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Neural Correlates of Heart Rate Variability: Threat and Safety Perception

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Abstract

The connection between the heart and the brain was coined 150 years ago by Claude Bernard and has since then been an interesting topic of research. Scientists have for many years searched for biomarkers of stress and health to map the current status of the organism. Heart rate variability (HRV) has been presented as an emerging objective and promising marker to achieve just this. HRV refers to the beat-to-beat variations in heart rate (HR) and is thought to be a useful signal in understanding and providing valuable information of the autonomic nervous system (ANS). HRV has also been proposed as a marker of stress and health by sharing neural correlates and functions with several executive functions. This thesis identified several regions, including the ventromedial prefrontal cortex and the amygdala, in which significant associations across several studies were found between threat and safety perception, emotional regulation and HRV. This suggest that HRV may function as an index of the brain mechanism and structures that guide and govern adaptive functions and thus, provide researchers with valuable information regarding the stress and health of an organism. Two major theoretical frameworks, which articulate and explain the role of HRV as an indicator of individuals ability to adapt to environmental changes and cope under stress is presented. HRV can also be used in practice in several ways and a growing and promising field of application is HRV biofeedback.

Keywords: heart rate variability, threat and safety perception, stress, neural correlates, heart-brain connection, cognitive neuroscience

Table of Contents

1. Introduction 4

2. A Historical Account of Heart Rate Variability 5

3. Stress 7

3.1. Autonomic Nervous System 8

3.2. Central Autonomic Network 9

3.3. Physical Stress 9

3.4. Psychological Stress 11

4. Measurement of Heart Rate Variability 12

4.1. Time Domain Analysis 13

4.2. Frequency Domain Analysis 14

4.3. High versus Low Frequency Heart Rate Variability 15

5. Executive Functions linked to Heart Rate Variability and Stress 15

5.1. Neural Correlates of Threat and Safety Perception 16

5.2. Neural Correlates of Emotional Regulation 18

6. Neural Correlates of Heart Rate Variability 19

6.1. Psychophysiological Theories Explaining Heart Rate Variability 20

7. Practical Applications of Heart Rate Variability 23

7.1. Heart Rate Variability Biofeedback 23

7.1.2. Studies of heart rate variability biofeedback in relation to threat and safety. 25

8. Discussion 27

8.1. Limitations and Future Directions 33

9. Conclusion 34

10. References 36

1. Introduction

The human heart is about the dimension of a closed fist, weighs between 250 and 350 grams, and beats approximately 100,000 times a day and a total of 2.5 billion times during an average lifetime (Marieb & Hoehn, 2007). The adult human brain is around 15 centimetres, weighs about 1300 to 1400 grams and contains about 86 billion neurons (Azevedo et al., 2009). The connection between the heart and the brain was coined 150 years ago by Claude Bernard and has since then been an interesting topic of research. Bernard explained the intimate relationship between the two organs by stating:

> when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumo-gastric (vagus) nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body (Darwin, 1999, pp. 71-72).

The field that investigates the *heart-brain connection* is known as *neurocardiology* and refers to the physiological interplay of the cardiovascular system and the nervous system (Van der Wall & Van Gilst, 2012). Thayer and Lane (2000) encapsulated the work of Claude Bernard and created the *neurovisceral integration model*, which maps the direct and indirect pathways between the heart and the brain.

Scientists have for many years searched for biomarkers of stress and health to map the current status of the organism. A special area of interest has been trying to understand how humans and animals are shaped by and tries to adapt to external and internal demands, also known as stress. *Heart rate variability* (HRV) has been proposed as an index capable of measuring both the health and level of stress put on an organism by supplying information regarding the heart-brain connection (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). HRV refers to the beat-to-beat variations in heart rate (HR; Thayer & Lane, 2000) and is thought to be a useful signal in understanding and providing valuable information of the autonomic nervous system (ANS; Acharya, Joseph, Kannathal, Lim, & Suri, 2006).

The main purpose of the ANS is to deal with internal and external stressors with the intent to maintain the homeostasis in the body (Porges, 1995). Cohen, Kessler, and Gordon, (1998) states that stress is a key factor in human disease and to be able to deepen our understanding of the stress process and how to better adapt to stressors is key to achieve several positive outcomes in life. There is also growing evidence for that the ANS plays a key role in a wide range of somatic and mental diseases (Thayer & Sternberg, 2006). For example, the dysfunction of the ANS has been shown to be one of the most prominent causes of cardiovascular disease, which is one of the leading causes of disability and death worldwide

(Thayer & Fischer, 2013). Thus, a way to map the activity of the ANS is important for health and medical purposes. According to Thayer and Sternberg (2006), HRV represents one of the most promising of such markers. Appelhans and Luecken (2006) state that the activity of the ANS is crucial in emotional responding and flexibility. Due to HRV's ability to map the ANS, it serves as an important tool in the study of individual differences in cognitive functioning during threatening conditions.

HRV is not just a promising marker mapping the heart function and the ANS. During the last decade HRV has been linked to several neural structures, in more detail structures associated with threat and safety experiences, and emotion (Thayer et al., 2012). Thayer et al. (2012) argues that HRV in fact can provide information regarding the brain's different systems responsible for adaptive regulation. Thus, HRV can serve as a relative simple and objective measure of the organism's neural network and capacity associated with function and adaption in the environment.

In this thesis the relationship between HRV and stress in the form of threat and safety will be investigated. The aim is to review and describe the neural correlates of HRV and stress with the heart-brain connection as foundation. The outline of the paper will be presented in the following chronological order: (a) a historical account of HRV is presented, (b) the stress concepts is described by reviewing the related nervous systems and defining the concept of stress, (c) HRV will be described in more detail by presenting two types of measures and reviewing the properties of low versus high HRV, (d) the neural correlates of emotional regulation, and threat and safety perception is presented and later tied to the neural correlates to HRV, (e) HRV is presented and explained through two psychophysiological theories, (f) practical applications of HRV are shown and (g) a discussion and conclusion of the thesis is provided, examining the content, limitations and future directions of HRV.

2. A Historical Account of Heart Rate Variability

The first documented observation of HRV dates back to 1733, and is credited to Stephen Hales, who observed a respiratory pattern in the pulse and blood pressure of a horse (Berntson et al., 1997). First in 1963, HRV gained clinical importance and was used to detect fetal distress (Hon & Quilligan, 1968). They noted that reduced beat-to-beat variations of the fetal heart were associated with distress before other symptoms could be detected, a method still used today. In 1965, Vallbona, Cardus, Spencer, and Hoff for the first time observed HRV changes in patients with brain injury. Wolf, Varigos, Hunt, and Sloman (1978) used HRV to properly map the status of the nervous system, while two years earlier in 1976, Ewing, Campbell and Clarke had used HRV for the first time as an index to predict the malfunction of the ANS. According to Ernst (2016) the real breakthrough of HRV probably came during the 1980s when Axelrod, Lishner, Oz, Bernheim, and Ravid (1987) and many other researchers started to analyse the *frequency domain* of HRV. Analysis of HRV frequency domain refers to a unique, non-invasive tool for assessment of autonomic function (Ori, Monir, Weiss, Sayhouni, & Singer, 1992) and made it possible to use short-term HRV of 10 min or less, thus enabling short measures of autonomic function linked to specific stimuli (Ernst, 2016).

In more detail, HRV refers to the variation over time of the period between consecutive heartbeats and reflects small fluctuations in the interval between consecutive heartbeats (Miu, Heilman, & Miclea, 2009), which is mainly dependent on the extrinsic regulation of the HR (Acharya et al., 2006). Thus, HRV refers to the time between successive heartbeats, not an analysis of the HR per se (Malik et al., 1996). What is important to note is that the beating of a healthy heart is highly irregular during steady-state conditions rather than being monotonously regular like a metronome. It is these small fluctuations in HR that is referred to as HRV (Shaffer, McCraty, & Zerr, 2014). Thayer and Lane (2000) refer to this phenomenon and HRV as beat-to-beat variations in HR (Thayer & Lane, 2000). Described in more clinical and practical terms, HRV is a non-invasive electrocardiographic (ECG) index of the ANS control of the heart (Miu et al., 2009). Several different physiological factors may influence HRV such as age, circadian rhythm, body position, age and gender (Bonnemeier et al., 2003).

Today, the use of HRV as a biomarker for stress and health is at an all top high. Within the field of HRV, more than 10,000 papers have been published and HRV is used both in every day situations as part of expensive pulse watches and in more clinic use in advanced experiments (Ernst, 2016). Easy accessible software and computer processing power, and simple measures of evaluating the successive heart beats of the heart have made the analysis of HRV widely accessible and applicable to psychologists and clinicians (Kara, Nykodym, & Somers, 2003). However, the meaning and significance of HRV and the many measures it provides are far more complex than often generally appreciated and can potentially lead to incorrect conclusions (Malik et al., 1996). Because of this, Malik et al. (1996) took the responsibility to develop appropriate standards regarding HRV. They established minimal technical requirements, specified methods of measurement, defined physiological and pathophysiological correlates, described current appropriate clinical applications and identified future areas of research. This paper is probably the most frequently cited paper related to HRV and most modern HRV studies refer to these important standards (Ernst, 2016).

The most prominent factor affecting an organism's HR and also the frequency of the HRV is the activity of the ANS. The activity of the ANS is in turn mainly dependent on psychological and physiological stressors of different forms (i.e., stress; Acharya et al., 2006). Therefore, to properly understand the underpinnings and practice areas of HRV, one has to also understand the function and foundation of the ANS. Before doing so, however it is necessary to properly define the concept of stress.

3. Stress

Stress has long been a major focus among researchers interested in psychosocial and environmental demands on health. However the definition of stress has been under much debate, even to the extent that the concept has been considered by some to have so many definitions that it has become useless (Cohen et al., 1998). The concept may refer to a stimulus, a response to that stimulus, or the physiological result of that response (Kemeny, 2003). Selye (1974) defines stress as the "nonspecific response of the body to any demand made upon it" (p. 137). Lupien, Maheu, Tu, Fiocco & Schramek (2007) divides the concept into *absolute threat* and *relative threat*. An absolute threat is created by, for example, an earthquake leading to a significant stress response for all humans facing the threat. Relative stress refers to an implied threat created by the interpretation of a situation as being unpredictable or uncontrollable, for example, a public speech. Relative threats are events or situations that elicit a stress response in certain type of individuals, depending on the interpretation.

Whatever the exact definition of stress, Lazarus (1993) argues that four concepts always must be considered: First, an internal or external stressor: Second, an evaluation that decides what is threatening or noxious from what is benign: Third, coping processes on how the mind or body should deal with the demands put forward by the stressor and fourth, a complex pattern of effects by the mind and the body often referred to as a stress reaction (Lazarus, 1993). Even though the stress concept has been a subject to much debate, some aspects of the concept have been in general accepted. The stimuli or event that causes a stressful experience is referred to as a *stressor* (Mason, 1975). Stimuli that threaten the maintenance of ones physical integrity is referred to as *physical stressors* and stimuli that threaten one's psychological well-being is referred to as psychological stressors (Lazarus & Folkman, 1993). In 1974, Selye divide the concept into two qualitative expansions called *eustress* and *distress*. Distress is referred to as an unpleasant event caused by stress like frustration or failure, which disturbs the bodily state. Eustress is described as a pleasant event caused by stress like excitement or arousal in relation to something positive, which is associated with healthy bodily states (Selye, 1974). The separation of psychological and physiological stress has since the mid 20th century been largely accepted and the relationship between the concepts has stimulated great interest (Lazarus, 1993). Early views of stress focused mainly on *physical stress* i.e. an event that disturbs the homeostasis of the body, such as changes in physical injury or temperature (McEwen & Seeman, 1999). More current views of stress also focus on *psychological stress* i.e. focus on the appraisal of the event and perceived coping resources as main features (Lupien et al., 2007).

This thesis will incorporate eustress, distress and physiological stress in relation to HRV and threat experiences. In other words, how external demands of threat affect our bodily process in relation to HRV and how our perception of the process is crucial for the result. First, to describe HRV and its relation to psychological and physical stress, parts of the human nervous system related to HRV needs to be properly described.

3.1. Autonomic Nervous System

The ANS is a set of nerves and nerve cells within the body of an organism surrounding the internal organs, mainly the blood vessels, viscera and a few other tissues (Gabella, 2001). The ANS is part of the peripheral nervous system (Gabella, 2001) and is mainly responsible of bodily functions not under our voluntary control like digestion, bladder control and respiration (Aubert, Seps, & Beckers, 2003). The ANS controls many functions within our body, but maybe the most prominent one and with certainty the most relevant for this thesis is the control over the cardiovascular system, including the heart (Thayer et al., 2012).

The ANS consist of two branches that originate in the brainstem, the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS) (Porges, 1995). The PNS is mediated by acetylcholine and deals mainly with anabolic activities concerned with conservation and restoration of bodily energy. In contrast, the SNS is mediated by norepinephrine and promotes the opposite bodily functions, with increased metabolic output to prepare the body for external challenges (Porges, 1995). Ernst (2016) describes the SNS, as a fast mobilizing system while the PNS is a more slowly dampening system. In general the two subsystems are reciprocally activated (i.e., when one system is activated, the other is deactivated) in a balancing action depending on the internal and external environment

(Porges, 1995). Jose and Collison (1970) showed that the heart is under tonic inhibitory control of the PNS by blocking the SNS and the PNS, which increased the HR. This means that under normal resting HR, the PNS is continuously affecting the heart and keeping the HR down. Together with cardiovascular mechanisms, the PNS and the SNS controls the HR via the heart's sinoartial node (Acharya et al., 2006). The sinoartial node acts as the main pulse generator of the heartbeat and is often referred to as the heart's natural pacemaker (Von Borell et al., 2007).

3.2. Central Autonomic Network

Several researchers have identified the *central autonomic network* as a functional unit within the central autonomic nervous system to support goal directed behaviour and adaptability. The central autonomic network is an integral component of the internal regulation system of the brain and is mainly involved in neuroendocrine, visceromotor, and pain modulating control mechanism essential for adaptation and survival in the environment. The central autonomic network consists of a group of interconnected areas of the brainstem, diencephalon and telencephalon, which control parasympathetic and sympathetic outputs (Benarroch, 1993). All the components of the central autonomic network will not be mentioned in this essay (for a full review see; Benarroch, 1993), hence regarding the interest of this essay it is enough to mention that the central autonomic network includes prefrontal and limbic structures including the amygdala, hypothalamus, nucleus solitary tract, orbitofrontal-, and ventromedial prefrontal cortices and the ventromedial medulla (Benarroch, 1993; Thayer & Brosschot, 2005). These structures are reciprocally interconnected, thus information is allowed to flow bidirectional between the higher and lower levels of the central autonomic network. The main output of the central autonomic network is mediated through the parasympathetic and sympathetic neurons, which affect the heart through the sinoartial node (a process already described), which creates HRV. Thus, the main output of the central autonomic network including its brain structures can be associated with HRV. This allows HRV to serve as an indicator of *central-peripheral neural feedback* i.e. the interplay between the central nervous system and ANS, also explained as the heart-brain connection (Thayer & Brosschot, 2005).

3.3. Physical Stress

Stressful experiences in the form of threat can have substantial effects on a variety of physiological systems. Three of the most carefully studied systems involved are the hypothalamic-pituitary-adrenal axis, the ANS and the immune system. Systems like these are believed to have evolved with the intent to support behaviours that enable the organism to deal with threats (Kemeny, 2003).

In this thesis the physical stress response will not be covered in full, hence this is not in direct relevance to HRV and out of the scope of this paper. In short, the physical response to stress involves the activation of the hypothalamic-pituitary-adrenal axis. This result in the secretion of the hormone corticotropin from the hypothalamus, a brain structure often referred to as the master gland (Lupien et al., 2007). The release of corticotropin affects another structure in the brain called the anterior pituitary, which releases the hormone adrenocorticotropic into the bloodstream of the organism. The hormone eventually reaches the adrenal cortex, where it starts the production and release of cortisol in humans. The cortisol targets several sites related to immune, cardiovascular, metabolic and central nervous system functions. This can be summarized into preparing the organism with increased energy for action to either fight or flight from a threat (Lupien et al., 2007).

What is in direct relevance with HRV and threat regarding the stress response is the activity within the ANS and the central autonomic network. The goal with the interplay between the SNS and PNS is to provide the ultimate and appropriate internal state for both external and internal stressors (Porges, 1995). When experiencing threatening situations, the PNS is no longer able to meet the needs put on the organism. Thus, the ANS responds by arousal of SNS and a decrease of PNS activity (Hansen, Johnsen, & Thayer, 2009). In general this leads to activation of the central autonomic network and the release of the neurotransmitter norepinephrine at various organs, including the adrenal medulla, causing a release of adrenaline in the bloodstream. This relatively rapid response system can be activated within seconds and create what is colloquially known as an adrenaline rush as a response to a threat (Kemeny, 2003). An increase of SNS activity or diminished parasympathetic activity also results in cardio acceleration (e.g., increased HR and blood pressure).

The processes involve sympathetic fibres increasing the firing rate of so-called *pacemaker cells* in the sinoartial node, which increases the HR. This means that the SNS affects the heart to beat faster, causing the *interbeat interval* to become shorter. The interbeat interval refers to time between heartbeats and in general a short interbeat interval results in a lower HRV (Acharya et al., 2006). The PNS on the other hand, affects the heart via the vagus nerve by having an inhibitory effect on the pacemaker cells and the sinoartial node, which produces a decreased HR (Castaldo et al., 2015). This occurs through an efferent effect in the vagal nerves triggering an acetylcholine release, thus slowing the rate of depolarization in the sinoartial node (Shaffer et al., 2014). During homeostasis and no external challenges, the PNS is more active than the SNS and lowers the HR, which causes the interbeat interval to become longer, thus enables HR to vary in more extent, resulting in a higher HRV (Thayer et al., 2012). During threat and stress, PNS activity is reduced and the inhibitory effect of the pacemaker cells and the sinoartial node is diminished, hence increasing HR. Thus, an increase in HR could result from either increased SNS activity or decreased PNS activity (Appelhans & Luecken, 2006).

3.4. Psychological Stress

According to Folkman and Lazarus (1985) how and to what extent one experiences psychological stress is in majority determent by two individual factors: *Cognitive appraisal* and *coping processes.* According to Kemeny (2003), how an organism cognitively appraises a situation can with profound effects shape the specific nature of the physiological response to a stressful encounter. Cognitive appraisal refers to the process in which the individual assesses whether a meeting with the environment is relevant to his or hers well-being, and if so, in what ways. Cognitive appraisal is based on that different emotional processes (including stress) are dependent on actual expectancies people manifest on the outcome and significance of a specific encounter (Folkman, Lazarus, Dunkel-Schetter, DeLongis, & Gruen, 1986). The concept is further divided into *primary appraisal* and *secondary appraisal*. Primary appraisal refers to the individual evaluating if an encounter involves any threat or benefit with respect to commitment (Folkman et al., 1986). Lazarus (1966) divided primary appraisal into three kinds: harm, threat and challenge. Harm refers to psychological damage that has already occurred and that cannot be changed. Threat is the anticipation of harm or loss that has the potential to take place and seriously block mental operations and impair functioning. Challenge results from difficult demands that we feel confident to overcome by using our coping resources. Secondary appraisal refers to the individual evaluating what can be done to overcome or prevent a potential threat or improve the prospect of a benefit (Folkman et al., 1986).

According to Blascovich and Tomaka, (1996) the subjective experience of threat is determined by how one perceives the demands of the situation outweighing the resources. On the other hand when the resources are perceived to approximate or exceed the demands of the situation the individual perceives the experiences as a challenge instead of a threat. These two different states create distinctive alterations of the ANS. Challenge are associated with increases in sympathetic arousal coupled with reduced or unchanged blood flow. Threat is also associated with increased sympathetic arousal, but involves increased blood flow, leading to increased blood pressure (Kemeny, 2003).

Coping is defined as the individuals effort in constantly changing his or hers behavioural and cognitive efforts to manage specific internal and/or external demands. If these demands tax or exceeds the individual capacity is decided by cognitive appraisal (Lazarus, 1991). Coping shapes emotion as well as psychological stress by altering the person-environment relationship. Coping involves two widely recognized functions: *Emotion focused coping*, which refers to regulating stressful emotions and *problem-focused coping*, which refers to changing the troubled persons-environment relation that is causing the distress (Folkman & Lazarus, 1980; Folkman & Lazarus, 1985). Regarding threatening experiences, emotion-focused coping is commonly used (Folkman & Lazarus, 1985). In fact Lazarus (1993) went so far as to suggest that psychological stress and emotions are intertwined to such a degree that they ought to be considered as the same field. Lazarus (1991) identified 15 basic emotions tied to psychological stress, appraisal and coping. By implementing emotions as a source of information regarding psychological stress it gives researches valuable information in how individuals adapt and cope with the environment.

4. Measurement of Heart Rate Variability

The most prominent factor affecting the interbeat interval and HRV is the *vagal tone*, which primary influencer is respiration and refers to the activity of the vagus nerve. Breathing air into the lungs temporarily depresses the activity of the PNS on the heart and increases HR. Breathing air out of the lungs reinstates the PNS and decreases HR. This phenomenon is known as *respiratory sinus arrhythmia* and creates rhythmic fluctuations in HR. These fluctuations in the time between the beats of the heart are referred to as vagal induced HRV and are in close association with high respiratory sinus arrhythmia and high self-regulation. Reduced respiratory sinus arrhythmia in people has been shown to be associated with negative states and abilities like emotional disorders, poor attention control, inflexibility of behaviour and dysfunction of emotion (Grossman & Taylor, 2007).

Due to different signalling mechanism, sympathetic effect on the heart occurs rather slowly, with a peak in effect around 4 seconds and return to baseline within 20 seconds. In contrast, parasympathetic effects on the heart have a very short latency with a peak in effect around 0.5 seconds and return to baseline within 1 second. Because of the PNS's ability to respond fast enough to vary with respiration, respiratory sinus arrhythmia is a phenomenon only facilitated by PNS activity. Thus, rapid changes in HR are always the result of shifts in parasympathetic activity and not the slower SNS (Berntson et al., 1997). The difference in latency effect on the heart between the two systems creates different fluctuations in HR occurring at different speeds, or frequencies (Appelhans & Luecken, 2006). The frequency difference between the two systems allows HRV analysis to differentiate and map parasympathetic and sympathetic effect separately (more described below; Berntson et al., 1997).

Measurements of HRV are highly reproducible and non-invasive (Sztajzel, 2004). To be able to measure and analyse HRV from 0.5 to 5 minutes, special laboratory equipment and controlled conditions is typically needed, but HRV can also be calculated using HRV from a 24-hour portable and real life measures (Van Ravenswaaij-Arts, 1993).

4.1. Time Domain Analysis

HRV can be evaluated by a number of methods. Possibly the simplest measure are *time domain measures*. These measures involve HR at any point in time or intervals between successive heartbeats (Malik et al., 1996). This requires a continuous measure of HR, in general achieved through the use of ECG (Appelhans & Luecken, 2006). There exist several types of ECG configurations, with varying numbers of pros and cons, used for both stationary and portable monitoring. A standard configuration of the ECG electrodes involves a placement of two electrodes on each side of the chest and a third electrode placed central just under the chest (Shaffer et al., 2014). Data needs to be sampled at a rate between 500-1000 Hz to provide a high-resolution signal (Berntson et al., 1997). After collection, the series of interbeat intervals needs to be scanned and corrected for artefacts and abnormal beats. Available software is then used to define the interbeat intervals within the ECG recording. From a raw ECG recording, usually of 24 hours, several waveforms can be identified, each waveform referring to different components of the heart (Appelhans & Luecken, 2006). Analysis of HRV and interbeat intervals is almost always based on the temporal distance between the heartbeats, which corresponds to the depolarization and contraction of the heart's ventricles. These interbeat intervals are defined by consecutive "normal" beats due to depolarization of the sinoartial node and are thus often referred to as "*normal-to-normal*" intervals (Appelhans & Luecken, 2006).

Statistical analyses are often reported and consist of variance-based calculations of the set of interbeat intervals and resulting in numerical values of HRV in temporal units (e.g., milliseconds; Appelhans & Luecken, 2006). These may be divided into two categories, (a) those resulting from direct measurement of the instantaneous HR or normal-to-normal intervals and (b) those resulting from differences between normal-to-normal intervals. The standard deviation of normal-to-normal intervals is the simplest variable to calculate and serves as a global index of HRV. It reflects all the long-term components and circadian rhythms responsible for HRV during the recording period and is calculated over a 24-hour period. Thus, it is able to reflect both short-term high-frequency variations as well as the lowest frequency components (Malik et al., 1996). Another variable is the standard deviation of the average normal-to-normal interval, which serves as an index of HRV over the average of 5 min intervals over a 24 hours period (Sztajzel, 2004).

4.2. Frequency Domain Analysis

The *frequency-based technique* of *power spectral analysis* is a relatively sophisticated method to measure HRV. Power spectral analysis uses ECG signals to derive the quantity of HRV occurring at different frequencies expressed in Hz. This analysis results in a power spectrum, a spreading of variance in HR at different frequencies. The spectrum of power contains valuable information regarding the major oscillatory components of HRV (Appelhans & Luecken, 2006). The spectrum ranges from 0 to 0.5 Hz and consist of four bands: *the ultra low frequency*, *the very low frequency*, *the low frequency and the high frequency* (Sztajzel, 2004). The high-frequency component of HRV is in general associated with PNS activity and vagal modulation (Berntson et al., 1997). These HR changes are related to the respiratory cycle and are known as respiratory sinus arrhythmia (Shaffer et al., 2014). Low-frequency HRV ranges from 0.04 to 0.15 Hz and is in general associated with different types of stressors (Sztajzel, 2004). But controversy exists regarding the causation of low-frequency HRV. Is low-frequency HRV a direct marker of SNS activity, is it a product of both SNS and PNS activity or is it in majority mediate by the PNS? (Appelhans & Luecken, 2006). Many researchers agree on that the low-frequency component reflects a mixture of PNS and SNS activity. The ultra low-frequency and low-frequency of HRV are spectral components involving very low fluctuations (Sztajzel, 2004). Sztajzel (2004) states that the ultra low-frequency component might reflect neuroendocrine and circadian rhythms, while the very low-frequency component has been found to be a significant determinant of physical activity and proposed as a marker of SNS activity.

4.3. High versus Low Frequency Heart Rate Variability

The low-frequency component of HRV has been linked with a number of negative consequences, while high-frequency HRV has been associated with a range of positive effects. Low-frequency HRV has been shown to be associated with a variety of conditions related to increased stress and poor health (Thayer & Sternberg, 2006) for example, increased mortality, cardiovascular morbidity (Thayer et al., 2012), depression, increased anxiety (Porges, 1992), subjective experience of threat, psychological stress (Thayer & Lane, 2009) and diabetes (Thayer & Sternberg, 2006). The high-frequency component of HRV is most common used in examination of HRV and is closely related (or referred to as) respiratory sinus arrhythmia (Grossman & Taylor, 2007). The high-frequency component has been associated with numerous health benefits, for example a greater willingness to approach novel objects (Thayer et al., 2012), greater ability in emotional regulation (Lane et al., 2009), a smaller negativity bias (explained later; Shook, Fazio, & Vasey, 2007) and a more efficient and quicker extinction of threat full objects and situations (Pappens et al., 2014). Increased HRV has also been linked with superior executive function and performance during different cognitive tasks compared to low-frequency HRV (Hansen, Johnsen, Thornton, Waage, & Thayer, 2007; Hansen et al., 2009).

Up to this point, it is rather clear how HRV can be used as an index of stress and health mediated by the heart and the ANS. But, HRV has also been suggested to be a useful index of stress mediated by the brain. Thus, HRV cannot only serve as a useful index of the status of the heart, but also an index to map the status of the brain (Thayer et al., 2012). To do this, Thayer et al. (2012) states that HRV needs to be tied to neurological correlates of important executive functions in the brain.

5. Executive Functions linked to Heart Rate Variability and Stress

Thayer et al. (2012) states that two of the most important executive functions involved in the stress process are emotional regulation and perception of threat and safety. If HRV is to be considered a marker of stress it needs to be tied to perception of threat and safety and emotional regulation. Thayer et al. (2012) argue that if HRV can be associated with certain neural structures that are responsible for the conscious or unconscious appraisal of threat and safety as well as the ability regulate emotions, HRV can illustrate a useful index of stress, not just only via the heart, but also the brain and the connection between the two.

5.1. Neural Correlates of Threat and Safety Perception

Threat and safety perception is presented as a core element in perception of negative stress associated with mental events. These perceptions and its related actions are vital factors for the survival of the organism and ultimately for the human species. Two major neural correlates have been found in relation to threat and safety perception: The amygdala and the prefrontal cortex. The concept of threat and safety perception will further be explained by presenting these neural structures and their relation to each other.

5.1.1 Amygdala. The amygdala has been observed as the main structure involved in threat perception. It serves as a fast detector of potential threats and a mediator of fear responses (Belova, Paton, Morrison, & Salzman, 2007). The amygdala consist of neurons that encode both negative and positive emotional outcomes, however according to Paton, Belova, Morrison, and Salzman (2006) a predominance of single neurons encode negative outcomes, which results in a bias towards negative information. This bias is referred to as the "*negativity bias*" which is a phenomenon that describes our tendency to focus more on negative information rather than positive (Cacioppo, Gardner, & Berntson, 1999). This is explained as an evolutionary advantage that represents a system during uncertainty to prepare for the worst, thus maximizing adaptive resources and adaptive responses (LeDoux, 1996). Thayer et al. (2012) argues that this system responds to threat by sympathetic preparation of the fight or flight response (Seeman, McEwen, Rowe, & Singer, 2001).

In today's society a constant perception of threat is maladaptive for an organism and has been shown to be associated with several negative consequences including a cognitive and general health decline (Seeman et al., 2001) as well as a dysfunction of the hippocampal circuits (McEwen & Sapolsky, 1995). Thayer et al. (2012) adds that for an organism to be able to live a life without a chronic state of threat, it is important to determine if and when appraisals of threats are appropriate depending on the context. The prefrontal cortex and in more detail the medial prefrontal cortex have been shown particularly essential in this process. Thus, regarding threat perception and the interest of this thesis, the brain structures of interest is the amygdala and prefrontal cortex, including subdivisions.

5.1.2. Prefrontal cortex. During safe contexts, representations in the amygdala appear to be under tonic inhibition by the prefrontal cortex and specially the ventromedial prefrontal cortex. By using pharmacological (Amat, Paul, Watkins, & Maier, 2008) or electrical stimulation (Milad, Vidal-Gonzalez, & Quirk, 2004) of the ventromedial prefrontal cortex, researchers have displayed the importance of the ventromedial prefrontal cortex activity in threat perception. It has been shown that the stimulation of the ventromedial prefrontal cortex during threatening experiences results in an inhibition of certain threat circuits, and reduced stress response and fearful behaviour. But this process has been shown to be more complicated than an automatic inhibition by the ventromedial prefrontal cortex on the amygdala during threatening experiences. First, the stimulation of the ventromedial prefrontal cortex does not automatically result in fear extinction or a reduced fear response. Instead the studies cited above also shows that the ventromedial prefrontal cortex plays an important role in retrieval and consolidation of safety context memories. Second, the structure has been shown to be associated with appraisal processes of the higher level under certain contexts. It is believed that the ventromedial prefrontal cortex and its inhibition of the amygdala are dependent on the perceived controllability of the context (Amat et al., 2005).

The tonic inhibition by the prefrontal cortex on the amygdala was first described by Jackson (1884) with the so-called *Hughlings Jackson principle*. He argued that during threat, areas of the prefrontal cortex become hypoactive. The principle implies that removal of the inhibition caused by the prefrontal cortex on the amygdala permits rather than causes an increase in physiological activity. In modern times this process is described as the disinhibiting of SNS circuits, which leads to mobilization of energy (McEwen & Seeman, 1999). Buchanan et al. (2010) showed that people suffering from damage to the medial prefrontal cortex perceived a challenging social situation as more threatening than people with damage to other brain structures or controls with no brain damage at all. Thus, the correct functioning of the ventromedial prefrontal cortex is considered crucial to the detection of threat and safety and also therefore vital to the normal function and the health of an organism.

In 2006, Amodio and Frith conducted a review study on the exiting literature related to the medial prefrontal cortex and its anatomical and functional characteristics in relation to social cognitive processing. They propose three functional subdivisions of the medial prefrontal cortex, each with different purposes. A first, dorsal and posterior region of the rostral prefrontal cortex was linked with more “cognitive” sensorimotor selection and action-monitoring tasks. A second most ventral sub region covering the part of the pregenual anterior cingualte cortex and the medial orbitofrontal cortex, the subgenual anterior cingulate cortex and the anterior ventral prefrontal cortex were found. These subdivisions was linked to experiences of rewards and punishment and visceral and autonomic aspects of emotional responses. Finally, the third region covering the anterior rostral medial prefrontal cortex, parts of the pregenual anterior cingualte cortex and the medial prefrontal cortex (medial

Brodmann's Area 9) were found and linked with emotional tasks and engaging in perception and social cognition.

Thayer et al. (2012) states that if HRV can be tied to the structures and functions of this neural network including the medial prefrontal cortex and the amygdala, then HRV can serve as useful index of threat and safety, and thus also stress.

5.2. Neural Correlates of Emotional Regulation

The ability to regulate emotion is closely related to the ability to flexibly shape perceptual and affective brain processes in response to changing contexts (Thayer et al., 2012, p. 750). Emotions reflect the status of one's on-going adjustment to continually changing environmental contexts. Resting HRV (explained in more detail later on) has been put forward as a marker for flexible dynamic regulation of autonomic activity. This implies that higher HRV could be argued to signal the availability of context-based control of emotions (Thayer et al., 2012).

Emotional regulation has been tied to HRV and, perception of threat and safety via the brain structures amygdala and medial prefrontal cortex (Appelhans & Luecken, 2006). HRV and emotional regulation has in majority been investigated on two different levels, the *trait* and *state level*. The trait level refers to individual differences in resting HRV and its associations with differences in emotional regulation. Thayer and Brosschot (2005) showed that individuals with lower resting HRV, compared to those with higher resting HRV, reacted to positive, neutral or harmless stimuli as if they were threatening and aversive. Individuals with high resting HRV was best able to match their response to the environmental demands and thus respond most appropriate. Persons with low resting HRV compared to high resting HRV has also been shown to be associated with delayed recovery from psychological stressors of endocrine, cardiovascular and immune responses (Weber et al., 2010). Thus, individuals with higher resting HRV appear to be more able to produce appropriate responses to the context (Thayer & Brosschot, 2005) and more appropriate recovery after experiencing a stressor (Weber et al., 2010).

The state level of analysis refers to HRV increase during successful regulation of emotion. Lane et al. (2009) has shown that increases in HRV are associated with effective emotional regulation and regional cerebral blood flow changes in several brain structures important for emotional regulation including the prefrontal cortex. Wager, Davidson, Hughes, Lindquist, and Ochsner, (2008) investigated the prefrontal cortex role in emotional regulation and found that the ventromedial prefrontal cortex and dorsomedial prefrontal cortex activity during cognitive appraisal of obnoxious images was associated with an increased reduction in negative emotions. They highlight two sub regions of the medial prefrontal cortex, the pregenual anterior cingulate cortex and the rostral dorsal anterior cingulate cortex that are responsible for emotional regulation and modulation. Wager et al. (2009) adds that emotional regulation and physiological responses to threat shares neurological correlates including the lateral orbitofrontal cortex, the anterior cingulate cortex, the ventromedial prefrontal cortex and anterior insula. Taken together, HRV can serve as an index of emotional regulation and thus also perception of threat and safety on two levels, the trait and state levels. Thayer et al. (2012) argue that HRV is associated with certain neural structures that are responsible for the conscious or unconscious appraisal of threat and safety. If HRV can be linked to these brain structures, it can illustrate a useful index of stress and health.

6. Neural Correlates of Heart Rate Variability

Thayer et al. (2012) performed a meta-analysis on existing literature regarding the human neural correlates of HRV. The goal of the meta-analysis was to identify the neural correlates of HRV associated with emotional versus cognitive/motor tasks. The overall analysis presented the prefrontal cortex as the structure showing the most activation in association of HRV. In more detail, the right pregenual anterior cingualte cortex and the subgenual anterior cingulate cortex located in the medial prefrontal cortex was identified as regions associated with HRV. Also a third region showing activation in association with HRV was the left sublenticular extended amygdala. To clearly understand the functional significance of HRV, it is of importance to know more about how they are associated to the brain.

The ventromedial prefrontal cortex, a region previously discussed and associated as important regarding reduction of context dependent fear behaviours and emotional regulation has also been tied to HRV. A previously mentioned study of Wager et al. (2008) described that activity of the prefrontal cortex and in particular the ventromedial prefrontal cortex during cognitive appraisal of obnoxious images was associated with an increased reduction in negative emotions. A link between the finding of Wager et al. (2008) and HRV was suggested by Thayer et al. (2012) by referring to Butler, Wilhelm and Gross, (2006) study on respiratory sinus arrhythmia and emotion. The study showed that cognitive appraisal and experiences of positive and negative emotions was associated with HRV. Participants with higher HRV experienced less negative emotions compared to those with lower levels. Wager et al. (2009) identified a region of the ventromedial prefrontal cortex that was active during social evaluative threat. They also found that the deactivation of the ventromedial prefrontal cortex predicted threatening experience, which resulted in increased activation in the periaqueductal gray, a region responsible for mediating behavioural and physiological responses to threat. In addition to this, Delgado, Nearing, LeDoux and Phelps, (2008) showed that cognitive reappraisal of fearful stimuli could reduce the fear response and that this modulation was associated with increased ventromedial prefrontal cortex activity.

Several studies have also tied vagal mediated HRV to prefrontal cortical activity. Lane et al. (2009) used electroencephalography (EEG) and positron emission tomography (PET) to map HRV and its associated neural correlates during emotional arousal. They found that high-frequency HRV was correlated with regional cerebral blood flow in the right superior prefrontal cortex, the right dorsolateral prefrontal cortex, the left rostral anterior cingulate cortex and the right parietal cortex. During emotional arousal and low-frequency HRV these regions was associated with decreased activity. Thus, HRV is argued to be able to serve as a vital index of the neural mechanism of the integration between the central nervous system and the ANS (Friedman & Thayer, 1998).

6.1. Psychophysiological Theories Explaining Heart Rate Variability

HRV's function as a general indicator of the ability to adapt to environmental changes and cope under stress is put forward through two major theories: *the polyvagal theory* and *the neurovisceral integration model* (Pappens et al., 2014). Both theories are similar in that they (a) specify a critical role for parasympathetic mediated HRV in relation to individuals' capacity in adapting to the environment, (b) proposes HRV as a promising index for measuring this capacity (Appelhans & Luecken, 2006), c) suggest that bidirectional connections between the heart and the vagus nerve evolved with the intent to support high flexible, environmental contingent mammalian behaviours (Butler et al., 2006), and d) is considered to help researchers generate more accurate hypotheses about the interaction of autonomic, behavioural and cognitive aspects of emotional regulation and expression (Appelhans & Luecken, 2006).

However, some significant differences between the theories exist. The polyvagal theory in large focuses on the neural connections between the vagus nerve and other cranial nerves that control peripheral structures involved in behaviours of emotional responding, whereas the neurovisceral integration model rest on neuroanatomical links between brain regions involved with emotional responding and the ANS (Appelhans & Luecken, 2006).

6.1.1. Polyvagal theory. The polyvagal theory was introduced by Porges (1995) and later updated by Porges (1997, 1998, 2001, 2003, 2007, 2011). The polyvagal theory is based on an evolutionary framework, which comprehends features in human functioning and genetically based characteristics. These characteristics are presumed to have aided in survival and/or reproduction through human history (Porges, 1998). In more detail, the polyvagal theory suggests that evolution and developing of the ANS has provided neurophysiological substrates to support affective processes and emotional experiences that are major components in social behaviour (Porges, 1997).

According to Porges (2011) the polyvagal theory suggests that two branches of the vagus nerve, the unmyelinated fibres and myelinated fibres are each associated with different competing adaptive behavioural strategies. The unmyelinated fibres originated in the dorsal motor complex are involved in regulating the "*freeze response*", which refers to threats through immobilization, passive avoidance, feigning death and shutdown. Porges (2011) argues that when encountering threat, human beings are not limited to fight, flight or freezing but that we can also choose to initiate pro-social behaviours (tend-and-befriend response). Porges (2011) calls this *the social engagement system* that involves the functioning of the myelinated fibres of the vagus. The myelinated fibres of the vagus originate in the nucleus ambiguous and are theorized to be a form of a vagal brake on the hearts sinoartial node. Porges (2011) states, "Our heart's pacemaker, we learn, has a high intrinsic rate which, in safe states, is inhibited by the vagal brake" (p. 229). The myelinated fibres have a tonic inhibitory effect on the sinoartial node and by rapidly withdraw or reinstate its inhibitory effect it can quickly mobilize or calm an individual and at the same time inhibit the SNS. Thus, the vagal brake can briefly release its tonic influence on the sinoartial node (releasing the brake) as a response during external stressors and reinstating the influence (pressing the brake) to calm the body down to its normal state without the metabolic cost of activating the slower SNS. According to Porges (2011) the vagus nerve supports adaptive behaviour through neural connections with peripheral structures involved in executive functions. Porges (1992) states "Specifically, high vagal tone is associated with the ability to self-regulate, through the organization of physiological resources and appropriate response selection. Low vagal tone on the other hand, is associated with poor self-regulation and a lack of behavioural flexibility" (p.208). This supports the notion that assessment of vagal tone and hence HRV could serve as a potential index for emotional regulation flexibility and behaviour during stressful experiences.

6.1.2. Neurovisceral integration model. The neurovisceral integration model was created in 2000, by Thayer and Lane and was later updated by Thayer and Lane (2009) and Thayer et al. (2012). The model builds of the pioneering work by Claude Bernard 150 years ago, trying to map the intimate relationship between the heart and the brain. The neurovisceral integration model relates emotional, cognitive and physiological regulation with HRV through a dynamical system perspective and describes how a set of neural structures involved in cognitive, autonomic and affective regulation is related to HRV (Thayer & Lane, 2000). These structures provide the organism with the capability to integrate signals from inside and outside the body and adaptively regulate perception, action, cognition and physiology. The system is referred to as a “super system” that always scans the environment for signs of threat and safety with the intent to prepare the organism for appropriate action. In addition, it observers the match between the external environment and the body’s internal homeostatic processes with the intent to generate adaptive physiological adjustments and states of motivational drive. A critical idea is that HRV may serve more than just an index of healthy heart function, but may in fact provide and index of to which degree this “super system” of the brain operates. Thus, HRV can serve as an easy measured index of this neural network and provide valuable information about the organism capacity to effectively function and adapt in a complex environment (Thayer et al., 2012).

Brain structures involved in this system are the insula, the ventromedial prefrontal cortex, the hypothalamus, the anterior cingulate cortex and the amygdala, all structures located in the forebrain. The model proposes that this network serves as an integrated system for internal regulation by which the brain operates neuroendocrine, visceromotor and behavioural responses. These responses are considered critical in health, goal-directed behaviour and adaptability. The anatomical details of the central autonomic network are suggested to link these structures to the nucleus solitary tract in the brainstem (Thayer & Lane, 2000).

In 2012, Thayer et al., extended the neurovisceral integration model and contended that dynamic connections between the amygdala and the medial prefrontal cortex, two structures previously mentioned to be involved in the evaluation of threat and safety, help regulate HRV through connections with the nucleus solitary tract. They propose that higher executive functions are related to vagal mediated HRV and that HRV reflects higher-level capacity of brain structures responsible for working memory and physiological and emotional self-regulation. Important, the neurovisceral integration model considers the central autonomic network as the neurophysiological command centre overviewing and directing cognitive, physiological and behavioural elements into regulated emotion states (Thayer & Lane, 2000). The central autonomic network does this by inhibiting other possible responses that could lead to maladaptive and preservative behaviour. The inhibition by the central autonomic network is considered to be mediated synaptic in the brain and vagal in the periphery (Thayer & Friedman, 2002). From a neurovisceral integration model's standpoint, Appelhans and Luecken (2006) argues that HRV can serve as a useful index for the central autonomic network's ability to regulate the magnitude and timing of an emotional response by inhibition of maladaptive responses in accordance with occurring contextual factors.

So far, the main content of this thesis presented has been focused on theoretical aspects of HRV with exception of the section regarding measurements of HRV. What is important to know is that the field of HRV can in fact be applied in many different settings and situations with the intent of helping patients with multiple deficits or problems, including threat and anxiety problems. Below follows a review of one particular application of HRV in relation to reducing threat and anxiety.

7. Practical Applications of Heart Rate Variability

During the last two decades, HRV analysis has been widely used for investigating normal physiology. Prior to this, investigation and research of the autonomic physiology and health of the organism required highly invasive techniques using animal models or imprecise reflex based tests in human organisms. HRV analysis provides researchers and individuals with a simple and reproducible method of non-invasive assessment of autonomic function (Pumprla, Howorka, Groves, Chester, & Nolan, 2002). Multiple findings indicate that HRV is associated with stress and anxiety with certain specific executive functions aiding us in survival during threat. For example functions like, emotional regulation, attention processes of threat and safety, and flexibility of behaviour. What is not clear is, if and how one can use HRV to reap all the advantages it possess. In recent years, an alternative intervention of HRV has received increased attention regarding this purpose, called *HRV biofeedback training*. HRV biofeedback has been shown to be a potential treatment for a variety of disorders, including stress and anxiety (Goessl, Curtiss, & Hofmann, 2017), which are related to threat and safety perception (Muris et al., 2000)

7.1. Heart Rate Variability Biofeedback

Biofeedback in general can help individuals control various physiological processes. In general, a biofeedback participant watches an instantaneous electronic display of his physiological function with the goal to change it (Schwartz & Andrasik, 2017). Although biofeedback has a relatively long history, the intervention has been infrequently used because of high cost. If HRV biofeedback shows promise, it can provide individuals with portable and wearable devices, such as fitness watches and trackers (Goessl et al., 2017).

HRV biofeedback was introduced during the 1980s, with the intent to target the PNS instead of other techniques that mainly focused on the SNS (Gevirtz, 2013). In recent years there has been substantial support for HRV biofeedback for a variety of disorders and practices like physical performance enhancement with the intent to increase HRV (Lehrer, 2013). The use of HRV biofeedback with the main goal to restore homeostasis has shown to have multiple positive effects on individuals cardiovascular system, behaviour, emotional reactivity, anxiety disorders, respiratory system (Lehrer, 2013), sleep, hypertension, depression, chronic muscle pain and anxiety (Gevirtz, 2013). Goessl et al. (2017) states that HRV biofeedback is associated with a large self-reported stress and anxiety reduction. Kim et al. (2013) adds that HRV biofeedback training with the goal to modulate the activity of the ANS can enhance the prefrontal cortex role in executive function and thus, the individual's ability to regulate behaviour and emotional responses. Gevirtz (2013) views HRV biofeedback as an effective way to increase recovery and flexibility from fight and flight adaptive situations.

The goal of HRV biofeedback is to assist individuals to increase the amount of respiratory sinus arrhythmia in the HRV signal thus, increasing vagal induced HRV (Kim et al., 2013). As previously mentioned, respiratory sinus arrhythmia refers to the change in RR intervals that is synchronized with respiration and is associated with high-frequency HRV. To increase the respiratory sinus arrhythmia the individual it typically instructed to breath slowly and making the exhalation longer than the inhalation. The individual is also instructed to breathe at his *resonant frequency*, i.e. the exact frequency at which the individual could voluntarily generate the highest amplitude of HRV. The resonant frequency is determined by measuring the amplitudes of the HR fluctuations while the individual breath for intervals of two minutes during differences frequencies, which is later measured by breaths/min (Lehrer et al., 2003). Usually the resonant frequency for a human is around 6 breaths per minute, a rate that matches the resonant frequency of the cardiovascular system (Wells, Outhred, Heathers, Quintana, & Kemp, 2012). When the perfect resonant frequency is found, HR and respiration covary perfectly so that the individual inhales until their HR peaks and exhales until it begins to rise again. This ultimately leads to strengthened and increased homeostatic functioning (Lehrer et al., 2003).

7.1.1. Heart rate variability biofeedback in practice. The method of HRV biofeedback can be outlined in several different ways. In general all methods tries to maximize the respiratory sinus arrhythmia of the individual by feeding back beat by beat HR data during slow breathing thus, matching respiratory sinus arrhythmia with HR patterns (Kim et al., 2013). Lehrer, Vaschillo and Vaschillo (2000) have described a validated procedure for HRV biofeedback training with the intent to increase respiratory sinus arrhythmia. This method has later been used as a foundation for HRV biofeedback. Important to note is that during recent years new technology has been developed and the HRV biofeedback process can differ using different measurements and techniques.

The individual is first taught to breathe at his individual resonant frequency ranging between 4-7 breaths per minute while the researchers measure the individuals HR fluctuations. The trainee accomplishes this by breathing in and out in the accordance with a pacing stimulus consisting of a light display that moves up and down on a screen. In subsequent sessions, the trainee is given HRV biofeedback for cardiac variability and is instructed to increase the amplitude of HR fluctuations that occur in conjunction with respiration. The HRV biofeedback can be presented in several forms. One type of display involves live HRV values in the form of a graph being showed on a screen. The individual is instructed to increase the HRV levels by breathing at his resonant frequency. The trainee is instructed to match his breath with changes in HR, thus increasing respiratory sinus arrhythmia and ultimately HRV (Lehrer et al., 2000).

The use of HRV biofeedback has during recent years also become available for the layperson through the use of pulse watches, fitness trackers and smartwatches (Ernst, 2016; Goessl et al., 2017). According to the standards of Malik et al. (1996) the use of other methods than ECG to measure HRV is not allowed, but some studies have in fact compared pulse watches with regular approaches and equipment. Nunan et al. (2009) found a pulse watch demonstrating a good to near perfect validity measuring short-term HRV of 5 min compared to the use of ECG equipment.

7.1.2. Studies of heart rate variability biofeedback in relation to threat and safety. Several qualitative reviews have investigated HRV biofeedback in relation to stress and anxiety, and found support for the notion of HRV biofeedback treating stress and anxiety symptoms (e.g., Gevirtz, 2013; Futterman & Shapiro, 1986). Goessl et al. (2017) conducted a meta-analysis on HRV biofeedback effects on stress and anxiety. They used 24 studies, including a total of 484 participants who all had received HRV biofeedback training for stress and anxiety. They found that HRV biofeedback training is associated with a large reduction in self-reported stress and anxiety. They conclude that more well-controlled studies are needed, but HRV biofeedback definitely offers a cheap, wearable and promising intervention and approach for treating stress and anxiety.

Reiner (2008) examined and supported the effectiveness of HRV biofeedback in persons with anxiety disorders and other disorders related to dysfunction of the ANS. In a single group study, participants received a portable HRV biofeedback device for three weeks measuring respiratory sinus arrhythmia. Before the experiment participants were taught in which resonant frequency and how they should breath to maximize their respiratory sinus arrhythmia. The HRV biofeedback devices indicated for the participants when they maximised their respiratory sinus arrhythmia. For each time, the participant was awarded one point. During the three weeks, the participants were instructed to gather 100 points each day. The result of the study supports the use of HRV biofeedback in treatment of autonomic imbalance and experiencing anxiety. The use of HRV biofeedback resulted in significant decreased trait and state anxiety as well as stress and increased relaxation. But, important to note is, hence the study was a single group study, it is in need of a control group to validate its results.

In 2012 Wells et al. did just this by investigating HRV biofeedback training in relation to performance anxiety under intense pressure and experiences of threat. The study did not find any significant effects of HRV biofeedback, but it includes some important aspects of HRV biofeedback and threat and safety perception.

The experiment consisted of two experimental groups (one HRV biofeedback group and one breathing group) and one control group preparing for a videotaped musical performance in front of an audience. Before the musical performance, the experimental groups was instructed to breath for 30 minutes in accordance to a breathing pacer consisting of a small ball rising for inhalation and descending for exhalation, prolonging the exhalation compared to the inhalation. The speed of the pacer resembled a resonant frequency of six breaths per minute. The HRV biofeedback condition was based on and validated by Lehrer et al. (2000) and was provided by a colour-coded graph on a screen, indicating the participants HRV levels. By using slow breathing in accordance with the pacer and receiving HRV biofeedback, the goal was to increase respiratory sinus arrhythmia by increasing the amplitude of HR fluctuations. In addition to the HRV biofeedback, group also received diaphragmatic breathing instructions. The breathing group received the same instructions with the exception of no HRV biofeedback. The control group received reading materials free of choice.

The result of the study showed that by breathing slow in accordance with the pacer individuals had a significant increase in high-frequency HRV and decrease in low-frequency HRV compared to controls during the anticipation task. Subjectively, the participants also reported a significant decrease in experienced anxiety during the anticipation task. This indicates increased levels of vagal induced HRV. Adding the HRV biofeedback intervention to the slow breathing did not alter the results significant, but Wells et al. (2012) adds that the significance of HRV biofeedback needs a more longitudinal study to make it justice. Thus, these findings indicate that a single session of slow breathing, regardless of HRV biofeedback is enough to control physiological arousal and increase HRV during anticipation of intense psychological stress. Wells et al. (2012) argue that slow breathing increases vagal tone and decrease SNS activity during a performance situation. On the other hand, during no slow breathing (control condition) the results is reversed, with low vagal tone and increased SNS activity. These physiological factors feedback to cortical areas affecting the individual's interpretation of the environment as either safe or threatening. During slow breathing, typically perception of safety and coping abilities is induced and during the control condition perception of threat and experience of performance anxiety is induced.

One study that found significant results regarding the use of HRV biofeedback in relation to performance anxiety and threat was Thurber, Bodenhamer-Davis, Johnson, Chesky, and Chandler (2010). They also investigated HRV biofeedback's effect on musical performance anxiety and found that HRV biofeedback can serve as a relative quick and inexpensive biofeedback training with a large effect on decreasing physiological, emotional and mental aspects of performance anxiety.

8. Discussion

The aim of this thesis has been to investigate and present research on the neural correlates of HRV in relation to stress in the form of threat and safety perception in humans. The presentation of this thesis begun with an introduction and a historical display of HRV, followed by a review of the stress concepts and related nervous systems. After this a deeper review of HRV was presented by describing two methods of measurement and the different properties and effects of low versus high HRV. Subsequently, the focus was directed towards the brain and the neurological correlates of HRV, emotional regulation and threat and safety perception with the intent to describe several important associations. In order to clarify and interpret the research literature, two psychophysiological theories were also presented, thus allowing deeper description and interpretation of the neural correlates of HRV and threat and safety perception. The thesis ended with a review of the practical applications available for HRV, especially in relation to threat and safety, with the aim to present how HRV could be used in more practical ways instead of just research.

Six major conclusions can be drawn from this essay. First, HRV and perception of threat and safety, and emotional regulation share neurological correlates in the prefrontal cortex and the amygdala. Second, this overlap of neurological correlates allows HRV to serve as an index of stress and health of an organism. Third, the links between HRV, ANS and central autonomic network (i.e., the heart-brain connection) suggests that autonomic regulation may be an important outcome shaped by cognitive appraisal and learning. Thus allowing HRV to be a marker of the degree to which a healthy brain provides context-based regulation. Fourth, an important property of HRV is its ability to function as an index of the ANS and provide information about PNS, SNS and/or overall autonomic regulation of the heart through a number of analyses. Fifth, high HRV compared to low HRV has been linked with several positive consequences. Sixth, a practical non-invasive and promising application of HRV to reduce stress and anxiety is the application of HRV biofeedback, which in general uses HRV analysis and breathing instructions to increases respiratory sinus arrhythmia. These conclusions are further presented with supporting studies and discussed in more detail throughout the discussion.

First of all, HRV can function as a marker of stress and health because it can be associated with perception of threat and safety, and emotional regulation via neurological and psychological correlates. The overall analysis of the thesis presents the prefrontal cortex as the structure most associated with HRV, threat and safety perception, and emotional regulation. In more detail, the pregenual anterior cingulate cortex and the subgenual anterior cingulate cortex located in the medial prefrontal cortex are areas showing functional differences during HRV (Thayer et al., 2012), threat and safety perception (Amodio & Frith, 2006) and emotional regulation (Wager et al., 2008). Both the pregenual anterior cingulate cortex and the subgenual anterior cingulate cortex are two structures highly involved in controlling visceromotor functions and autonomic regulation, which is based on just fear conditioning and emotional regulation (Thayer et al., 2012). In addition, the left subventicular extended amygdala has been identified as a region associated with HRV (Thayer et al., 2012). The amygdala has been observed as the main structure involved in threat perception (Belova et al., 2007), which can be argued indirectly links HRV with threat perception. In addition, the ventromedial prefrontal cortex has been presented to reduce fear perception by acting as a tonic inhibitor (i.e., break) for the amygdala, thus creating perceptions and experiences of safety instead of threat (e.g., Wager et al., 2009; Milad et al., 2004). Thus, the proper functioning of the ventromedial prefrontal cortex can be argued to be crucial for survival, both by releasing its inhibition on the amygdala and allowing an individual to perceive a threat, and by inhibiting the amygdala so that an individual can experience safety.

If HRV can, as it is argued through shared neural correlates, function as an index of the ventromedial prefrontal cortex, it can also function as an index of threat and safety perception and ultimately the stress and health of an individual. Several studies supporting this argument have associated vagal mediated HRV with successful emotional regulation and correlated this to activity to the ventromedial prefrontal cortex. Lane et al. (2009) found vagal mediated HRV during emotional arousal correlating with activity in the ventromedial prefrontal cortex and medial prefrontal cortex. Wager et al. (2008) concluded that activity in the ventromedial prefrontal cortex and medial prefrontal cortex during negative emotional experience reduced the emotional impact on the individual. Butler et al. (2006) supported this conclusion by presenting results of individuals with higher HRV experiencing less negative emotions than individuals with lower HRV. Wager et al. (2009) showed that when the ventromedial prefrontal cortex was deactivated it resulted in threatening experience, thus creating increased activation in periaqueductal gray, a region responsible for mediating behavioural and physiological responses to threat. In addition to this, Delgado et al. (2008) supported the notion that emotional regulation is a key component in threat perception by showing that cognitive reappraisal of fearful stimuli reduced the fear response and that this modulation was associated with increased ventromedial prefrontal cortex activity. Example of studies like this support the statement that HRV can serve as an index of how the brain deals with perception of threat and safety, and emotional regulation to adapt to the environment. By reviewing this thesis it is already clear that HRV is argued to be an index of stress and health through its associations with threat and safety perception. But, what is interesting by drawing these conclusions regarding HRV and threat perception is that they are merely conclusions based on associations. There are no real results in any study presented that can present any causation or unfolding process of HRV and threat perception in the brain. In addition to this can no study present valid results of what exactly HRV indexes in the brain. For example, does decreased HRV cause changes in ANS and differences in neurological activity in the prefrontal cortex, hence causing perception of threat? Is it the other way around, with perception of threat causing neurological changes in activity followed by decreased HRV? Is the process a bottom-up or a top-down process and how does the process unfold and what affects it?

Two major theories, the polyvagal theory and the neurovisceral integration model have been put forward trying to answer questions like this and how HRV can function as an indicator of how individuals adapt to environmental changes and cope under stress related to threat. Both theories posit that the human nervous systems' ability to track changes in the environment and respond with physical arousal that is both well integrated with behaviour and cognition and appropriate for the context is crucial for adapting to the environment. Even though both theories are very similar in many ways, the neurovisceral integration model will be favoured over the polyvagal theory in this discussion, hence its detailed description of the connection and process between the heart and the brain, and involved neurological structures. The neurovisceral integration model (Thayer & Lane, 2000; Thayer et al., 2012) considers the central autonomic network as a dynamical system that organizes different changes and regulation in the behavioural, cognitive, emotional and physiological subsystems. These systems are considered to be a form of a dynamical organized, flexible network of neural structures that is responsible for responses to environmental challenges. Vagal mediated HRV is put forward as an index of these abilities and neural structures (e.g., amygdala and medial prefrontal cortex) due to its relationship with important physiological, emotional and cognitive regulative functions (Thayer et al., 2012). Appelhans and Luecken (2006) adds that HRV can serve as a useful index for the central autonomic network's ability to regulate the magnitude and timing of an emotional response by inhibition of maladaptive responses in accordance with occurring contextual factors. This regulation is suggested to be mediated synaptic in the brain and vagal in the periphery. HRV is suggested to index how 'top–down' appraisals, mediated by cortical-subcortical pathways, shape brainstem activity and autonomic responses in the body. By providing the neurovisceral integration model, a description of how and why HRV can function as an index of the neural correlates of several adaptive functions and thus, also stress and health is provided. Event though it for now is just a theory, it has substantial and supported arguments with several supporting studies and results, making the neurovisceral integration model, in my opinion, credible. Important to note is that continued research and more concrete brain measures is needed in relation to HRV and the neurological correlates to consider the neurovisceral integration model highly valid.

One can debate back and forth regarding HRV's ability to serve as an index of brain structures involved in adaptive function, but an important property and well-established function of HRV that should not be forgotten, is its ability to function as an index of the ANS. To be able to index the ANS and especially the dysfunction of the ANS is very important to map several health aspects, especially stress. The main purpose of the ANS is to deal with internal and external stressors with the intent to maintain the homeostasis in the body (Porges, 1995). There is also growing evidence for that the ANS plays a key role in a wide range of somatic and mental diseases (Thayer & Sternberg, 2006). Cohen et al. (1998) highlighted the need of measuring stress by adding that, stress is a key factor in human disease and to be able to deepen our understanding of the stress process and how to better adapt to stressors is key to achieve several positive outcomes in life. Well, the measure of HRV does exactly this by providing information about the PNS, SNS and/or overall autonomic regulation of the heart through a number of analyses (e.g., time and frequency domain analysis). The PNS and the SNS affects the heart under different frequencies, creating different fluctuations in HR occurring at different speeds (Appelhans & Luecken, 2006). These frequency differences are the foundation for HRV analysis to differentiate and map parasympathetic and sympathetic effect separately, two subsystems of the ANS that is highly involved in the stress process (Berntson et al., 1997). This ability alone makes HRV a valuable and cost-efficient measurement of several body functions, especially in relation to stress and health. Autonomic dysfunction involving decreased PNS activity has been presented as the possible mediator in this process (Thayer & Sternberg, 2006). Respiratory sinus arrhythmia is the most prominent factor affecting the frequency of HRV and refers to changes in ANS, HR and HRV due to respiration (Grossman & Taylor, 2007). This has been presented through several studies displaying the evident differences between low and high HRV and its effect on a number of physical and psychological consequences, many of them outside the scope of this paper (e.g., Grossman & Taylor, 2007; Porges, 1992).

The high-frequency component of HRV is closely related to respiratory sinus arrhythmia and has been associated with a number of positive consequences, while the low-frequency component is associated with diminished respiratory sinus arrhythmia and increased SNS activity. Regarding the interest of this thesis, Thayer et al. (2012) showed that high-frequency HRV is linked to a greater willingness to approach novel objects and situations. Lane et al. (2009) showed that increased ability in emotional regulation was associated with high-frequency HRV and Pappens et al. (2014) presented results supporting the notion that increased HRV results in a quicker and more efficient extinction of threat full objects and situations. On the other hand, the low-frequency component of HRV has been associated with increased anxiety, subjective experience of threat and psychological stress

(Thayer & Lane, 2009). Thayer and Brosschot (2005) showed that individuals with lower resting HRV, compared to those with higher resting HRV, reacted to positive, neutral or harmless stimuli as if they were threatening and aversive. Individuals with high resting HRV was best able to match their response to the environmental demands and thus respond most appropriate. So, to conclude, we can evidently see that a high HRV compared to low HRV involves several health benefits, some of them vital for everyday functioning, making HRV as an index of the ANS crucial in many ways. But, if increased HRV is so good and associated with multiple health benefits, we should find ways to increase our HRV and reap all the advantages it posses. This is where HRV biofeedback comes into the picture.

Prior to the use of HRV, investigation and research of an organism's autonomic physiology and health required high invasive techniques using imprecise reflex based tests in humans or animals. During recent years, HRV biofeedback has been presented as a practical intervention for treating a variety of disorders, including stress and anxiety. In general, HRV biofeedback uses HRV analysis and breathing instructions to increasing respiratory sinus arrhythmia and maximise a persons HR. This leads to increased vagal modulation of the heart, diminished SNS activity and increased PNS activity (Lehrer et al., 2000). Regarding threat and safety perception, Kim et al. (2013) argued that HRV biofeedback training with the goal to modulate the functions of the ANS can enhance the role of the prefrontal cortex in executive function and thus, increase the adaptability of an individual by regulating behaviour and emotional responses. What is interesting here is that Kim et al. (2013) suggest that HRV biofeedback in fact can alter the connection between heart and the brain. In other words, by using HRV biofeedback and breathing instructions, an individual increases its respiratory sinus arrhythmia, which alters the ANS and affects the heart. This in turn affects the central nervous system and the central autonomic network, thus enhances the role of prefrontal cortex, which involves several functional changes in the brain (i.e., increased tonic inhibition on the amygdala by the ventromedial prefrontal cortex) leading to increased homeostasis and decreased threat perception. If Thayer et al. (2012) described HRV as an index of top–down processing through cognitive appraisals, Kim et al. (2013) provides the field of HRV with an alternative way of how HRV can affect an organism through bottom-up processing by the use of HRV biofeedback coupled with breathing instructions. HRV biofeedback is also becoming more available for- and used by laypersons due to cheaper and more accessible equipment in the form of pulse watches, smart watches and fitness trackers. Studies have shown (e.g., Nunan et al., 2009) that HRV measures using pulse watches can in fact give valid and reliable data.

A number of related areas of interest to the topic that has been out of the scope of this paper exist, for example meditation, subjective well-being, PTSD, cardiovascular diseases, treatments of phobias and maladaptive threat disorders, physical performance, work related stress, and positive psychology.

8.1. Limitations and Future Directions

Some of the limitations of this thesis have already been brought up in the discussion, hence those who will not be reviewed here. First of all, the field of HRV in relation to threat and safety needs to establish valid casual relations regarding the several described correlates. Is the process of HRV and threat and safety perception a top down or bottom up process, or maybe both? What and how can in fact HRV provide an index of in the brain? Sztajzel (2004) presents several important limitations with standard HRV measurements. First, clinical application of HRV analysis is limited by an absence of standardized methodology due to variability of several parameters including age, drug interferences, gender and concomitant diseases. Second, even though Malik et al. (1996) created guidelines and standards of HRV analysis, measures of HRV can still be completed using different types of equipment and no real consensus exits regarding the most accurate HRV parameter for clinical use. Finally, Sztajzel (2004) adds that because HRV deals with variations between heartbeats, the measurement is limited to individuals with sinus rhythm and with a low number of ectopic beats (i.e., disturbance of the cardiac rhythm). Thus, approximately 20 to 30% of high-risk post-myocardial infarction patients are eliminated from any HRV measure due to frequent ectopy or episodes of atrial arrhythmias, particularly atrial fibrillation. Vaschillo et al. (2008) adds that substantial individual differences and underlying psychological differences exist e.g. ANS responsiveness to stress and other negative and emotional experiences that can alter HRV measures. Another factor that in the highest degree can alter HRV is respiratory sinus arrhythmia. Despite the importance of respiratory sinus arrhythmia in HRV, controlling for respiratory sinus arrhythmia when measuring HRV is far from routine and a big confounding factor (Krygier et al., 2013). Regarding the use of HRV biofeedback, Goessl et al. (2017) states that no studies exist investigating the long-term effects of HRV biofeedback.

The future of HRV looks bright, but the field and practice of HRV analysis is in need for some adjustments. Due to HRV’s sensitivity for drugs, age, racial differences, gender and diseases, the use of HRV analysis needs to control for individual differences as much as possible to receive valid results. Racial differences in autonomic function have been discovered and have been pointed out as a potential mechanism for cardiovascular disease

(Thayer, Yamamoto, & Brosschot, 2010). Allen, Jennings, Gianaros, Thayer, and Manuck (2014) ads that racial differences in HRV measures may also be due to racial differences in neural correlates of vagal activity. This is yet to be examined and a factor that is in deep need of investigation. HRV analysis also needs to control for respiration and respiratory sinus arrhythmia. This can be done by using direct measures of respiration, thus eliminate profound changes in respiration depth and frequency (Lehrer, Sasaki, & Saito, 1999). HRV biofeedback is an intervention regarded to have the future ahead of it. But, some functional changes need to be implemented to make it more complete. HRV biofeedback needs to be more frequently incorporated into the participant's life, thus making the intervention more suited to use for laypersons and increasing HRV's ecological validity. An example of this could be in the form of in-home training sessions of HRV biofeedback. The intervention is also in need of more long-term studies including follow-up studies of the participants (Kim et al., 2013). It would also be of interest to see if and how HRV biofeedback or/with emotional regulation training, with promising new technology and knowledge, could be of real use in disorders related to stress, anxiety or maladaptive threat perception. In other words, applying all the research and putting it into practice. Researchers should also continue building on the neurovisceral integration model and/or other explanations of the neural correlates of HRV and threat perception, hence to increase the knowledge of anxiety and stress. More valid results and explanations on the relationship and process between HRV and the brain (or in more detail, the ANS and the central autonomic network) need to be presented to really give the neural correlates and the neurovisceral integration model firm ground within the field. Finally, the guidelines and standards presented by Malik et al. (1996) needs an update. To base such a big and growing field as HRV on guidelines and standards that is over 20 years old is not optimal and needs to be revised and updated. In my opinion, this is the most crucial change for the future of HRV.

9. Conclusion

HRV has been proposed as an index capable of measuring both the health and level of stress put on an organism by supplying information regarding the heart and the brain and the connection in between. HRV refers to beat-to-beat variations in HR and is thought to be a useful signal in understanding and providing valuable information of the ANS. Increased HRV has been associated with several health benefits and superior executive functions including a greater willingness to approach novel objects, greater ability in emotional regulation, a smaller negativity bias, and a more efficient and quicker extinction of threat full objects and situations. On the other hand, lower HRV has been associated with a number of negative consequences like cardiovascular morbidity, depression, increased anxiety, psychological stress, mortality and subjective experiences of stress.

Research has also linked HRV to several brain regions involved in emotional regulation and perception of threat, and safety including the amygdala and the medial prefrontal cortex. These structures form a system, which integrates interoceptive, perceptual, motor, and memory systems to create accurate representations of threatening situations and form adaptive response for survival. This thesis presents research of the idea that HRV can in fact provide an index to which degree the medial prefrontal cortex controls and guides this “core integration” system in the brain that directly regulate the heart including autonomic function. This supports the notion that HRV not only is an index of the function of ANS and the heart, but also an index for certain executive functions in the brain and how these affect the heart. Ultimately, this suggests that HRV is a potential and promising marker for the stress and health of an organism associated with adaptability and adaptive behaviour like perception of threat and safety as well as the heart-brain connection. The problem with these results is that they are merely results and theories based on correlations and associations. No studies of the neural correlates of HRV and stress present any valid and significant results of how the process unfolds or what actually HRV is an index of. Researchers have argued for HRV to be mediated and index both top-down processes and bottom-up process. To really present HRV as an index capable of index stress mediated by the brain, research need to present clear and valid results of how and what HRV actually measures. In my opinion, one can with good support state that HRV is one way or another associated with the neurological correlates of stress and that it is only a matter of time until valid research can describe the process in more detail.

A practical application of HRV has emerged during recent years called HRV biofeedback. The intervention typically uses HRV as biofeedback coupled with breathing techniques with the goal to increase HRV and reap all the advantages increased HRV posses. Though studies of HRV biofeedback show controversial support in regards of decreasing threat perception and anxiety, the intervention definitely looks promising for future research. Several limitations exist regarding HRV both in clinical and practical use. The most important problem that needs to be addressed in the future is an update of the guidelines and appropriate standards of Malik et al. (1996).

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