refers to the inherited behavior that is just determined by biological factors. Consequently, temperament is permanent and cannot be modified by external agents. On the contrary, the concept of personality involves influences of biological characteristics of the organism but even from the surrounding environment. Therefore, personality is not just related to innate behavior but also to emotions and cognition patterns.

Historically, studies concerning the relationship between personality and stress are centered on specific personality traits that seem to lead to predispositions for specific diseases. Current investigations are instead focused upon the consideration of the global personality structure. Such an approach tends not to give an exaggerated attention to specific traits and their association with specific diseases but tries to see each different personality style as a homogeneous aggregation of interacting forces that can produce vulnerability to stress. Despite the current research's orientation, for several years the role of single traits has been systematically investigated.

Eysenck's theory conceives personality as a set of varied traits based on psychometric analysis. The traits raised from the interaction between four main dimensions: introversion, extroversion, stability, and neuroticism. For many years researchers disagreed on which personality dimensions should be used to describe personality. However, to describe people systematically, more agreement has recently grown around the "Big Five" trait dimensions: neuroticism, agreeableness, openness, extraversion, and conscientiousness.

Neuroticism is a broad dimension of normal personality characterized by a quite stable tendency to experience chronic negative emotions. It depends on the inherited

functioning of the nervous system and neurotic people, compared to the stable ones, tend to react in a stronger way to stressful events. As MacCrae and Costa (1987) assessed in their validation of the Big-Five taxonomy: "Neuroticism appears to include not only negative affect, but also the disturbed thoughts and behaviors that accompany emotional distress."[23]

During the 20th century, more than neuroticism, the interest of researchers has been piqued by the dimension of hostility. This latter is a typical trait of a particular kind of personality: Type A. Rosenman and Friedman's theory concerns both personality types and how people respond to stress. The two cardiologists (1959) observed that people characterized by a Type A personality in high pressure environment work differently compared to those with a Type B personality. These latter were more relaxed, less competitive and found it easier to delegate responsibilities to others. On the contrary. Type A personality individuals are depicted as highly competitive and hostile, extremely alert, and thus more vulnerable to premature coronary heart diseases (CHD). CHD is used to refer to a group of syndromes that results from a narrowing of the arteries that supply blood to the heart, including angina pectoris and myocardial infarction. Between 1960 and 1961, Rosenman and Friedman initiated a big project to demonstrate how strongly Type A can be related to the CHD incidence. The study is known as "Western Collaborative Group Study" (WCGS) and it was a longitudinal and epidemiological investigation based on 3,524 men employed in ten California companies. After a follow-up of 8.5 years, the analyses showed that type A affected physical non-fatal manifestation of CHD. However, data from the second

[23] McCrae, R. R., & Costa, P. T. (1987). Validation of the five-factor model of personality across instruments and observers. Journal of Personality and Social Psychology, 52(1), 81–90. https://doi.org/10.1037/0022-3514.52.1.81, p.87

follow-up, after 22 years, did not result in a correlation between mortality due to CHD and Type A behavior. On the other hand, interestingly, it was discovered that other factors may influence CHD mortality and are, therefore, important to predict the risk of it. Age, parental risk of premature CHD, cigarette smoking, high cholesterol or triglycerides, and elevated systolic and diastolic blood pressure are still studied in conjunction with the pattern A of personality.

Since the first discoveries, many studies have been conducted and reviewed to understand better the constituents of coronary-prone-behavior. The Edinburgh Artery Study started in 1987 as prospective and longitudinal investigation on male and female Edinburgh residents aged from 55 to 74. The study's aim was to analyze the association between cardiovascular diseases and a specific trait of Type A personality: hostility. The authors found out that hostility may affect coronary risk in part because of the association with some dangerous behaviors, such as cigarette smoking and alcohol consumption. On the other hand, it must be considered that the association is bilateral and thus even risky behaviors can have an influence on hostility, reducing the ability to control anger.

Effectively, subsequent approaches to the study of Type A behavior are more focused on the putative foundation of this pattern of personality, speculating about the evidence that the need of control may represent a compensation caused by feelings of insecurity related to self-esteem (Price, Friedman and Ghandour; 1995). Furthermore, Watkins and colleagues (1992) had already supported the insecurity hypothesis, linking it to the possible consequences on the quality of interpersonal relationships. The Type A individual seems indeed to see others more as competitors than supporters.

The investigations around Type A and Type B personalities in the field of cardiovascular diseases related to stress have been carried out for a long time. However, in the last decades, studies that concern the Type D personality have reached greater agreement within the scientific community. This pattern of personality is characterized by increased levels of negative affectivity (NA) and social inhibition (SI). Negative affectivity can be described as a tendency to experience several negative emotions, such as feelings of dysphoria, anxiety, and irritability. Social inhibition refers instead to inhibition of the expression of emotions during social interactions, because of the constant fear of other's disfavor. O'Riordan and colleagues (2021) examinate if Type D personality is associated with cardiovascular reactivity to acute stress in a healthy sample of undergraduate students (n=173), considering both NA and SI components and their interaction. Participants were subjected to an arithmetic stressor from the Trier Social Test Task (TSST) and three different cardiovascular measures were observed: heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP). The research team found out that Type D personality is associated with a lower SBP reactivity just among women, hypothesizing that these gender gap on CVR to acute psychosocial stress can represent a different psychosomatic mechanism or differences in social norms that concern social inhibition and assertive behaviors.

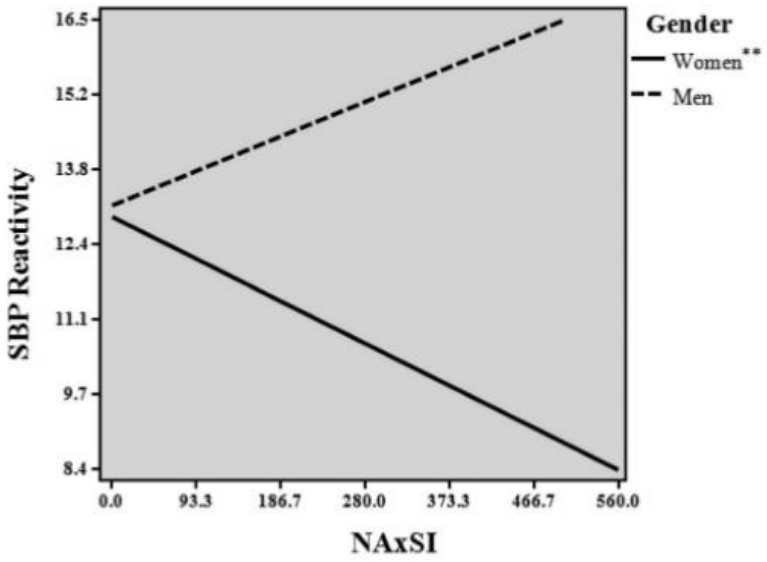

Figura 5 The association between Type D (NA × S I) and SBP reactivity.[24]

3.3 Social factors

The Biopsychosocial model of challenge and threat points out the weight that the environment can have on the adaptative balance that determines the stress response. Personality traits (with their specific dimensions) and coping strategies are involved in the biological mechanism that cause the reaction of an organism in front of a difficult situation. However, as various studies on evolution claimed, the result of the human being of today is mostly due to its particular social disposition.

Human behavior is indeed quite similar to the behavior of those animal species recognized as "domesticated". With these animals, human beings have paedomorphic traits and tameness in common. However, humans have not been domesticated by other species, therefore anthropologists speak of "self-domestication" as an adaptative trait selected during the long process of evolution of the species.

[24] O'Riordan, A., Howard, S., Keogh, T. M., & Gallagher, S. (2022). Type D personality is associated with lower cardiovascular reactivity to stress in women. Psychology & Health, p.12

Richard Wrangham in “The Goodness Paradox” (2019) analyzes self-domestication as a possible evolutionary advantage which allowed Homo Sapiens to prevaricate on Neanderthals. The docility due to a lower reactive aggressiveness, according to Wrangham, would therefore have led to the development of a greater sociality which then allowed Homo Sapiens a rapid evolution, through the ability to accumulate cultural adaptations. Thanks to domestication, the period of socialization is therefore prolonged, leading to a different maturation of the physiological stress systems. The response of the stress axes (HPA and SAM), and therefore the production of cortisol and catecholamines, decreases and, consequently, there is less activation of the fight or flight response. To conclude, Wrangham claims that the evolution of our species could have been allowed by a decisive element that characterizes every aspect of our life: sociality.

For this reason, it would be a sever error ignoring the large number of social factors that influence our response to stress. Epigenetic mechanisms can offer a plausible explanation of how individuals sharing similar genome may manifest even large differences in disease vulnerability. Epigenetics is a reversible system that contributes to understand the way in which life events provoke persistent modifications in the brain, representing evidence of the idea that environmental factors can have a strong effect on the magnitude of stress responsiveness. Moreover, these organism's changes have the power to be heritable without altering the DNA sequence itself. It happens because the transmission takes place above the level of the genetic code employing DNA methylation, several non-coding RNA mechanisms, and the modifications of histones. Specifically, histones modifications and DNA methylation have been the most studied underlying mechanisms related to stress and

to the HPA axis. Examinations of the hippocampus demonstrated the role of epigenetic mechanisms and their heritability, linking early life events (like childhood abuse) to the down, or up-regulation in the expression of the GR and on BDNF. As a result, epigenetic changes regard the expression of glucocorticoid receptors and persist across generations, producing significant differences in stress responsiveness and affective behaviors (Weaver et al 2004). The dysregulation of epigenetics has indeed been studied in stress-related psychopathological disorders, such as anxiety and depression.

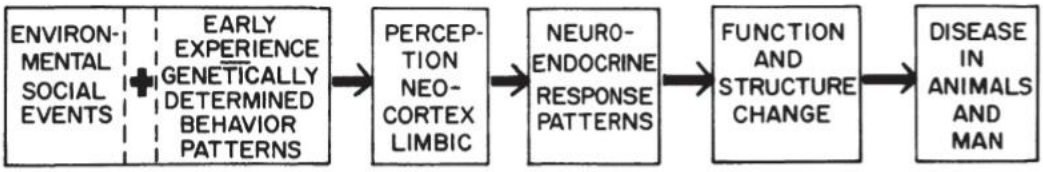

Figura 6 Representative scheme of the interaction between genetic and environmental factors that determine the onset of stress-related disease.[25]

3.3.1 Life events

As previously explained, an allostatic overload is the accumulation of chronic stress in the organism overload. It may be due to or even triggered by particularly painful events, but most of the time stress is caused by a combination of minor stressful life events. Even if the way to deal with stressful situations can be decisive in the response to stress, the surrounding environment exists and very often defines what we are and what we will become in the future. In the literature that regards coping with stress there is a well-known association between the number of life events that the individual can experience during a period and the following onset of stress-

[25] Henry, J., & Stephens, P. (2011). Stress, health, and the social environment: A Sociobiologic Approach to Medicine. Springer, p.17

related illness. In 1967 T. H. Holmes and R. H. Rahe created a statistical prediction model that examined the role of everyday stressful events and the consequential risk of illness. In the scale that the authors made, even minor variations in life, such as changes in responsibilities at work, are associated with a specific score which, added to other more or less serious events, can determine the arise of diseases. Therefore, for the consequences of stress to be evident, it is not necessary to face a bereavement: an allostatic overload can be reached even experiencing a micro-change that, in a specific moment of life, requires an amount of resources that the individual may not own.

In a study of K. Kershaw et al. (2014) it has been examined the associations of stressful life events (SLE) and social strain with the risk of developing coronary heart disease (CHD), considering several covariates, such as depressive symptoms, cigarette smoking, alcohol use and dietary quality. In the study, 93676 postmenopausal women between 50 and 79 years old had to fill out questionnaire related to SLE, social strain, medical history and demographic factors. Statistical results showed that higher levels of SLE and social strain were both associated with higher risk of CHD and stroke. As the authors claimed, "higher accumulation of stressful life events over 1-year period and social strain were both significantly associated with incident CHD and stroke independent of sociodemographic factors and depressive symptoms"[26].

[26]Kershaw, K. N., Brenes, G. A., Charles, L. E., Coday, M., Daviglus, M. L., Denburg, N. L., Kroenke, C. H., Safford, M. M., Savla, J., Tindle, H. A., Tinker, L. F., & Van Horn, L. (2014). Associations of stressful life events and social strain with incident cardiovascular disease in the Women's Health initiative. Journal of the American Heart Association, 3(3). https://doi.org/10.1161/jaha.113.000687, p.8

One of the factors that may determine the course of life events is the socioeconomic status (SES). A low SES can increase the number of stressors, creating adverse experiences and dangerous environments around the individual. McEwen (2017) reports that a low SES is effectively correlated with early cardiovascular diseases. In addition, the author highlighted that a low SES can be also associated with brain modifications, such as a smaller volume of the hippocampus or the reduction of the prefrontal cortical grey matter.

Life events associated with social stress and social status have been extensively studied in monkeys. Specifically, cynomolgus monkeys appears appropriate for the investigation of social consequences of stress, since they are characterized by elaborate patterns of positive social interaction and a well-defined social status is guaranteed by solid hierarchies, which identify dominant and subordinate members. In the animal world hierarchies represent the glue for the social group because, once formed, fights among members of the group occur less frequently. In this particular species, female use to remain with their group of birth and, on the other hand, males change their natal group during adolescence. This social dynamic involves the continuous reconstruction of hierarchies according to the new arrivals. As a result, the frequent social group instability predisposes cynomolgus monkey males to the arise of coronary atherosclerosis, due to the excessive activation of the SAM system. Kaplan et al. (1999) investigate the increment of the sympathoadrenal activation and of the cardiovascular diseases in male specimens of cynomolgus monkey through an experimental paradigm that used the manipulation of social hierarchies. Dominant males were forced to repeated challenges with strangers, developing more atherosclerosis than subordinates because of their tendency to maintain the social

control of the group. Studies on the social status of monkeys are often ducts in order to understand how human SES can impact our bodies and our stress mechanisms. However, the translation of results from monkeys to people is not always so linear. Even if primates represent the closest species to the human being, in fact social status in monkeys and social class in people are not stackable constructs.

With the aim of understanding the impact of social events in humans, mice and rats have also been used in various studies as they are species that are simple to manipulate and characterized by a high similarity to the human genome. As early as 1957 Richter described episodes of sudden death in wild Norway rats forced to swim, arguing that this phenomenon resulted from excessive vagal inhibition associated with acute emotional arousal. It was in fact a period in which the animal's perception of the environment, and in particular, of the social environment, began to be taken into consideration in the experimental paradigms. In 1964 Barnett reported the death of specimens of wild rats following their introduction as "intruders" in a cage of rats that already possessed a structured hierarchy with a dominant male. This kind of experimental manipulation is called “psychosocial stimulation”, and, in the case of Barnett's study, it drove the new subordinate intruder to his death within a few days, although the attacks of the dominant rat were not that lethal. A few years later, in the same way, Weber and Van der Walt (193) demonstrated the onset of cardiovascular disease in white rabbits forced into psychosocial interaction. Due to myocardial necrosis, ten of them died in the first week, ten more during the first month and the rest during the following months.

As already introduced in the first chapter, comparative studies on animals only followed the awareness that emerged in the early twentieth century regarding the

possible negative consequences of social stress on the organism. In “Psychosocial Medicine: A Study of the Sick Society” the epidemiologist Halliday (1949) described how dysfunctional social interactions can have an impact on health. For the author of the book, the main suspect of stress-related diseases was urban industrial life, characterized by less attunement to the rhythms of nature, such as the shift between day and night. Furthermore, the society of Halliday's time had lost the stratification of social classes that gave people the comfortable security of knowing their status and their place in the community.

For the epidemiologist these factors related to the construction of society represented the cause of the growth of cardiovascular pathologies. These cultural macro-changes are a natural example of a psychosocial stimulation that already affected society in Halliday's time. Many years later Cassel and Henry (1969) reviewed the epidemiology of hypertension from the psychosocial perspective, pointing out that not all cultural groups of the world show a relative increase in cardiovascular problems. In fact, there are populations in which the incidence is lower, if not rare. The authors were referring precisely to those cultural groups characterized by a stable society and a familiar environment that does not exceed the resources of the individuals.

3.3.2 Social support

Once the importance that social dynamics have always had in the history of humanity has been analyzed and understood, the need to study how these can be improved automatically arises to minimize the impact of social stress and, consequently, the onset and growth of illness. One of the most extensively studied social factors in the

research aimed at investigating the best way to cope with stress is social support. It has been related to lower cardiovascular disease mortality because it decreases the potentially deleterious effects of cardiovascular reactivity during chronic stress. This perspective is called “stress-buffering model of support” because support, as an essential psychosocial resource, acts like a “buffer” between the stressors and the disease outcomes. Studies indicate that individuals who receive higher levels of social support tend to experience reduced impacts or remain unaffected by negative life events. Supportive relationships enhance well-being by offering sources of intimacy, acceptance, and the opportunity to share emotions (emotional support), which in turn act as protective factors in the face of various life stressors. Additionally, supportive individuals may provide valuable counsel and guidance (informational support). Apparently, the effectiveness of support relies on the alignment between the demands of the stressor and the type of support received, emotional or informational. The mere presence of the support given is therefore not sufficient, what plays a fundamental role in the real minimization of stress is how the support is perceived by the subject based on the context that surrounds him and on his personal characteristics. For example, in a study conducted by Phillips and colleagues in 2009, it was discovered that women exhibited reduced cardiovascular reactivity when receiving emotional support from their male friends. Conversely, they experienced heightened reactivity when receiving emotional support from their female friends. It can be also a noteworthy variable the type of relationship that the person has with the supporter or the phase in which support is given. Effectively, a differentiation exists between the anterogatory phase (before seeking support) and the postrogatory phase (after deciding to seek support) in the support process.

According to Bolger and Amarel (2007), it has been contended that support received is more likely to be advantageous during the postrogatory phase, following the decision to seek support.

Consequently, loneliness can instead represent a risk factor and a worsening of the stress condition. In a recent study (Brown et al., 2021) loneliness has been linked to an atypical cardiovascular reactivity to stress and therefore possible negative health outcomes. The study aimed to investigate the connections between feelings of loneliness and cardiovascular stress responses, including blood pressure, heart rate (HR), cardiac output (CO), total peripheral resistance (TPR), and ejection time (EJT), in a group of elderly individuals during exposure to two standardized laboratory stress-inducing tasks: mental arithmetic and public speaking. Statistical results show that the main effect of loneliness on EJT was significant because higher loneliness predicts lower EJT. However, all the other cardiovascular parameters did not vary significantly. Moreover, age did not influence or impact the relationship between loneliness and cardiovascular reactivity.

Up to this point, most research on cardiovascular reactivity (CVR) has concentrated mainly on the receipt of social support, while giving social support has received comparatively little consideration. Nevertheless, a growing body of evidence indicates that providing social support also has health-protective benefits. Indeed, studies indicate that humans have an inherent inclination to nurture and show concern for others, potentially contributing to stress reduction. From a biological standpoint, providing support activates areas of the brain associated with reward processing while suppressing neural and physiological responses linked to threats. In a study of Gallagher et al. (2021) 82 healthy young adults were recruited to

understand how subjectively receiving or giving emotional or instrumental support influence CVR. The original 20-item 2-Way Social Support Scale (SSS) was developed to assess the subjective and multidimensional experience of support and measures of CVR were taken using a Finometer Pro hemodynamic cardiovascular monitor during a math task and a speech task. Research has shown that both providing and receiving emotional social support were linked to increased reactivity in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during the stress-inducing task. Specifically, individuals who reported giving more support to others or receiving more support from others exhibited higher cardiovascular reactivity (CVR) responses to the task. Hence, while previous studies have identified a stress-buffering impact of social support, where it reduces cardiovascular reactivity (CVR) responses, this particular study noted an elevation in CVR for both systolic blood pressure (SBP) and diastolic blood pressure (DBP).

It is important to highlight that not every study uncovers a buffering effect of social support on cardiovascular reactivity (CVR). Instead, as seen in this study, some research shows that various forms of support, including real-life social support, can be linked to heightened CVR reactivity. Additionally, it has been proposed that social support can encourage individuals to engage with stressors actively and aid in active coping. For instance, active stressors, such as public speaking or math tasks, are situations where individuals can potentially influence the outcome, in contrast to passive stressors.

Another variable that researchers have examined in the context of the connection between cardiovascular reactivity and social support is attachment. Attachment refers to the enduring emotional connection between individuals, as elucidated by

Ainsworth in 1979 and Bowlby in 1969. Although attachment theory traditionally centers on childhood, the significance of attachment in adulthood has also gained recognition. In a manner reminiscent of how children seek security from their primary caregivers during moments of fear, uncertainty, or illness, adults similarly turn to their attachment figures in times of stress. Individuals with secure attachment bonds (those who possess confidence in the support of others and are open to depending on them) report a heightened perception of the availability of social support. Conversely, individuals with insecure attachment bonds fall into two categories: those with anxious attachment (characterized by a strong desire for intimacy and a fear of rejection) and those with avoidant attachment (who feel discomfort with closeness and intimacy due to a fear of emotional harm). Individuals with these insecure attachments tend to perceive lower levels of social support.

McMahon et al. (2019) investigated the way individuals perceived the accessibility of support and how subsequently this perception shapes their reactions to stress, expecting to register an influence of attachment on CVR. The group of participants consisted of 138 young adults with no diagnosis of cardiovascular or immune system disorders. The results indicate that both anxious and avoidant attachment styles were linked to reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) stress responses. Therefore, both kinds of insecure attachment were associated with lower reactivity or "blunted reactivity" which, as higher reactivity, is also associated with various adverse health consequences. As anticipated, the relationship between unhealthy outcomes and social support is mediated by the perception of affectionate support that derives from the attachment style. In simpler terms, support might not

act as an all-encompassing safeguard for health, particularly for individuals who lack strong and meaningful attachment bonds with others.

To conclude, recently social support has also been associated with the emotional dimension of gratitude. Gratitude can in fact co-occur with social support, influencing cardiovascular reactivity as a variable with an independent effect. Some studies, however, investigate the mediating role that gratitude can have in the relationship between CVR and social support. As a trait, gratitude is defined as a comprehensive inherent inclination to recognize and value the positive aspects of life. Viewed as an essential mechanism for interpreting everyday experiences in a positive light, expressing gratitude in response to life's circumstances, as well as social support, can serve as a protective buffer against the adverse impacts of stress. Additionally, research by Frinking et al. in 2020 has shown that gratitude not only diminishes feelings of social isolation but also strengthens social connections. Therefore, it is plausible that gratitude exerts its influence on cardiovascular reactivity (CVR) through its impact on social support, a factor already recognized for its significant associations with CVR. Gratitude serves as a mediator because it is inherently a social emotion, and such emotional experiences facilitate our connections with others. Consequently, gratitude has the potential to heighten our perceptions of social support. Hence, several studies investigate the combined influence of the two variables on the cardiovascular system under conditions of stress. Gallagher et al. (2021) highlighted that both gratitude and perceived support were indeed linked to certain aspects of cardiovascular reactivity (CVR).

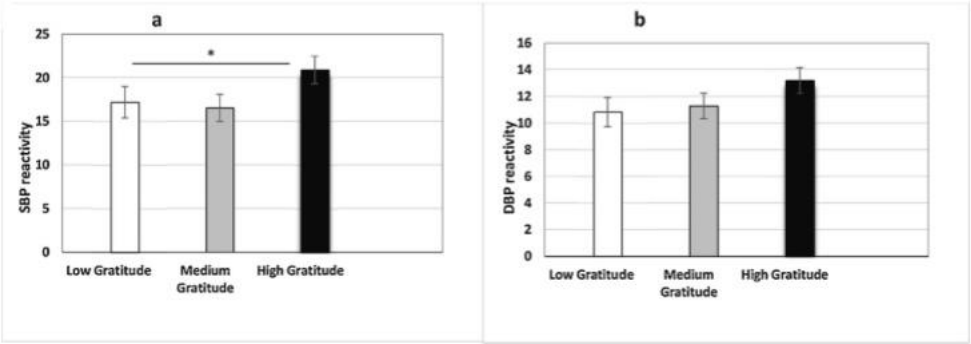

Figura 7 The graphics portray the relationships between one's inherent level of gratitude and their reactivity in systolic blood pressure (SBP) during the math task (1a), as well as diastolic blood pressure (DBP) reactivity (1b). These associations are explored while taking into account potential confounding factors, including PASAT scores.[27]

However, contrary to the stress-buffering hypothesis, both constructs exhibited positive associations with CVR. Using a mathematical task as a stressor, it was discovered that trait gratitude heightened total peripheral resistance (TPR) responses during acute psychological stress, and social support emerged as a mediator in this connection. Individuals reporting greater levels of gratitude and perceived social support, particularly in terms of emotional support, displayed elevated TPR reactivity when confronted with the mental arithmetic task. Despite these unexpected results, the relationship between gratitude, social support, and cardiovascular reactivity could be interpreted in the context of an alternative theoretical framework: the circumplex model of emotion (Pressman and Cohen, 2005). In accordance with this model, activated emotions such as excitement and joy tend to correlate with heightened heart rate (HR) and blood pressure (BP), whereas low-activation emotions like pleasantness are linked to a reduction in cardiovascular response. Given that the study utilized a trait-based measure of gratitude, it is plausible that trait gratitude is

[27] Gallagher, S., Howard, S., Ginty, A. T., & Whittaker, A. C. (2021). Gratitude, social support and cardiovascular reactivity to acute psychological stress. Biological Psychology, 162, p.5

closely associated with emotions like joy, which falls within the category of activated emotions linked to increased cardiovascular reactivity (CVR) measures. This connection might help explain the positive associations observed between trait gratitude and TPR in the study. Another plausible explanation could be rooted in the idea that social support may enable individuals to better engage with stressors and enhance their active coping strategies. In this context, social support might have contributed to heightened cardiovascular reactivity (CVR) as individuals with greater social support networks could potentially confront stressors more effectively, leading to increased physiological responses during challenging tasks. In a previous study by Gallagher et al. (2020), researchers focused also on the state gratitude dimension. At the trait level, gratitude is typically measured by evaluating individual variations in the frequency with which individuals experience gratitude as an emotion in their daily lives. On the other hand, at the state level, gratitude is perceived as the sensation of being thankful and appreciative for favors or kindness received from others. State gratitude was assessed using the 3-item Gratitude Adjective Checklist (GAC), a Likert scale comprising three adjectives: 'Grateful,' 'Thankful,' and 'Appreciative.' Participants were instructed to indicate the degree to which they had experienced these emotions over the past week by providing ratings on the scale. To recap the study's findings, it was determined that there existed a negative link between systolic blood pressure (SBP) reactivity and state gratitude. In other words, individuals who expressed higher levels of gratitude, thankfulness, and appreciation during the week of testing demonstrated reduced SBP reactivity when confronted with the stressor. It can be concluded that non-permanent feelings of gratitude have

the potential to act as a buffer, mitigating the adverse impacts of stress on cardiovascular responses during acute stressors.

CHAPTER 4

Religiosity, spirituality, social support & CVR

4.1 SASHLab

SASH is the acronym for "Study of Anxiety, Stress and Health" and it actually represents a cluster of researchers based at the University of Limerick's Department of Psychology. The aim of the group is to investigate the impact of stress on human health encompasses various aspects, ranging from its physiological mechanisms, such as hormonal and biological responses, to identifying the demographic groups most susceptible to its consequences and the factors rendering them susceptible. These factors may include personality traits, prolonged exposure to stressors, and feelings of isolation and distress. Stress is thoroughly investigated using a combination of laboratory and non-laboratory research methods, as it is recognized as a pervasive factor of the twenty-first century with far-reaching consequences for both mental and physical health. Consequently, comprehending the diverse ways in which it can be detrimental provides valuable insights for shaping the development of interventions aimed at alleviating its adverse effects on health and well-being. Within the laboratory, there are two separate but interconnected testing suites designed specifically for conducting cardiovascular stress reactivity studies. These suites are fully equipped with advanced cardiovascular monitoring devices, precise height and weight measurement scales, and access to a comprehensive library of psychometric measurements. Additionally, the facility includes a fully-equipped wet-lab that serves the purpose of conducting immunological and hormonal measurements.

Multiple projects are concurrently in progress, enabling the attainment of diverse outcomes, all of which fall under the overarching umbrella of psychobiology and psychophysiology of stress. Factors such as attachment, social support, caregiving, gratitude, personality traits and life events are therefore investigated separately. The final aim, however, is to achieve a multidisciplinary communication that can allow researchers to achieve more significant results, looking from afar at the general picture of the largest project called, precisely, "SASHLab".

4.2 Religiosity and spirituality on CVR

“Religiosity, spirituality, social support & CVR” is an ongoing study whose procedures are carried out in the psychophysiology laboratories of the Psychology Department at the University of Limerick.

In recent years, the impact that social support can have on cardiovascular reactivity has been widely studied in several research that are part of the larger project called “SASHLab” (Gallagher, 2021; McMahon, 2019; Brown 2021). However, the promotion of social support could also be considered one of the mechanisms that links the spiritual dimension to the individual's health. Therefore, based on less recent studies (Edmondson, 2005), SASHLab members wondered whether spirituality and religiosity could actually play a role in determining the cardiovascular response to stress and, consequently, a different impact on physical health. To begin with, it's important to establish a conceptual differentiation between spirituality and religiosity. Spirituality pertains to an individual's inclination towards the profound and transcendent aspects of existence. On the other hand, religiosity represents an outward expression of spiritual encounters, which may occasionally

encompass a communal setting where people collectively embrace beliefs and rituals. Many people find meaning, purpose, and a sense of connection to something greater than themselves through spiritual exploration, even if they do not identify with any particular religious tradition. Hence, it is plausible to possess spirituality without embracing any religious affiliation.

Due to these fundamental theoretical distinctions, the Spiritual Well-being Scale (SWBS) encompasses two distinct subscales: the existential (EWB) and the religious components (RWB). In a laboratory study conducted by Lawler and Younger in 2002, it was discovered that adults' scores on the religious subscale of the Spiritual Well-being Scale (developed by Paloutzian & Ellison in 1982) could predict mean diastolic and mean arterial pressure levels during a betrayal interview and rest periods. Furthermore, the existential subscale exhibited a negative correlation with stress levels, physical symptoms of illness, and medication use. These findings suggest that spirituality and/or religion may indeed influence the extent of stress and its associated effects on health. Edmondson et al. (2005) instead used the following questionnaires relating to well-being and spirituality to understand how significant differences in these areas can impact blood pressure: The Spiritual Well-being Scale (SWBS), The Satisfaction with Life Scale (SWLS), The Cohen-Hoberman Physical Symptoms Checklist (CHIPS) and The Acts of Forgiveness Scale. As a result, all the spirituality scales from the SWBS shown associations with lower level of perceived stress and higher life satisfaction. Moreover, the existential subscale of SWBS (EWB) was associated with a reduced occurrence of physical health symptoms, and it was also predictive of lower medication usage. On the other hand, the religious subscale of SWBS (RWB) was associated with lower SBP. Consequently, both religiosity and

existential factors, made distinct and independent contributions to the prediction of physical health symptoms but existential factors may have a more prominent influence on overall subjective well-being compared to religiosity. Furthermore, forgiveness was linked to one's sense of spirituality and greater levels of forgiveness were indicative of reduced medication usage. Forgiveness towards oneself and others is in fact an aspect of spirituality that could be implicated in the ability to adequately deal with stress, thus contributing to maintaining a better state of health (Worthington et al., 2007).

However, it's important to acknowledge that the limitations of Edmondson's study include the exclusive inclusion of women as participants, which may constrain the broader applicability of our findings. Additionally, since the participants were college students, it's possible that their religious well-being is still in a phase of developmental maturity, which could impact the generalizability of the results.

Summing up, it is possible that a well-structured religious or spiritual belief system can represent an effective coping strategy in dealing with stress and anxiety, contributing to the development of personal resilience (Seery, 2011). Moreover, having a strong faith could in fact provide the illusion of control in those unpredictable and uncontrollable situations which often, if prolonged, contribute to an inadequate stress response, damaging the organism.

4.2.1 Method

In the current SASHLab's study about spirituality and religiosity effects on CVR, students of Limerick's University are recruited to attend a 60-minutes testing session at the health and psychophysiology laboratory of the Department of Psychology.

To mitigate the influence of potential variables that could distort the results, participants abstained from consuming alcohol and engaging in strenuous exercise for a minimum of 12 hours before the study. Additionally, they refrained from consuming caffeine, using nicotine, and eating any food for at least 2 hours and 1 hour, respectively, prior to their participation. Furthermore, they are asked to report the possible presence of cardiovascular pathologies.

The Paced Auditory Serial Addition Test (PASAT), as introduced by Gronwall in 1977, serves as the stress task. This task has been utilized in laboratory-based studies and has proven effective in eliciting cardiovascular responses (Gallagher et al., 2014; Phillips et al., 2009). During the task, participants listen to a 5-minute audio track in which single-digit numbers are read aloud via a computer. Participants must listen carefully and, for each number, add it to the previous one and vocalize the answer. The numbers are presented at a rate of 2.4 seconds per digit during the initial minute, with the presentation speed increasing by 4 seconds for each subsequent minute. Throughout the entire procedure, a Finometer Pro hemodynamic cardiovascular monitor from Finapres Medical Systems BV, located in Arnhem, The Netherlands, was employed to collect data on SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), HR (Heart Rate), CO (Cardiac Output), and TPR (Total Peripheral Resistance). This monitor provides continuous, non-invasive measurements on a beat-to-beat basis and adheres to the validation criteria established by the Association for the Advancement of Medical Instrumentation. It has also been utilized in numerous similar studies (O'Riordan et al., 2019).

Upon arriving at a health laboratory, participants provide informed consent. Their height and weight get documented. Once seated, the Finometer cuff gets applied to

the participants' nondominant hand. They receive instructions to use their free hand for all tasks and are requested to minimize foot movement and speak only when necessary. Participants furnish sociodemographic information and respond to questionnaires related to the variables under investigation by completing a questionnaire booklet. After a 20-minute acclimatization period, baseline measurements are taken for 10 minutes. Subsequently, participants complete a pre-task questionnaire before commencing the stress tasks. The experimenter turns off the main lights in the laboratory, leaving participants illuminated solely by a table lamp. Additionally, the experimenter dons a white laboratory coat throughout the entire experimental process and directs participants to speak aloud while they complete the stress tasks. These conditions were intentionally established to create a psychological divide between the experimenter and the participant, thereby heightening stress conditions. After the stress task, the main lights are switched back on, and participants proceed to complete the post-task questionnaire. After a recovery interval of 8 minutes, the stress task is repeated accompanied by pre- and post-stress task questionnaires. Once the second stress task is finished, cardiovascular monitoring concludes, and participants receive a debriefing. The stress task measurements involve asking participants to rate how stressed they anticipated the stress task would be (pre-task measure) and how stressed they found it to be (post-task measure). Participants assessed their expected and perceived stress levels using a 7-point Likert scale that ranged from 0 (not at all stressful) to 6 (extremely stressful). These items were included to assess whether the stress task was perceived as psychologically stressful.

Measures of spirituality and religiosity are instead taken during the acclimatization and the baseline period through the following questionnaires: Beliefs and Values Scale (Kings et al., 2006); The Bried RCOPE (Pargament et al., 2011); The Centrality of Religiosity Scale (Huber & Huber, 2012).

The Belief and Values Scale is a 20-item questionnaire known for its strong test-retest and internal reliability. This scale is designed to assess spirituality from a wide-ranging perspective that encompasses both religious and non-religious viewpoints.

The Brief RCOPE is a 14-item assessment tool designed to gauge how individuals use religious coping mechanisms when facing significant life stressors. As one of the most frequently utilized measures of religious coping in academic literature, it has played a pivotal role in advancing our understanding of the functions of religion in managing crises, traumatic events, and life transitions.

The Centrality of Religiosity Scale (CRS) is a tool used to assess the centrality, significance, or prominence of religious meanings within an individual's personality. It quantifies the overall intensities of five distinct core dimensions of religiosity that have been theoretically defined. These dimensions encompass public practice, private practice, religious experiences, ideology, and intellectual aspects. Together, they provide a comprehensive representation of an individual's religious life.

To conclude, other dimensions that can be easily related to spirituality and religiosity were taken into consideration through further questionnaires: The Ten Personality Inventory, The Hospital Anxiety and Depression Scale, NIH Toolbox Adult Social Relationship Scales (for social support), The DS14 (for Type D personality), The The UCLA Three-Item Loneliness Scale and The Preference for Solitude Scale

CHAPTER 5

Blunted reactivity

5.1 Mid-range CVR

During this systematic review, the mechanisms underlying the stress response were investigated, highlighting the correlation between high levels of cardiovascular reactivity and the possible onset of cardiovascular pathologies. Obrist's CVR hypothesis (1981) has in fact dominated scientific literature and research purposes for a long time, thus leading to the natural and automatic assumption that, instead, low cardiovascular reactivity can be healthy for the organism.

On the contrary, several recent studies have shown that low cardiovascular reactivity to stress can lead to serious negative health consequences. Low reactivity cannot only be associated with personality traits that, as previous seen, are characterized by a plausible vulnerability for the maladaptive response to stress (Type D and neuroticism), but it is also related to the development of addictions, to obesity and to depression. Researchers use the term 'blunted cardiovascular reactivity' to describe this observable cardiovascular response pattern that is notably lower than what is observed during normal states of physiological balance when encountering stress.

Furthermore, as already pointed out, it is important to remember that an exaggerated response to stress is not always maladaptive, since the different animal species possess it primarily to implement the adaptive response of fight or flight during dangerous situations.

Hence, it appears that both extremes are disadvantageous for the body, indicating that the most optimal and healthy response to stress lies in a moderate reaction

(Hughes et al., 2018). For this reason, the association between stress reactivity and health is recognized as an inverted U-shaped curve rather than a linear one.

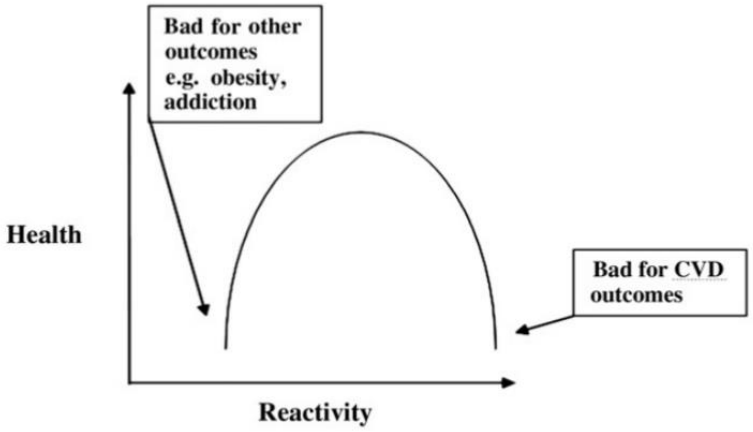

Figura 8 The model that connect low and high reactivity and their different health outcomes.[28]

5.2 Theories and causes of blunted reactivity

The exact mechanism that underlies blunted reactivity is still unclear and a topic of further research. For this reason, the theoretical bases concerning it need to be investigated more.

One of the possible hypotheses claims that it is the participant's lower effort during the stressful task that causes the blunted response to manifest. According to this point of view, therefore, it would not be a cognitive or biological factor but a behavioral one, which could be attributed to the characteristics of the participant in relation to that specific task or to the task itself.

The thesis that takes the cognitive side more into consideration states that blunted reactivity derives from a tendency to process dangerous stimuli as not worrying. This

[28] Phillips, A. C., Ginty, A. T., & Hughes, B. M. (2013). The other side of the coin: Blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. International Journal of Psychophysiology, 90(1), 1–7, p.4

is therefore a purely perceptive theory, which calls into question the individual's attention and its vigilance mechanisms.

Finally, the third hypothesis rejects the behavioral and cognitive explanation, arguing that it is instead a disengagement of biological systems that causes lower reactivity. According to this perspective, due to pathologies such obesity and depression, the sympathetic nervous system shows high levels of activity and increased plasma noradrenaline concentrations.

Moreover, there is also a theory that mixes the reduced level of effort and motivation of the individual with his biological correlates. In fact, it could happen that certain subjects may present lower motivation due to a lower activation of those areas of the brain that process the reward, such as the mid-cingulate cortex.

Once the different theories have been taken into consideration, it is interesting to investigate what the causes that lead to a condition of blunted cardiovascular reactivity are. On the one hand, the literature on early life stress such as maternal separation can fuel the belief that low reactivity to stress is caused by prior psychological or physiological factors. Lovallo et al. (2012) demonstrated that adults who underwent significant adverse life events during childhood exhibit reduced heart rate and cortisol responses when facing stress during mental arithmetic and public speaking tasks. On the other hand, it is always fundamental to consider stress response mechanisms as the result of the evolution of species and adaptation to their environments. Therefore, since blunted reactivity has been associated with dysfunctional mechanisms such as anxiety and depression, the best adaptive response appears to be, as previously argued, the one characterized by a mid-range intensity.

5.3 Experimental evidence and future directions

The lines of research that, in recent years, have investigated blunted cardiovascular reactivity have moved into different areas.

First of all, one area of research concerns individual differences related to personality that could contribute to the emergence of lower cardiovascular reactivity during stressful situations. Bibbey and colleagues (2013) investigate the relationship between key personality traits from the Big Five taxonomy and both cortisol and cardiovascular reactions to acute psychological stress. The research team administered to 2414 participants three different stress tasks: the Stroop task, the mirror tracing, and the speech task. Saliva samples for cortisol and continuous blood pressure and heart rate values were taken and examinated. Results showed how individuals with a higher neuroticism score showed smaller cortisol and cardiovascular stress reactions, as well as people with lower agreeableness and openness. As the authors concluded "neurotic individuals will experience maladaptive psychological states, high subjective stress and low feelings of control, each time they encounter acute stress."[29]

In a further study, Gallagher et al. (2018), examined the potential interplay between stress resulting from life events and an individual's personality when forecasting cardiovascular stress reactions. In this research, 184 university students without serious health implications were subjected to an arithmetic stress task (PASAT), under continuous recording of cardiovascular parameters using the Finometer Pro hemodynamic cardiovascular monitor. Additionally, participants were administered The 36-item Life Events for Students Scale (LESS; Linden, 1984) and The 10-item

[29] Bibbey, A., Carroll, D., Roseboom, T. J., Phillips, A. C., & De Rooij, S. R. (2013). Personality and physiological reactions to acute psychological stress. International Journal of Psychophysiology, 90(1), 28–36, p.33

Personality Inventory (TIPI; Gosling et al., 2003). Measurements relating to body mass index (BMI) were also considered in the data analysis. A moderation by the "openness" dimension of personality emerged in the negative association between life event stress and blood pressure (both systolic and diastolic). Instead, the "conscientiousness" dimension would appear to moderate the significant negative association between life event stress and TPR (total peripheral resistance). Therefore, in this model stressful life events are associated with lower cardiovascular reactivity, which is seen not so much as a cause of disease but as a characteristic linked to specific personality traits. This underlines the importance of the perception of stress (stress appraisal) in the way the individual responds to it.

Much of the research on blunted reactivity instead focuses on its possible health consequences. Several studies outlined the association between a lower reactivity and the following factors: obesity, depression and addictive behaviors. Hence, it is conceivable that low reactivity serves as an indicator of the presence of other non-cardiovascular comorbidities and disease processes, which are likewise linked to various disparities in neurological activity.

A significant portion of these data originates from the West of Scotland Twenty-07 study, initiated in 1986 with the aim of examining the health status of 4,510 individuals over a span of 20 years. This study delves into various socio-economic factors, including age, gender, socio-economic status, ethnic background, and family structure, to assess their influence on overall health.

In the context of obesity as a risk factor related to blunted reactivity, Carroll et al. (2008) emphasized a noteworthy negative correlation between body mass index and heart rate. Importantly, this association was observed independently of other

variables such as age, gender, employment status, depression, or any addictive behaviors. This study contradicted a prevailing line of research that posited a positive connection between abdominal adiposity and cardiovascular reactivity, which was thought to lead to the emergence of cardiovascular issues. As well as obesity, depression has been taken into account basing on data from The West of Scotland Twenty-07 study (Carroll et al. 2007). Even in this particular instance, significant negative associations were observed between depression and reactivity, both in terms of systolic blood pressure (SBP) and heart rate (HR). Furthermore, those individuals who displayed lower reactivity were more likely to show an increased depression score five years later, as demonstrated in the study conducted by Phillips et al. in 2010.

The third most explored domain concerning adverse health outcomes associated with blunted reactivity is addiction. Research has shown that both cardiovascular and cortisol hypo-responsiveness can predict relapse among individuals who have recently quit smoking, as demonstrated by studies like al'Absi in 2006. Additionally, individuals addicted to alcohol have been found to exhibit diminished cardiovascular and cortisol stress responses, as indicated in studies conducted by Lovallo et al. in 2000.

Moreover, it's not limited to substance addictions; blunted cardiovascular reactivity appears to correlate with other behaviors. For example, women with exercise-dependent habits, identified through a questionnaire on exercise behaviors, displayed reduced cardiac and cortisol responses when exposed to a mental arithmetic stress task, as shown in the study by Heaney et al. in 2011.

One potential explanation for these correlations can be found at the neurobiological level, involving a malfunction in the amygdala. As proposed by Lovallo in 2007, a deficient amygdala response to environmental challenges, leading to altered amygdala-prefrontal signaling, may contribute to risk-taking behavior. The amygdala plays a pivotal role in signaling the presence of danger and in orchestrating a normal stress response, including the release of cortisol and sympathetic activation, to support fight-or-flight reactions. Individuals with an impaired amygdala response are more inclined to seek out situations that others perceive as dangerous and prioritize immediate pleasure over long-term planning. This model aligns with behaviors like excessive alcohol consumption, recreational drug use, and the overconsumption of high-calorie foods.

However, although the findings in this field are growing, it is becoming evident that the mechanisms through which low reactivity appears to be associated with various negative health outcomes and diseases remain unclear and may differ among individuals. It's equally significant to acknowledge that it's not just negative psychological and behavioral traits that are linked to blunted or diminished stress responses. As previously discussed, several studies have demonstrated that positive psychological characteristics, concerning self-esteem and affective well-being, are also connected to reduced responses to stress.

In summary, numerous psychological and behavioral variables, including depression, obesity, early life adversity, personality, and addictions, have been explored in relation to stress blunted reactivity. It is possible that physiological blunted responses are expressed through specific behaviors or personality traits but to comprehensively grasp the connections between reactivity and health, it's crucial to consider a

multitude of factors, thereby achieving a more comprehensive understanding of gene-environment interactions.

For future directions it may be premature to suggest the use of cardiovascular stress reactivity as an absolutist clinical biomarker. However, delving deeper into these complex associations will provide valuable insights into the pathways leading to risky health behaviors and subsequent poor health outcomes. This understanding may certainly offer a good potential for health investigation and early intervention.

CONCLUSION

In this five-chapter investigation, the primary aim was to unravel the intricate web of variables that continually shape our response to stress.

Firstly, through a meticulous analysis of scientific literature, it has been assessed the necessity of a more functional conceptualization of stress. This theoretical framework has than compelled the discussion to move away from the one-sided, negative view of stress and instead embrace its adaptive side. Stress should be indeed recognized as a process that mobilizes energies throughout the entire organism when a threat appears, although it can have the potential to lead to negative consequences when too prolonged.

Furthermore, it has been delved into the intricate interplay of various factors that influence an individual's response to stress. These factors often interact in complex ways, emphasizing the need for a comprehensive model that incorporates both genetic and environmental elements within a unified system called “epigenetic”. These inseparable components jointly govern the unique cardiovascular reactivity to stress (CVR) experienced by each individual. Within this second framework, it has been explored how personality traits, coping strategies, social support, and spirituality influence stress responses and their potential impact on subsequent adverse health outcomes.

The central focus of this review remained firmly, from begin to end, on cardiovascular reactivity to stress, to better understand its association with the mentioned above variables and its implications for the onset of cardiovascular pathologies.

What emerges from the systematic review is that for many years, researchers have observed the impact of an high CVR on the cardiovascular system. However, following the examination of how various genetic and environmental factors may or may not correlate with CVR, a new field of study has been considered: blunted cardiovascular reactivity. This recent perspective recognizes that not only excessive cardiac reactivity can be detrimental to the organism but also an excessively low reactivity. Blunted reactivity has indeed shown association with diagnosis, such as depression, addiction and obesity, that are far from the conventionally studied cardiovascular field.

This recent revelation holds the potential to provide invaluable insights into how we can identify and mitigate the adverse health consequences of stress, ultimately safeguarding the well-being of global population.

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