

## REVIEW ARTICLE

## Autonomic dysfunction and heart rate variability in depression

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Depression occurs in people of all ages across all world regions; it is the second leading cause of disability and its global burden increased by 37.5% between 1990 and 2010. Autonomic changes are often found in altered mood states and appear to be a central biological substrate linking depression to a number of physical dysfunctions. Alterations of autonomic nervous system functioning that promotes vagal withdrawal are reflected in reductions of heart rate variability (HRV) indexes. Reduced HRV characterizes emotional dysregulation, decreased psychological flexibility and defective social engagement, which in turn are linked to prefrontal cortex hypoactivity. Altogether, these pieces of evidence support the idea that HRV might represent a useful endophenotype for psychological/physical comorbidities, and its routine application should be advised to assess the efficacy of prevention/intervention therapies in a number of psychosomatic and psychiatric dysfunctions. Further research, also making use of appropriate animal models, could provide a significant support to this point of view and possibly help to identify appropriate antidepressant therapies that do not interfere with physical health.

**Keywords**

Animal models, autonomic function, cardiovascular disease, depression, emotion, heart rate variability

**History**

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**Introduction**

The three leading causes of burden of disease in 2030 are projected to include HIV/AIDS, unipolar depressive disorders and ischemic heart disease (Mathers & Loncar, 2006). Impressively, depression scores second in this seeding and, at present, have an extremely high prevalence worldwide. Depressive disorders are common mental disorders that occur in people of all ages across all world regions and were found to be the second leading cause of years lived with disability in 2010. Noticeably, also because of population growth and aging, the global burden of depressive disorders increased by 37.5% between 1990 and 2010 (Ferrari et al., 2013). One of the underlying pathophysiological mechanisms characterizing depression is autonomic dysfunction, which also appears to be a central biological substrate linking depression to a number of concurrent physical (e.g. cardiovascular) dysfunctions (Kemp et al., 2012; Licht et al., 2008; Udupa et al., 2007; Thayer & Lane, 2007). Therefore, it is not surprising that an accurate, non-invasive evaluation of autonomic nervous system activity – as obtained by measuring heart rate variability (HRV) – has become extremely popular in various research fields, ranging from cardiology to psychiatry.

The literature supports the idea that vagal outflow has a crucial inhibitory function in the regulation of a number of

allostatic systems and therefore would have a central role in preventing stress-related psychosomatic disorders (Thayer & Lane, 2009). At the same time, there are studies supporting the view that HRV is a promising marker of the efficiency of the prefrontal cortex in modulating emotional reactivity, psychological flexibility and social engagement (Geisler et al., 2013).

Nevertheless, further proof is needed (possibly obtained also via highly controllable experimental paradigms with animal models) on the validity of HRV as an endophenotype for a broad range of physical and psychological dysfunctions, which could hopefully open the way to innovative prevention and intervention programs.

**Depression and cardiovascular disease**

Depression is an established risk factor for cardiovascular disease (CVD) and mortality (Barefoot & Schroll, 1996; Carney et al., 2003; Frasure-Smith et al., 1995; Freedland et al., 2003; Glassman, 2007; Lett et al., 2004; Penninx et al., 2001; Zellweger et al., 2004). Individuals with major depression are much more likely to suffer coronary artery disease and acute cardiovascular sequelae such as myocardial infarction, congestive heart failure and hypertension (Nemeroff & Goldschmidt-Clermont, 2012). In addition, elevated depressive symptoms predict mental stress-induced myocardial ischemia after acute myocardial infarction (Wei et al., 2014) as well as long-term cardiovascular mortality in patients with atrial fibrillation and congestive heart failure (Frasure-Smith & Lespérance, 2010).

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This comorbidity is a relevant public health concern, given that CVD and depression are some of the leading causes of disability worldwide and are forecasted to be the two main disease burdens by 2020 (Licinio et al., 2002; Mathers & Loncar, 2006; Murray & Lopez, 1997).

The association between altered mood and cardiovascular dysfunction is found in individuals both with and without cardiac antecedents, and is independent of traditional cardiovascular risk factors such as body mass index, physical activity, hypertension and hypercholesterolemia (Carney et al., 2003; Penninx et al., 2001). For these reasons, Lichtman et al. (2014) recently proposed, on the basis of an extensive literature review, that the American Heart Association should formally allocate depression as a risk factor for adverse medical outcomes in patients with acute coronary syndrome.

Despite the evidence of a strong clinical association between affective disorders and CVD, little is understood regarding the pathophysiology and possible biomarkers underlying these comorbid disorders. A few biological substrates have been proposed as mediators of this link, including alterations in the platelet clotting cascade, inflammatory processes, endothelial dysfunction, altered autonomic neural regulation, sympatho-adrenomedullary hyperactivity, changes in the activity of the hypothalamic–pituitary–adrenocortical axis and hypothalamic–pituitary–thyroid axis (Carney et al., 1995, 2002; Glassman & Shapiro, 1998; Laghrissi-Thode et al., 1997; Maes et al., 1997; Stein et al., 2000).

### Autonomic dysfunction, low HRV and poor health

Among the biological factors that are hypothesized to account for the association between depression and CVD, autonomic neural dysfunction appears to be a serious mechanistic candidate (Gehi et al., 2005; Licht et al., 2008).

Alterations of autonomic nervous system functioning that promotes vagal withdrawal are reflected in reductions of HRV. However, lowered HRV is a widely recognized prognostic risk factor for adverse cardiovascular events (e.g. myocardial infarction and arrhythmias) as well as cardiac mortality (Bigger et al., 1993; Carney & Freedland, 2009; Dekker et al., 2000; Tsuji et al., 1996; Udupa et al., 2007, van der Kooy et al., 2006).

A few years ago, Thayer and Lane (2007) reviewed the literature on the relationship between vagal activity and the risk of CVD and underscored the evidence that decreased vagal function is associated with each of the eight risk factors for heart disease, as listed by the National Heart, Lung, and Blood Institute of the US National Institute of Health. These factors are hypertension, diabetes, high cholesterol, smoking, physical inactivity, obesity, age and family history of heart disease. In addition, an emerging risk factor for CVD such as psychosocial stress was also shown to correlate significantly with decreased HRV (Brosschot et al., 2007; Thayer & Fischer, 2005).

Interestingly, a few large epidemiological studies proved that decreased HRV is a risk factor for all-cause morbidity and mortality (Liao et al., 2002). Indeed, several physiological systems that are important for health and disease have been linked to vagal function and HRV, including glucose regulation, hypothalamic–pituitary–adrenocortical axis function and

inflammatory processes. Decreased vagal function and lowered HRV were shown to be associated with increased fasting glucose and glycated hemoglobin levels, increased overnight urinary cortisol and increased proinflammatory cytokines and acute-phase proteins (Thayer & Sternberg, 2006), all of which have been associated with increased allostatic load and poor health (McEwen, 1998). Therefore, vagal activity, which plays an inhibitory function in the regulation of these allostatic systems, might serve as a useful endophenotype for a number of emotional dysregulations, psychological disorders and physical dysfunctions.

### Emotion regulation, the central autonomic network and HRV

Thayer and Lane (2009) nicely outlined a model of neurovisceral integration in the context of emotion regulation and dysregulation. According to the authors, emotional regulation is a skill that has strong implications for health. An adequate emotional activation implies the selection of an appropriate response and the inhibition of less functional ones, in such a way that energy use is matched to fulfill situational requirements. HRV represents a resource that can be used in situations where emotional regulation is called for. These authors reported that individuals with higher degrees of baseline HRV produce more context appropriate emotional responses; moreover, phasic activations in HRV in response to situations that require emotional tuning were shown to facilitate effective emotional regulation. In other words, HRV functions at both the trait and state levels as a tool that can be used to modulate emotional activation. Therefore, the relationship between HRV and emotional regulation has important implications in studying the link between physical health and specific emotional states such as depression, anxiety, alexithymia, anger and hostility (Thayer & Lane, 2009).

Other studies support the notion that HRV may be considered an index of the individual capacity for psychological flexibility, self-regulation and social engagement. Again, higher HRV in resting conditions seems to be associated with positive aspects of one's psychological makeup, namely more adaptive self-regulation and social engagement (Geisler et al., 2013). Interestingly, Kemp et al. (2012) reported that exogenously administered oxytocin, a neuropeptide that plays a pivotal role in human social behavior and cognition, is able to increase resting HRV.

At the central nervous system level, sympathoexcitatory, cardioacceleratory subcortical circuits are controlled by the prefrontal cortex (Amat et al., 2005, Thayer & Lane, 2009). The amygdala, which has outputs to endocrine, autonomic and other physiological regulatory systems, becomes active in case of threat and uncertainty and is under tonic inhibitory control via GABAergic mediated projections from the prefrontal cortex. Under stress conditions, specific areas of the prefrontal cortex become hypoactive, which implies disinhibition of sympathoexcitatory circuits and energy mobilization.

In order to gain a deeper understanding of these regulatory processes, the central autonomic network (CAN) has to be briefly describe (Figure 1). It includes the insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus of the tractus solitarius and

ventrolateral medulla (Benarroch, 1993). The output of the CAN controls the cardiac sinoatrial node via the stellate ganglion and the vagus nerve. The output of the CAN is under inhibitory control via GABAergic neurons in the nucleus of the solitary tract (NTS). There are both direct and indirect pathways linking the frontal cortex to autonomic motor circuits responsible for both the sympathoexcitatory and parasympathoinhibitory effects on the heart. Prefrontal cortical areas, including the orbitofrontal cortex and medial prefrontal cortex, tonically inhibit the amygdala via pathways to intercalated GABAergic neurons (Barbas et al., 2003). Disinhibition of the central nucleus of the amygdala (CeA) leads to increased HR and decreased HRV by three pathways: (1) activation of sympathoexcitatory neurons in the rostral ventrolateral medulla (RVLM) by decreased inhibition from tonically active neurons in the caudal ventrolateral medulla (CVLM) leading to a net increase in sympathetic activity; (2) inhibition of neurons in the NTS that brings about inhibition of tonically active nucleus ambiguus (NA) and dorsal vagal motor nucleus (DVN) neurons, leading to a decrease of parasympathetic activity and (3) direct activation of sympathoexcitatory RVLM neurons leading to an increase in sympathetic activity (Saha, 2005) (Figure 1). Thus, decreased activity of the prefrontal cortex would lead to disinhibition of tonically inhibited CeA, which in turn would lead to disinhibition of

sympathoexcitatory neurons in the RVLM and inhibition of parasympathoexcitatory neurons. These two mechanisms would be primarily responsible for the increase in HR and decrease of vagally mediated HRV (Thayer & Lane, 2009) (Figure 1).

It has been proposed that the prefrontal cortex is switched off during threat to let automatic processes regulate behavior (Arnsten & Goldman-Rakic, 1998). This prefrontal inactivation may be adaptive by facilitating involuntary behaviors, which organize appropriate responses without delay from the more deliberative and consciously guided prefrontal cortex. However, when such a state is prolonged, it may bring about allostatic overload and has implications for the organism health (McEwen, 1998). Interestingly, psychopathological conditions such as depression, anxiety and post-traumatic stress disorder are associated with prefrontal cortex hypoactivity and lack of inhibitory neural mechanism, as revealed by poor habituation to novel neutral stimuli, failure to recognize safety signals and poor affective information processing and regulation (Thayer & Friedman, 2004).

Shook et al. (2007) have showed that larger resting HRV is associated with (i) smaller negativity bias and (ii) greater willingness to approach positive novel objects. This suggests that appropriate functioning of inhibitory processes is vital to the preservation of the integrity of the system and therefore is crucial for health. These inhibitory processes can be evaluated via indexes of parasympathetic function obtained through the measurement of HRV. Thus, as nicely stated by Thayer et al. (2012), ‘‘HRV may serve as a proxy for vertical integration of the brain mechanisms that guide flexible control over behavior with peripheral physiology, and as such provides an important window into understanding stress and health’’.

This point of view is rooted in Porges’ polyvagal theory (Porges, 1995), according to which HRV is associated with the experience and expression of social and emotional behavior. This theory distinguishes between the myelinated and unmyelinated vagus nerves: the myelinated vagus underpins the changes in HRV and approach-related behaviors including social engagement, while the phylogenetically older unmyelinated vagus – in combination with the SNS – supports the organism during emergency and life-threatening events. This theory draws on the Jacksonian principle of dissolution in which higher neural circuits inhibit lower circuits, but when higher circuitry is functionless, the lower rises in activity (Porges, 2009). This process is a potential mechanism for the expression (and disruption) of positive social behaviors. According to the theory, social engagement can only occur when the environment is perceived as safe and the defensive circuits are muffled; if these circuits are not inhibited when they are supposed to be, then the ability to detect and express positive social cues is hampered.

### Measuring HRV

What is measuring HRV? What kind of information is provided by this type of analysis on electrocardiographic recordings? HRV is an indirect, non-invasive measurement of beat-to-beat temporal changes in heart rate, which reflect the output of the CAN and the modulating role of the autonomic nervous system. It can be obtained from ECG recordings and

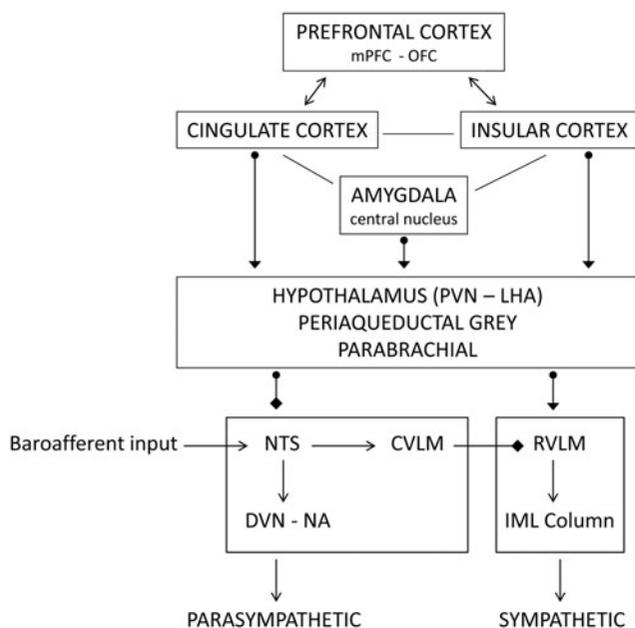


Figure 1. Schematic illustration depicting the central neural network that regulates the autonomic input to the heart. The prefrontal cortex (specifically the medial prefrontal cortex – mPFC, and the orbitofrontal cortex – OFC), in conjunction with the cingulate and the insula cortices, establish bi-directional interconnections with the amygdala, the latter being under tonic inhibitory control by the PFC. The activation of the amygdala (more specifically the central nucleus) inhibits the nucleus of the solitary tract (NTS, solid square), which in turn inhibits inhibitory caudal ventrolateral medullary (CVLM) inputs to the rostral ventrolateral medullary (RVLM) sympathoexcitatory neurons (solid square), and simultaneously inhibits vagal motor neurons in the dorsal vagal nucleus (DVN) and the nucleus ambiguus (NA), thus increasing heart rate. The central nucleus of the amygdala can produce this effect also via direct activation of the sympathoexcitatory neurons of the RVLM. PVN, paraventricular nucleus; LHA, lateral hypothalamic area; IML column, intermediolateral column of the spinal cord. Adapted from Thayer and Lane (2009).

allows to get information about the dynamic changes of sympathovagal modulation at the cardiac sinoatrial node. It is broadly applied in different research areas including psychophysiology, biological psychology, cardiology and psychiatry. Not coincidentally, it has been recognized as a reliable diagnostic tool by the American College of Cardiology and the American Heart Association, which recommended education and skill in HRV assessment as a prerequisite to competence in ambulatory ECG interpretation (Kadish et al., 2001). Moreover, the American College of Cardiology/American Heart Association 2004 practice guidelines recommended the use of HRV to assess the risk of ventricular arrhythmias in the management of patients recovering from myocardial infarction (Antman et al., 2004).

Analysis of HRV was first used in clinical practice about 50 years ago. The first application of HRV dates back to 1965 when Hon & Lee (1965) noted that the reduction of HRV preceded fetal distress, in particular hypoxia, before any appreciable change occurred in heart rate itself. Then, in the late 1970s the reduction of HRV was first correlated with increased mortality and arrhythmic events in survivors of myocardial infarction (Wolf et al., 1978). The clinical importance of HRV became appreciated in the late 1980s, when it was confirmed that HRV was a strong and independent predictor of mortality after an acute myocardial infarction (Kleiger et al., 1987). More recently, HRV analysis has been increasingly used to assess autonomic dysfunction in different pathological conditions, including diabetes, obesity, anxiety and depression (Thayer & Lane, 2009).

The first step for the analysis of HRV is obtaining high quality ECG recordings under stationary conditions. The ECG signals are analogue/digital converted for computer processing and, in order to have a good time resolution, a sampling rate of at least 250 Hz for human ECG signals and 1000–5000 Hz for rats and mice is recommended. HRV is quantified by analyzing the variations of the time intervals between consecutive normal heart beats. The usual definition of an inter-beat interval is the time between consecutive R wave peaks (R–R interval). The time-course of the R–R interval is called tachogram and further quantitative analysis of this curve allows the HRV parameters to be obtained. Advances in computer technology allowed sequential R–R intervals to be measured accurately and recorded in real time. Note, it is crucial that before processing these signals are corrected for ectopic and missed beats.

There are a number of methods for quantifying HRV based on different mathematical approaches, which can be classified in three main categories: time domain, frequency domain and nonlinear dynamics methods (Task Force, 1996).

### Time domain indexes

The time domain parameters are calculated with simple mathematical methods to measure the amount of variability present in a specific time period in a continuous ECG signal. The most frequently used time domain indexes of HRV are the following.

The standard deviation (SD, ms) of the average R–R interval is the square root of the variance and reflects all the cyclic components responsible for variability in the recording

epoch; it measures the state of the balance between sympathetic and parasympathetic control of HR. In other words, it estimates overall HR variability and therefore includes the contribution of both branches of the ANS to the HR variations. SD depends largely on the duration of the recording and, therefore, values from recordings of different duration should not be compared. The root mean square of the differences between adjacent R–R intervals ( $r$ -MSSD, ms) is a widely used, highly reliable index. To obtain the value of this parameter each difference between successive R–R intervals is squared, summed, the result averaged and then the square root obtained. R-MSSD reflects short-term HRV measured over a much longer period of time. Another useful parameter is the one that quantifies the percentage of successive R–R interval differences that are larger than 10 or 20 ms for rodents (pNN10 and pNN20, %) and 50 ms for humans (pNN50, %); therefore, this index is obtained by counting the number of beat to beat changes that exceed a pre-set threshold in a recording.

Time-domain measures based on R–R interval variations such as SD are useful clinical tools for detecting abnormalities of autonomic neural activity, but cannot be used to quantify specific changes in sympathetic or parasympathetic activity (Pumprla et al., 2002). However,  $r$ -MSSD and pNN10 (20 or 50) can be considered as reliable vagal indexes because they quantify the short-term, high frequency (HF) variations of the R–R interval, which are due solely to the activity of the parasympathetic nervous system (Stein et al., 1994). Therefore, these latter indexes provide sensitive and interchangeable measurements of parasympathetic activity, which are easy to measure in human ambulatory ECGs (Kleiger et al., 1993) as well as in rodents' radiotelemetric ECG recordings (Sgoifo et al., 1998).

### Frequency domain indexes

Spectral analysis decomposes a time-dependent fluctuating signal into its sinusoidal components and allows to detect and quantify the amount of cyclical variation present at different frequencies (Malliani et al., 1991). Graphically, it is presented by plotting the amount of variation on the  $Y$ -axis against the frequency at which it occurs on the  $X$ -axis. This graph is usually named the power spectrum and the area under the curve at different frequencies (expressed as spectral power) provides a quantitative measure of the amount of high and low frequency (LF) variability contained in the signal. Various algorithms can be used to evaluate the oscillatory components and they are generally classified in non-parametric and parametric methods (Task Force, 1996). The most commonly used non-parametric algorithm is fast Fourier transform (FFT), which is characterized by computational efficiency and simple implementation. FFT is usually employed with *a priori* selection of the number and frequency range of the bands of interest. However, the reliability of this method is affected by the frequency resolution, which is directly related to the duration of the recording period (Aubert et al., 1999). The autoregressive (AR) modeling, the most used parametric algorithm, can decompose the overall spectrum into smoother spectral components, which can be distinguished independent of preselected frequency bands. The AR algorithm allows the

automatic calculation of low- and high-frequency power components with an easy identification of the central frequency of each component (Task Force, 1996). The most important advantage of this method is that it can provide a reliable and accurate spectral estimation even with short segments of data.

Spectral analysis of HRV requires to be performed on stationary records of at least 200–500 consecutive heart-beats. To obtain a reliable spectral estimation the analyzed ECG signal should satisfy several requirements. To attribute individual spectral components to well-defined physiological mechanisms the signal should be stable, i.e. the mechanisms modulating heart rate should not change during the recording. In addition, for a reliable estimation it is important to select the proper sampling rate. Ectopic beats, arrhythmic events, missing data, pauses, non-periodic R–R interval changes and noise may alter the estimation of the power spectral density of HRV. Therefore, artifacts have to be removed from the signal before spectral analysis is performed (Task Force, 1996).

Since the first studies on power spectral analysis (Akselrod et al., 1981; Penaz et al., 1968; Sayers, 1973), it appeared clear that the HRV signal contains well-defined rhythms, which correspond to underlying physiological mechanisms. In a typical power spectral density curve three main frequency bands can be found: very low frequency (VLF), LF, HF.

These three specific components characterize the spectral profile of many mammals, but the frequency range of each band depends on the heart rate of each species (Aubert et al., 1999). The amplitude of each component is assessed by its power spectral density, measured as the integral of the amplitude-frequency curve and expressed in  $\text{ms}^2$ . VLF component (normally ranging from 0.00 Hz to 0.03 Hz in humans and from 0.00 Hz to 0.25 Hz in rats) contains long period rhythms and its power is due to long-term regulation mechanisms, such as thermoregulation, renin–angiotensin system and other humoral factors (Kitney & Rompelman, 1977). The LF band is set in the range 0.03–0.15 Hz for humans and 0.25–0.75 Hz for rats, with a central frequency generally located, respectively, at 0.1 and 0.50 Hz. Its physiological interpretation is still controversial. Actually, both sympathetic and parasympathetic contributions are considered to determine LF (Eckberg, 1997). However, an increase in its power has been observed as a consequence of sympathetic activation, such as rest-tilt maneuver, stress, hemorrhage. For this reason, many authors consider the LF power as a marker of increased sympathetic activity (Malliani et al., 1991). The H component is set in the range 0.15–0.4 Hz for humans and 0.75–2.5 Hz, with a central frequency at the respiratory rate around 0.25 and 1.5 Hz, respectively. The parasympathetic activity is considered to be responsible for HF power density. It is also associated to respiration-linked oscillation of HR due to the intrathoracic pressure changes and mechanical variations caused by breathing activity. The role of the vagus nerve in determining the HF band of the spectrum was confirmed after experiments with vagotomy (Chess et al., 1975) or after muscarinic receptor blockade (Convertino, 1999).

Power in the LF and HF bands can be expressed in absolute values ( $\text{ms}^2$ ) or normalized units (nu). Normalized units are obtained by dividing the power of a given component by the total power from which VLF has been

subtracted and multiplying by 100. The LF/HF ratio estimates the fractional distribution of power, which is taken as an indirect measure of sympathovagal balance.

### Nonlinear methods

In recent years a series of complex techniques has been developed based on nonlinear dynamics and chaos theory that could be able to quantify those characteristics that cannot be revealed by linear methods (Merati et al., 2004; Porta et al., 2009). The variability of heart rate is determined also by nonlinear phenomena, which are the result of complex interactions between hemodynamic, electrophysiological, humoral and neural mechanisms. Methods of nonlinear dynamics define parameters that quantify complicated interactions of independent and interrelated components. Some evidence suggests that a reduction in complexity of cardiac activity comes along with a decrease in parasympathetic modulation, suggesting that a considerable amount of nonlinear behavior is provided by this component of the autonomic nervous system (Beckers, 2002).

Examples of these new methods based on chaos theory are: fractal dimension, approximate entropy, detrended fluctuation analysis, Lyapunov exponents, symbolic analysis. Nonlinear dynamics methods for HRV analysis may provide a more sensitive approach to characterize function or dysfunction of the autonomic control mechanisms. Up to now, chaos analysis for evaluation of autonomic regulation has been investigated both in normal subjects and patients with CVD (Guzzetti et al., 2000; Kagiya et al., 1999). However, these techniques are mathematically complicated and require more powerful computing. In addition, they are still under development and evaluation.

### HRV and depression

Reduced HRV has been described in a variety of psychiatric conditions, including bipolar disorder (Lee et al., 2012), schizophrenia (Berger et al., 2010) and attention deficit hyperactivity disorder (Buchhorn et al., 2012). This evidence points to the negative effect of various psychological dysfunctions on the activity of the autonomic nervous system, which appears to be linked to emotion dysregulation (Thayer & Lane, 2009).

Reductions in HRV, specifically in HF variability (parasympathetic modulation), have been reported in major depressive disorder patients in comparison with healthy control subjects. Consistent with this, the LF/HF ratio is higher in these patients than in controls, suggesting a sympathetic prevalence and an overall reduction in HRV (Udupa et al., 2007; van der Kooy et al., 2006).

However, special caution has to be used when relating autonomic dysfunction to psychiatric conditions, as many potential confounding variables might be interfering. In particular, apart from the individual history of CVD, the presence/absence of different pharmacological medications and the time elapsed after their discontinuation seems to play an important role. The latter point, in particular, characterizes an ongoing debate on whether cardiac autonomic dysfunction is a feature of depression *per se* or whether it is a consequence of pharmacological antidepressant treatment. Indeed there

seem to be data supporting both points of view. On one hand, Kemp et al. (2010) suggest, based on a large meta-analysis, that depression without CVD is associated with attenuated HRV, which seems to decrease with increasing depression severity. On the other hand, Licht et al. (2008) maintain that the association between depression and lowered HRV appears to be driven mostly by the effect of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and other antidepressants such as monoamine oxidase inhibitors (Licht et al., 2008).

In Kemp's meta-analysis, unmedicated depressed patients display reduced HRV compared to control subjects, suggesting an underlying autonomic dysfunction (Kemp et al., 2010). The authors concluded that such reductions are most apparent with nonlinear measures of HRV. More recently, the same research group extended these meta-analytic findings and confirmed that HRV is reduced in an independent and otherwise healthy, unmedicated sample of patients with major depressive disorder (Kemp et al., 2012). This study also indicated that patients with major depression and comorbid generalized anxiety disorder display the greatest reductions in HRV relative to depressed patients without comorbidity or with comorbid panic and posttraumatic stress disorder. The authors suggested that subjects with generalized anxiety disorder, a disorder characterized by worry and hypervigilance, might have difficulty disengaging from threat detection, which may lead to a chronic withdrawal of parasympathetic neural activity, an over-activation of the sympathetic branch and persistent reductions in HRV, subsequently increasing the risk for CVD and sudden cardiac death (Kemp et al., 2012). These publications have great relevance as previous studies linking HRV with depression had been conducted on patient samples with prior history of CVD (Carney & Freedland, 2009; Taylor, 2010). Although providing a significant contribution in understanding the relationship between depressed mood physiology and morbidity, the latter ones left open the question whether HRV is also decreased in CVD-free subjects with depression, as factors concomitant with CVD would likely contribute to HRV parameter reductions.

A rather different opinion is supported by the research group coordinated by Brenda Penninx. These researchers found that depressed individuals have significantly lower total HRV and significantly lower HRV in the respiratory frequency range (lower cardiac vagal modulation) (Licht et al., 2008), and their results were in keeping with a previous meta-analysis of smaller studies (Rottenberg, 2007). Comorbid anxiety and life style factors (including physical activity) did not seem to explain the lower HRV values in depressed individuals. However, the authors maintain that the association was driven mainly by the effects of antidepressants. Depressed patients using antidepressants showed significantly lower values of HRV parameters, whereas differences between control and depressed individuals not taking antidepressants were much smaller or even non-significant depending on the HRV index considered. In their study subjects, the use of TCAs, SNRIs and SSRIs was associated with decreased HRV, whereas associations were weaker or even non-significant when HRV was compared between antidepressant-naïve depressed subjects and healthy control

subjects. In addition, they also found indications for a dose-response effect, as a higher derived daily dose was significantly associated with lower HRV (Licht et al., 2008).

Nevertheless, the reported autonomic neural dysregulation in antidepressant users could have been resulted either from the effects of the drugs or from underlying differences between patients taking and not taking antidepressants. In a subsequent longitudinal study, Licht et al. (2010) provided support for a causal, lowering effect of antidepressants (TCAs, SNRIs and SSRIs) on cardiac vagal tone. Furthermore, they also showed that antidepressant discontinuation allowed the recovery of autonomic neural modulation of cardiac activity, suggesting that the unfavorable effects are (at least partly) reversible. The authors concluded that the antidepressant use inherent in having these disorders could explain part of the link between depression and the development of CVD.

Therefore, although antidepressants are effective for depression symptoms, their impact on CVD risk is open to question. It is possible that their peripheral increased sympathetic/decreased parasympathetic modulation could worsen sympathovagal imbalance or, alternatively, that such imbalance is caused by depression severity, indexed by antidepressant use (Brunoni et al., 2012).

### Animal models of depression and autonomic imbalance

In combination with studies involving human subjects, integrative research that employs valid and reliable animal models could (i) clarify whether autonomic imbalance is indeed associated with depression, regardless of comorbidities (e.g. cardiovascular) or pharmacological treatments, and (ii) improve our understanding of the neurocircuitry and neurochemical bases that underlie the association between mood and HRV.

Time- and frequency-domain indexes of HRV have been successfully used in animal studies investigating the autonomic correlates of stress and anxiety. Indeed, a number of publications showed that HRV analysis works well in discriminating among different acute and chronic, environmental and social challenges, between aggressive and non-aggressive individuals, as well as in anxiety studies or studies on mutant mice (Carnevali et al., 2012a, 2013, 2014a,b; Costoli et al., 2004, 2005; Sgoifo et al., 1997, 2005).

However, the literature is not so abundant when it comes to rodent models of depression-related autonomic dysfunction. Data obtained in rats using the chronic mild stress (CMS) protocol have indicated that depression-like symptoms are associated with autonomic dysfunction, including reduced HRV as well as elevated HR and sympathetic cardiac tone (Grippo et al., 2003). While the behavioral changes associated with CMS were shown to recover within a few weeks following cessation of the stressors, the cardiovascular disruptions did not normalize at the same rate. Specifically, at the time point when anhedonia and reduced somatomotor activity were no longer observable after cessation of the CMS paradigm, animals continued to display an increase in resting HR, a decrease in HRV, and exaggerated cardiac reactivity to stress (Grippo et al., 2003). These findings suggest that simple remediation of the depressive signs is not associated

with alleviation of underlying autonomic/cardiovascular pathophysiology. Consistent with these findings are those from Carney et al. (2000), suggesting that pharmacotherapy or psychotherapy for depression may partially improve behavioral symptoms and even HR and HRV, but may not be sufficient to repair cardiovascular status to baseline levels. Given these findings, it is important to gain a greater comprehension of the specific mechanisms underlying the autonomic changes associated with negative mood, to help developing more effective treatments for patients with depression and CVD. Studies with the CMS model have implicated the sympathetic nervous system as an important mechanism. Selective blockade of sympathetic inputs to the heart with a drug (propranolol hydrochloride) indicated that sympathetic drive was elevated in rats exposed to CMS, similar to the excess sympathetic drive observed in patients with CVD (Grippeo et al., 2002, 2003). In addition, CMS was associated with an increased vulnerability to ventricular arrhythmias when the cardiovascular system was challenged with a pro-arrhythmic drug (aconitine) (Grippeo et al., 2004). Depression may therefore be associated with exaggerated sympathetic drive to the heart and ventricular electrical instability, which in turn influence cardiovascular function and disease outcomes.

In another study, Grippeo et al. (2006) showed that chronic fluoxetine treatment prevented anhedonia in rats exposed to CMS. However, the pharmacological treatment only partially prevented specific cardiovascular changes associated with CMS, including elevated resting HR, exaggerated pressor and HR responses to an acute stressor, reduced cardiac output and stroke volume and HR exaggerated response to beta-adrenergic receptor blockade.

Another promising experimental paradigm for mimicking a depression-like state in rats implies the combination of a single episode of social defeat followed by social isolation. This animal model, with evident face and construct validity properties, was shown to produce a set of biological changes that are commonly taken as markers of depression, including decreased body weight gain, reduced preference for sucrose consumption (anhedonia), functional and structural changes of the hypothalamic–pituitary–adrenocortical axis, increased anxiety-like behavior in the elevated plus maze test. As far as cardiac autonomic balance is concerned, rats with depression-like behavior exhibited transitory HR circadian rhythm alterations and lack of habituation of cardiac vagal withdrawal when re-exposed to an acute non-social stressor (Carnevali et al., 2012b).

Similarly, female prairie voles (*Microtus ochrogaster*) exposed to long-term social isolation exhibited depression-like behaviors in validated operational tests, which were associated with a significant increase in resting HR, reductions in HRV (time-domain indexes), occurrence of arrhythmias and exaggerated heart rate responses during an acute stress episode. These cardiac changes in response to social isolation were ascribed to a disruption of autonomic balance including both sympathetic and parasympathetic neural modulation (Grippeo et al., 2007, 2012).

Another interesting study was performed using the Flinders-Sensitive Line rat, a validated genetic animal model of depression showing a number of behavioral and

neurochemical similarities to depressed humans. These rats exhibited cardiovascular autonomic abnormalities (reductions in HRV and spontaneous baroreflex sensitivity) which the authors ascribed to an abnormal serotonergic control of the vagal input to the heart (Hildreth et al., 2008). Specifically, they suggested that abnormal 5-HT<sub>1A</sub> receptor function might involve GABA synapses in the NA, leading to reduced inhibition of cardiac vagal preganglionic neurons and poor reflex control of HR.

On the way to establishing the neurobiological substrate of depression-related autonomic dysfunction, Wood et al. (2012) studied a cohort of rats exposed to intermittent social defeat and tested the efficacy of a corticotropin-releasing factor-1 (CRF1) receptor antagonist to prevent social stress-induced behavioral, neuroendocrine and cardiac autonomic changes. This study demonstrated that social stress in rodents concurrently elicits persistent depressive-like behaviors and cardiovascular changes consistent with exaggerated sympathetic drive as evidenced by decreased HRV and increased LF/HF ratio. The cardiac autonomic consequences of social stress observed in this rodent model corresponded rather well with the clinical literature indicating that depression is associated with a reduction in HRV (Kemp et al., 2010; Udupa et al., 2007). Moreover, this study suggested that CRF1 antagonism confers resistance to both depressive-like behaviors and cardiac autonomic changes, offering insight into deeper understanding and potential treatment of these comorbid conditions.

## Conclusion

The measurement of HRV allows to assess non-invasively parasympathetic influences and sympathovagal balance at the level of the heart. The available literature indicates that decreased HRV is a valuable marker of cardiovascular morbidity and mortality risk. However, it appears that lowered HRV is tightly linked also with other physical dysfunctions and with a number of psychopathological conditions.

A better understanding of the autonomic neural regulation changes that characterize depression is of great significance to public health since a large body of evidence indicates that depression is an independent risk factor for CVD. Many studies suggest that depression *per se* is associated with reduced HRV, although the causal role of pharmacological antidepressant treatment on cardiac autonomic dysregulation cannot be ruled out. Further research on animal models could provide a priceless contribution in solving this open issue and offer new insights in the neurobiological bases of the association between mood disorders and decreased heart rate variability, thus helping to identify appropriate antidepressant therapies that do not interfere with cardiovascular health.

## Declaration of interest

The authors report no conflicts of interest.

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