Heart and soul: heart rate variability and major depression

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There is a bidirectional relationship between affective disorders and cardiovascular abnormalities, often described as a downward spiral, whereas major depressive disorders (MDD, and anxiety disorders) significantly increase the risk of developing cardiovascular diseases (CVD); CVD are also associated with increased risk of developing MDD (and anxiety disorders). Moreover, the prognosis and progression of CVD is significantly worsened in the presence of MDD. Heart rate variability (HRV) has often been suggested as a potential mediator in this comorbidity. In this review, we discuss HRV alterations in MDD. However, we mainly focus on the direct relationship between HRV alterations and psychiatric symptoms, rather than its relationship with CVD, as this has been reviewed elsewhere. After a general introduction to HRV and how it can be measured, we review how HRV is altered in MDD. We subsequently describe how antidepressant drugs affect HRV, showing that some classes (such as tricyclics) generally worsen HRV, whereas others (most notably selective serotonin reuptake inhibitors) have a more positive influence. We also review the effects of several other treatments, with a special focus on vagal nerve stimulation, finishing with some further considerations and recommendation for further research, both in humans and animals. *Behavioural Pharmacology* 29:152–164 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Major depressive disorder (MDD) is characterized by a reduction in hedonic state (anhedonia), feelings of guilt or worthlessness, reduced motivation (avolition), and fatigue, alongside disruptions in sleep and appetite (American Psychiatric Association, 2013). Between 2005 and 2015, prevalence rates of depression increased by 18.4% (Hay *et al.*, 2017), with current prevalence estimates placing depression as the leading cause of disability worldwide (World Health Organization, 2017). In severe cases, depression can lead to suicide, which is the second leading cause of death in those aged 15–29 years. Despite the severity and increasing prevalence rates of depression, treatments still focus on the monoamine hypothesis of the disease, which posits that an imbalance in monoamines such as serotonin, noradrenaline, and dopamine underlie the disorder (Krishnan and Nestler, 2008). Although this approach has been useful in the development of pharmaceutical interventions, their effectiveness remains relatively low (Pigott *et al.*, 2010; Locher *et al.*, 2017), and the delayed onset of effectiveness is linked to several significant limitations, including increased suicidality in initial stages of treatment (Fergusson *et al.*, 2005) and reduced compliance (Keller *et al.*, 2002). Thus, it is obvious that novel therapies need to be developed, and therefore a better understanding of the disease process and the biological abnormalities is required.

An association between MDD and cardiovascular disease (CVD) has repeatedly been shown with rates of depression in patients with CVD ranging between 20 and 40% (Carney *et al.*, 1987; Gonzalez *et al.*, 1996). This association is troubling, as depressed patients have reduced medication compliance (Keller *et al.*, 2002) and have more difficulty coping with the stress of an illness (Blumenthal *et al.*, 1982; Mohr *et al.*, 1997). The directional relationship of this association has been controversial, with some proposing that depression is merely a response to the stress of having a significant illness (Musselman *et al.*, 1998), or that factors often associated with depression (anxiety, drug abuse, etc.) mediate this relationship (Hayward, 1995). However, there is substantial evidence that depression itself is an independent risk factor for developing CVD (Aromaa *et al.*, 1994; Everson *et al.*, 1996; Pratt *et al.*, 1996; Wassertheil-Smoller *et al.*, 1996; Musselman *et al.*, 1998). For instance, a meta-analysis involving over 120 000 patients concluded that depression increased the risk of CVD by 80–90% (Nicholson *et al.*, 2006). Importantly, depression also increased the risk of cardiovascular mortality and contributed not only to the onset but also to the progression and prognosis of CVD. Thus, the association between depression and CVD is often described as a downward spiral in which depression and CVD mutually reinforce each other (Penninx, 2017).

The association between CVD and MDD has been investigated by Musselman *et al.* (1998), who identified sympathoadrenal hyperactivity, modifications in platelet receptors, reduced heart rate variability (HRV) and

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hyperactivity of the hypothalamic–pituitary–adrenocortical axis, as key elements in increasing the risk of CVD. One key element in the link between MDD and CVD is a decrease in HRV. HRV refers to the beat-to-beat variation in heart rate and is a measure of the interplay between the two arms of the autonomic nervous system: the parasympathetic and sympathetic nervous systems. The sympathetic nervous system is involved in increased activity of physiological systems in response to stress, or the fight or flight response noted by Cannon (1911). The parasympathetic system plays a more regenerative role by reducing activity in these physiological systems. The balance between these systems is of crucial importance, as increased sympathetic activity or decreased parasympathetic activity can reduce HRV, whereas decreased sympathetic activity, or increased parasympathetic activity will result in increased HRV (Thayer *et al.*, 2010).

HRV, therefore, may not only represent an important link between MDD and CVD, as suggested by Musselman *et al.* (1998), but may actually be fundamentally related to the etiology of the psychiatric symptoms seen in patients with MDD. Intriguingly, many mental and physical illnesses, aside from MDD, are also associated with a reduction in HRV, including schizophrenia, bipolar disorder, and autism spectrum disorders (Boettger *et al.*, 2006; Licht *et al.*, 2009; Sevcencu and Struijk, 2010; Casanova *et al.*, 2014). Therefore, the aim of the present review is to investigate the extent to which alterations in HRV are related to the etiology of psychiatric symptoms, in an attempt to further our understanding of mental disorders in general and of MDD in particular.

Before investigating the relationship between MDD and HRV and the possible underlying mechanisms behind this association, it is important to understand the measurement and analysis techniques most commonly used to assess HRV, and where possible, identify what these parameters indicate.

The assessment of heart rate variability

A range of measures to investigate HRV have been compiled and summarized below in order to provide a simple and understandable overview of the parameters and the information they provide. These measures have been separated into linear and nonlinear techniques. However, for a detailed explanation of these measures and parameters, we would recommend reading the paper by Task Force of the European Society of Cardiology (1996) and a more recent review that includes nonlinear techniques (Acharya *et al.*, 2006).

In general, HRV parameters can be subdivided into linear and nonlinear measurements (see Table 1 for more details). Linear measurements typically use the interval between two heart beats (the so-called R–R interval) to construct a linear association between variables. Although these measures have dominated the field of HRV so far, it is increasingly recognized that the HRV signals are nonstationary and nonlinear (Faes *et al.*, 2009). This has led to the introduction of a series of nonlinear measurements, sometimes referred to as fractal indexes. Table 1 lists a large number of linear and nonlinear measurements. In the next section, we briefly summarize the relevant parameters for the present discussion.

Linear parameters

Linear parameters of HRV are computed through linear algorithms, whereby graphing the function will produce a linear association between variables. These parameters can be further subdivided into two main categories: time domain and frequency domain.

Time-domain

Time domain measures are linear measurements of HRV derived from the variation in the interval between subsequent R-waves from an ECG signal (Fig. 1). These measures can again be subdivided into statistical and geometric measures.

Statistical measures

RR measure: A measure of the mean of the RR intervals, where R represents the peak on the QRS complex, which represents the depolarization of the left and right ventricles of the heart.

SD of normal to normal R–R intervals measure: This is one of the most often reported HRV parameters. Although this measure is simple to obtain and calculate, it is important to note that, because this measure, including all cyclic components across the entire recording, is heavily dependent on the length of the recording, it makes it inappropriate to compare SD of normal to normal R–R intervals (SDNNs) calculated from ECG data of different durations (Task Force of the European Society of Cardiology, 1996).

Root mean square of successive heartbeat interval differences: The root mean square of successive heartbeat interval differences (RMSSD) is one of the core measures of HRV. It has been suggested to primarily measure the influence of the parasympathetic nervous system on HRV (DeGiorgio *et al.*, 2010), although some contribution of the sympathetic nervous system is also likely.

NN50: This measure is produced by the number of successive RR interval pairs that differ by more than 50 ms, which is reflected by the count within a defined time.

pNN50: This is another important HRV parameter that has been suggested to primarily reflect the parasympathetic influence on HRV (Lagana *et al.*, 1996).

Geometric measures

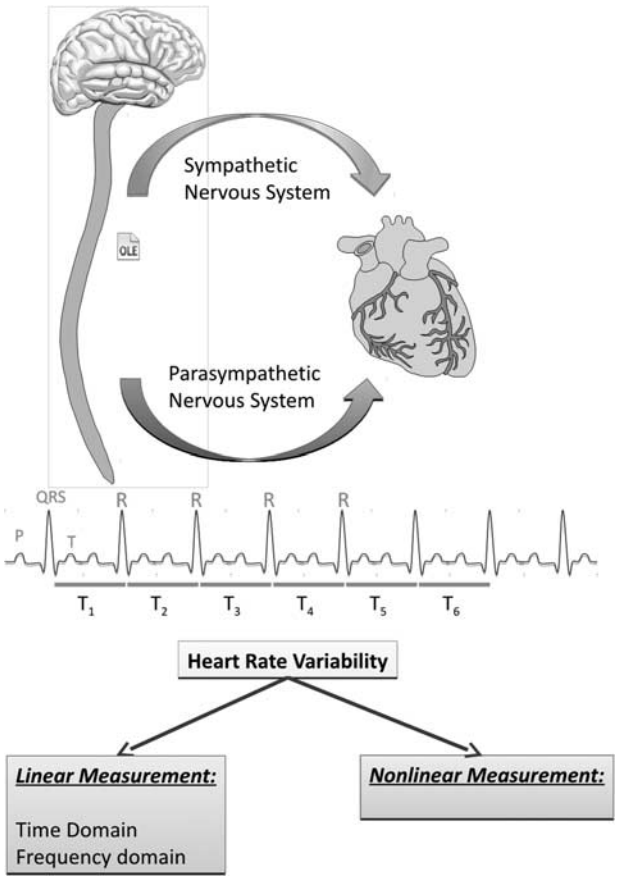
Heart rate variability triangular index: This is a less often used HRV index, as it requires large data samples to provide an adequate number of R–R intervals (20 min

Table 1 A brief description of the most relevant linear and nonlinear measures of heart rate variability

Parameters	Description
Linear measures (time domain)	
RR	The mean of all RR intervals
SDNN	SD of the normal to normal (R–R) intervals
RMSSD	Square root of the mean squared difference between successive RRs
NN50	The number of successive RR intervals that differ by more than 50 ms
pNN50	The percentage of NN50
HRV triangular index	The integral of the RR interval histogram divided by the height of the histogram
TINN	Triangular interpolation of N–N intervals. Calculation is based on taking the highest peak in the RR histogram and creating a triangle using the minimum squared difference
Linear measures (frequency domain)	
HF	Power band encompassing the 0.15–0.4 Hz range
LF	Power band encompassing the 0.04–0.15 Hz range
VLF	Power band encompassing the 0.003–0.04 Hz range
ULF	Power band encompassing the range below 0.003 Hz
TP	Total power within the HRV spectrum
LF/HF	The ratio between LF and HF
Nonlinear measures	
Poincare plot	A method of visually representing chaos as opposed to random noise, whereby each R–R interval is plotted against the previous interval in a scatterplot
ApEn	Approximate entropy is a method to quantify the predictability of fluctuations in a signal over time
DFA	Detrended fluctuation analysis represents a modified root mean square type of analysis

For more details see text.
ApEn, approximate entropy; DFA, detrended fluctuation analysis; HF, high frequency; HRV, heart rate variability; LF, low frequency; SDNN, SD of the normal to normal (R–R) intervals; TINN, triangular Interpolation of N–N intervals; TP, total power; ULF, ultra-low frequency; VLF, very low frequency.

Fig. 1



The relationship between the ANS and HRV.

minimum in humans). Given that the number of samples in the histogram will be equal in comparisons, the smaller the denominator (height of the histogram), the larger the product (greater HRV).

Triangular interpolation of NN interval: This is another interesting, but not very often used HRV parameter (Table 1). By subtracting the lowest point of the triangle from the highest, a value in milliseconds will be produced. Because of the nature of the linear function used to approximate the distribution, this method is mostly unaffected by artefacts and ectopic beats, which may otherwise influence the HRV analysis.

Frequency domain measures

Frequency domain measures are computed by the decomposition of the waveform of ECG-RR intervals (interbeat interval or RRIs) and are often used in an attempt to better differentiate between the influence of the parasympathetic and sympathetic nervous systems. To examine frequency domain parameters, data need to be transformed to produce a spectrum; thus, Fast Fourier transformation is typically used. Fast Fourier transformation decomposes the ECG trace into its component frequencies. This transformation is useful only if the signal is stationary, and therefore it may be incompatible if used to analyze nonstationary or transient signals. Following the required transformation of the data, analyses may be carried out using parametric or nonparametric analyses. Each parameter has been suggested to be indicative of aspects of autonomic activity. Traditionally, two different bands (high and low frequency) have been studied, although, more recently, two additional bands have also gained attention.

High frequency power band: The high frequency (HF) band is thought to reflect the variation in heart rate during the respiratory cycle (also referred to as respiratory sinus arrhythmia). The HF power band has been suggested to be almost exclusively dependent on the parasympathetic activity, that is, with reductions in HF measures of HRV, we are assessing a reduction in vagal tone (Roose *et al.*, 1989). HF measures can be assessed using long recordings (24 h) or short recordings (5 min).

Low frequency power band: The low frequency (LF) power band reflects a mixture of parasympathetic and sympathetic contributions (Koizumi *et al.*, 1985) with greater sympathetic sensitivity (Task Force of the European Society of Cardiology, 1996). As with the HF band, LF power can reliably be estimated from both short and long duration recordings.

Very low frequency power band: The very low frequency (VLF) band can be obtained from 5 min or 24-h recording durations; however, longer duration recordings are recommended. Compared with HF and LF, the VLF frequency is less understood (Musselman *et al.*, 1998), but it has been suggested that alterations primarily reflect parasympathetic inputs, and to a lesser degree, the activity of the renin–angiotensin–aldosterone system (Ciliberti *et al.*, 2017) and thermoregulation (Tripathi, 2011).

Ultra-low frequency power band: The ultra-low frequency (ULF) power band can only be reliably obtainable through long recording durations (24 h) and reflects the power in the frequency range below 0.003 Hz. The source of influence behind ULF alterations is unknown (Musselman *et al.*, 1998); however, it has high predictive value of mortality following myocardial infarction (Bigger *et al.*, 1992), and thus further investigations are warranted. Furthermore, similarities between VLF and ULF influences have been suggested (Serrador *et al.*, 1999).

Total power: Total power (TP) has been suggested to be a broad measure of autonomic activity, but it does not allow a distinction between the sympathetic and parasympathetic contributions.

Low frequency/high frequency ratio: The low to HF ratio is often used as an HRV parameter and has been suggested to interrogate the shift in dominance between the sympathetic and parasympathetic contributions to HRV. This concept has widely been accepted and used to assess sympathetic and parasympathetic dominance (Pagani *et al.*, 1984); however, doubt over the precise nature of this parameter has sparked controversy (Billman, 2011). Eckberg (1997) suggests that the LF/HF ratio rests upon four assumptions: (i) sympathetic nerve activity is almost exclusively responsible for the LF band; (ii) the HF band is exclusively influenced by the parasympathetic nerve activity; (iii) LF/HF ratio represents a balance that demonstrates an equal shift from parasympathetic to sympathetic dominance or *vice versa*; therefore, by reducing parasympathetic activity, we in turn increase sympathetic activity; and (iv) the interaction between parasympathetic and sympathetic activity is linear in nature. However, as demonstrated in the review by Billman (2013), none of the four assumptions are met, as LF has been shown to be influenced by parasympathetic alterations (Randall *et al.*, 1991), although to a much lesser extent, and changes in sympathetic activity impact HF power bands (Cohen and Taylor, 2002). Given this overlap, alterations in either sympathetic, or parasympathetic activity are unlikely to produce stable shifts in LF/HF ratios. Furthermore, the complexity of an organism produces multiple additional inputs influencing LF/HF ratios such as respiration (Taylor *et al.*, 2001); hence, the linearity assumption is not met. Given the inability to meet any of the assumptions, the underlying meaning behind LF/HF ratios remains to be fully elucidated and requires further examination.

Nonlinear measures

Nonlinear parameters of HRV do not just refer to analysis techniques that account for more than merely the beat-to-beat variation, but rather attempt to capture the entire range of dynamic processes at play. Although linear methods are well understood and simple to compute, which has resulted in their popularity, they fail to account for the interplay between many interconnected systems within an organism. Nonlinear parameters are less understood and more complex in nature; however, some key parameters used in HRV analysis are simplified below in the hope of promoting their use, which may lead to a greater understanding of their applications.

Poincare plot

Of the nonlinear methods, the Poincare plot is the most often used (Table 1). This method allows for the visual representation of data on the basis of their own scales, therefore allowing for the differentiation between randomness and chaos. A typical Poincare plot will show a cluster of data points in a positive linear fashion. A line of best fit will be drawn called the line of identity and points running parallel to this line will visually depict the long-term variation of R–R intervals (SD2) (e.g. sleep and wake cycles). A perpendicular line is placed through the center of the line of identity, which represents short-term variation of R–R intervals (SD1). On the basis of the spread of the data, an ellipse can be fitted, centered around the axis of the line of identity. This ellipse can be used to examine the short-term and long-term variation of the data, whereby an increased width of the ellipse depicts an increase in short-term HRV, while the length represents long-term variation of these beats. The spread of these data is dramatically reduced in depressed patients, with the most significant reductions being apparent in the SD1 (Vigo *et al.*, 2004). The Poincare plot provides an easily produced and understandable

nonlinear HRV analysis, with the ability to eliminate ectopic beats that present outside of the ellipse.

Approximate entropyThis is another method of discerning chaos from randomness [approximate entropy (ApEn)]. One key advantage of using ApEn is the ability to compute meaningful data using relatively limited number of data points (Beckers *et al.*, 2001) while also being able to detect meaning embedded in noisy data (Acharya *et al.*, 2006). Three key values are needed to compute ApEn: (i) length of compared runs (e.g. 1 h of ECG recording), (ii) filter used, and (iii) number of data points in the series. These values need to be fixed across samples in order to produce meaningful results. For a full review of the development of this method, we suggest referring to Pincus (1991) and Pincus and Goldberger (1994). However, for the purposes of this review, smaller values produced by ApEn analysis reflect a lower HRV, with completely regular signals producing an ApEn value of 0, whereas higher ApEn values would be expected in healthy participants, thus reflecting a greater HRV.

Detrended fluctuation analysis

This useful method, the detrended fluctuation analysis (DFA), identifies long-term correlations that may be hidden in nonstationary signals, which may be undetectable through linear analyses. DFA also avoids false detection of artefacts caused by nonstationarity of a signal. To compute the DFA, segmentation of data into boxes of equal length must occur. From here, line of best fit is plotted for the signal contained within each box, giving the local trend. On the basis of this parameter, long-term fluctuations in the data are nullified, thus removing the overall nonstationarity of the signal. Once this occurs, the signal can be considered stationary, and correlations can be made between each local signal. Peng *et al.* (1995) provided a detailed description of the statistical basis and underlying assumptions of DFA.

Heart rate variability and major depression disorder

Although the link between HRV and MDD is yet to be fully elucidated, a vast body of research has shown a relatively consistent association between reductions in HRV and MDD. Kemp *et al.* (2012) sought to examine this link in unmedicated patients with MDD. A significant reduction in HRV (reduced RMSSD, SDNN, and HF, with increased LF/HF ratio) was observed. The deficits observed were greater in the subset of patients with comorbid anxiety, suggesting a compounding effect may be occurring. Similar results have been reported by van der Kooy *et al.* (2006) who examined HRV in elderly patients with depression, and found reductions in HF, LF, RMSSD, and SDNN, indicating reduced vagal tone and an overall reduction in HRV. This study also demonstrated that reductions in HRV are associated with depression, irrespective of age. In a meta-analysis conducted by Kemp *et al.* (2011), depression, symptom severity, and treatments were examined with regard to their relationship with HRV alterations. Of the studies included, 11 examined depression and HRV directly, which included 401 depressed patients and 407 controls. Through this analysis, it was shown that depression was associated with decreased time domain measures of HRV, HF, and several nonlinear measures of HRV, whereas the LF/HF ratio showed a significant increase. It should be noted that data were obtained from unmedicated participants (either drug naive, or following a washout period), and time domain measures were combined into a single grouping, while, similarly, nonlinear parameters were combined. The need to combine these measures highlights a lack of consensus over which measures should be reported across studies.

More detailed studies provide evidence that symptom severity of patients with MDD is inversely correlated with HRV, especially with respect to the time domain parameters (such as RMSSD and SDNN) and HF, and possibly LF (Kemp *et al.*, 2010; Yeh *et al.*, 2017). This would suggest a potential avenue of research into novel treatments of MDD with a focus on HRV, outside of the effective yet invasive direct vagus nerve stimulation treatment for treatment-resistant MDD. Moreover, it suggests that reduced HRV may be a biomarker for MDD, or perhaps may even be predictive for the development of MDD. Jandackova *et al.* (2016) examined participants' HRV (SDNN, RMSSD, LF, and HF) and depressive symptomology using data from the Whitehall II study. Patients were assessed at two time points (10.5 years between assessments), and it was found that male patients who had lower HRV at time point 1 were less likely to report experiencing a depressive episode at time point 2, whereas female patients had a similar trend that failed to reach significance.

The exact relationship between MDD and HRV is still a matter of debate, as HRV is related to several important functional domains. Low baseline HRV, especially HF HRV has been associated with cognitive deficits, especially in tasks relying on the frontal cortex (Ottaviani *et al.*, 2016). In addition, reduced HRV (again predominantly HF HRV) has been associated with emotional deficits and in particular with emotional inflexibility (Balzarotti *et al.*, 2017). Consistent with this observation, a recent neuroimaging meta-analysis found a clear association between HRV and activation of the major neuronal areas involved in cognitive and emotional flexibility, most notably the anterior cingulate and prefrontal cortex, the insula and the amygdala (Vargas *et al.*, 2016). However, HRV is also influenced by many other processes, such as lifestyle and coping strategy, nutrition (Young and Benton, 2018) and personality traits (Appelhans and Luecken, 2006; Young *et al.* 2017). Moreover, drugs, including antidepressant drugs, are known to affect cardiovascular functioning. Therefore, in

the next section, we investigate to what extent antidepressants drugs influence HRV.

Standard antidepressants and heart rate variability

Many antidepressants significantly affect the cardiovascular system. Many antidepressants affect noradrenergic neurotransmission and thus directly influence the sympathetic branch of the autonomic nervous system. Likewise, many tricyclic antidepressants (TCAs) (especially TCAs) block muscarinic cholinergic receptors, and therefore directly inhibit the parasympathetic branch of the autonomic system. Moreover, there is evidence that changes in serotonin and dopamine neurotransmission affect HRV (McCall *et al.*, 1987; Mannelli *et al.*, 1999). Given the effects of antidepressants on monoamine neurotransmission, it has even been suggested that alterations in HRV seen in patients with MDD are predominantly (or even exclusively) related to treatment (Musselman *et al.*, 1998). However, as discussed above, HRV alterations are also found in treatment-naïve and drug-free patients. Nonetheless, antidepressants affect HRV, albeit in a complex way, ranging from (further) decreases in HRV to increases (normalization), depending mainly on the type of antidepressant drug used. Most studies have focussed on TCAs and the selective serotonin reuptake inhibitors (SSRIs).

Tricyclic antidepressants

TCAs are named after their chemical structure, which contains three conjoined ring-like structures. They exert their therapeutic actions primarily through a blockade of both the noradrenaline and serotonin transporters. However, they have substantial side effects because of their ability to also block several neurotransmitter receptors, such histamine receptors, muscarinic cholinergic receptors, and α-adrenoceptors. The impact of TCAs on HRV are relatively well established, as this class of drugs has long been known for its cardiotoxic effects. Indeed, HRV has been proposed as a potential biomarker of early detection of cardiotoxicity and TCA overdose (Rechlin, 1995), and anticholinergic effects (Jakobsen *et al.*, 1984).

Srinivasan *et al.* (2004) investigated the effects of imipramine on HRV in nondepressed children. The authors found a decrease in HF and an increase in LF following treatment. From this, it was concluded that the cardiotoxic effects observed in patients treated with TCAs may be explained by a reduction in vagal function and an increase in sympathetic tone. Likewise, Rechlin (1994) investigated the impact of amitriptyline and doxepine (both TCAs), and fluvoxamine and paroxetine (both SSRIs) on HRV in patients with MDD. Significant reductions were found in SDNN and RMSSD measures of HRV in both TCA treatment groups after 14 days compared with controls, whereas no differences were noted for the SSRI treatment groups. Although these data suggest that TCAs worsen HRV and SSRIs have no effect, the study has a number of limitations. First, in pretests, depressed patients did not differ from nondepressed patients in HRV, which differs from the majority of the literature (see above). This could in part be attributable to the low sample size in the treatment groups and/or to the inherent heterogeneity of patients. Second, the use of only RMSSD and SDNN (both time domain parameters) to assess participants' HRV may have obscured other drug-induced changes, such as changes in the frequency domain measures (especially HF). Nonetheless, the majority of studies suggest that TCAs reduce HRV and thus worsen the already lower HRV seen in patients with MDD.

Selective serotonin reuptake inhibitors

SSRIs are the most widely used class of drugs for the treatment of depression, along with other affective disorders. Their method of action involves blocking the reuptake transporter on the presynaptic terminal, thus preventing the reabsorption of serotonin from the synapse. This in turn results in an increase in extracellular serotonin.

Fluoxetine is one of the most prescribed antidepressant medications because of its relatively low risk profile and relatively high treatment efficacy. Given the popularity of fluoxetine, its physiological effects including its impact on HRV are surprisingly understudied. One study examined the response to treatment with fluoxetine in patients suffering from post-traumatic stress disorder. The depression subscale of the Clinical Global Impression Improvement scale showed significant reductions in depressive symptoms in response to the treatment. Response to medication was associated with a normalization of LF and HF parameters, indicating an increase in vagal tone and decrease in sympathetic activity, an effect only seen in responders (Kotler *et al.*, 2000). Udupa *et al.* (2007) examined the effects of escitalopram on HRV and compared these effects with those of repetitive transcranial magnetic stimulation (rTMS); however, no control groups were used. A significant increase in the HF parameter was observed for escitalopram, yet SDNN, RMSSD, LF, and LF/HF ratio parameters showed no significant difference in the escitalopram group, indicating that the effects of escitalopram may be limited to vagal tone. This study failed to find a correlation between improvement in depression scored and alterations in HRV parameters. Thus, in contrast to TCAs, SSRIs seem to have a more positive effect on HRV, generally leading to a normalization in patients with MDD.

Selective noradrenaline and serotonin reuptake inhibitors

Selective noradrenaline and serotonin reuptake inhibitors, such as TCAs, prevent the reuptake of serotonin and noradrenaline. However, they are much more selective than TCAs with respect to other receptors and subsequently have substantially fewer side effects.

The effects of SNRIs on HRV in general resemble those seen with TCAs, which may be related to the strong influence of both classes on the noradrenergic system. A study by Ravindran *et al.* (2016) that examined a wide range of HRV parameters found increases in the HF measure of HRV in response to desvenlafaxine (an SNRI) in comparison with pretreatment baselines. Furthermore, decreases were found in SDNN, RMSSD, RR triangular index, TP, and LF/HF ratio parameters. Finally, a relationship between response to treatment and HRV (triangular interpolation of NN interval and RR triangular index) was detected. As with many of the studies, a low sample size and lack of a control group, impact the reliability of these findings. Decreases in HRV in response to SNRI antidepressants have been observed by Terhardt *et al.* (2013) who found that venlafaxine resulted in a further decrease in HRV (TP) in depressed patients, and treatment response was not related to HRV alterations.

As the data clearly indicate, the effects of antidepressants on HRV are complex and often contradictory, and strongly dependent on the class of antidepressant drugs. Although TCAs in general lead to a (further) reduction in HRV, SSRIs treatment is more frequently associated with an increase in (normalization of) HRV. This has been substantiated by several meta-analyses. For instance, in the meta-analysis by Kemp *et al.* (2010), which included 18 studies, involving 673 patients and 407 controls, antidepressants did not have an overall effect on HRV in patients with MDD. However, as the authors acknowledge, the effect observed was primarily driven by studies on TCAs, with the result that increases in HRV parameters from other antidepressant treatments were masked by the reduction in HRV observed following TCA treatment. Given the clear differences between different classes of antidepressant drugs, and the relative small sample sizes used in most studies, it would be prudent to proceed with caution when trying to group the effects of antidepressants, and this may result in opposing drug actions canceling each other out.

Alternative major depression disorder treatments and heart rate variability

Given the issues surrounding traditional treatments based on the monoamine hypothesis, especially in relation to the relatively low compliance, and long treatment delay, alternative treatments have been and still are developed. These include both pharmacological treatments (such as agomelatine and ketamine) and non-pharmacological treatments [such as TMS and vagal nerve stimulation (VNS)]. Although many of these treatments are still in an experimental stage, it is interesting to see how they affect the cardiovascular system and in particular HRV.

Although agomelatine also blocks the 5-HT2C receptor, its main mode of action is thought to be related to the stimulation of the melatonergic MT1 and MT2 receptors. It has been reported to have a somewhat faster onset of action with improvements from placebo already seen after 2 weeks (Loo *et al.*, 2002), although later studies have questioned this. Interestingly, for the present discussion, agomelatine has a significant effect on vagal tone, leading to increases in HF and LF HRV, further suggesting a link between increases in HRV and treatment efficacy (Yeh *et al.*, 2017).

In the last decade, a large amount of interest has been given to ketamine and its potential as a rapid onset antidepressant (Mathew and Zarate, 2016). Ketamine is an NMDA receptor antagonist and also an antagonist of the ionotropic glutamate receptor (Tyler *et al.*, 2017), and it was originally used to induce anesthesia in patients injured in wartime conflicts because of the rapid onset of its dissociative effects and relatively reliable and safe action (Mercer, 2009). Ketamine has shown to be an effective method of rapid alleviation of treatment-resistant MDD and suicidality. Murrough *et al.* (2014) examined the rapid response of ketamine in comparison with another anesthetic agent, midazolam, 24 h after initial infusion. The 24-h follow-up showed that 64% of the ketamine group had significant reductions in their depressive scores in comparison with 28% in the midazolam group. It was suggested that these results provide evidence for the importance of the NMDA receptor modulation as a rapid means of treating resistant depression. Given this rapid onset, ketamine would seem to be a perfect fit for the treatment of crisis level suicidality. To examine this, DiazGranados *et al.* (2010) treated suicidal patients with a single intravenous infusion of ketamine. Suicidal ideation, anxiety, depression, and hopelessness were all significantly reduced from baseline 40 min after administration. Although the rapid resolution of depressive symptoms and suicidality are relatively well established, the efficacy of ketamine as a long-term antidepressant agent is less clear. Murrough *et al.* (2013a, 2013b) repeatedly administered ketamine intramuscularly to patients presenting with treatment-resistant MDD and followed-up the patients for 8 weeks. It was found that ketamine significantly reduced depressive symptoms when repeatedly administered up to six times across the initial 8 weeks. Following this time, patients were not given any further ketamine, and average relapse time was reported at 18 days following the final infusion. Given the strong association between MDD and CVD, it is important to understand the cardiovascular impact of ketamine. Although there is a significant gap in the literature examining the direct impacts of ketamine on HRV outside of its use as an anesthetic, these findings may provide a glimpse into the autonomic effects of ketamine. Komatsu *et al.* (1995) examined the effects of ketamine and midazolam on HRV (LF, HF, and TP) at anesthetic doses of the drugs. Ketamine was observed to increase LF while simultaneously decreasing

HF and TP. On the basis of these observations, it was concluded that ketamine increases sympathetic effects on the heart, leading to an overall decrease in HRV. Bollag *et al.* (2015) examined the effects of low-dose ketamine on anaesthetized patients undergoing a hysterectomy. HRV was monitored through the PhysioDoloris analgesia monitor (MDoloris Medical Systems SAS, Lille, France) and showed no significant differences following ketamine administration. This led the authors to suggest that low doses of ketamine lack the sympathetic influences observed in previous studies. One key issue arises from this study: this monitor assesses LF/HF ratio (which in itself is controversial), through vagally mediated HRV, from which the authors inferred a lack of sympathetic modulation of ketamine. However, ketamine has been shown to have sympathetic effects that are unlikely to be detected through parasympathetic influences, especially subtle differences resulting from lower doses. On the basis of the limited information, it is recommended that the effects of ketamine on HRV should be thoroughly studied, as it may further predispose depressed patients to CVD because of the possible sympathetic effects. However, it should be kept in mind that the doses used for anesthesia are substantially higher than those used for the treatment of MDD, and it is currently unknown whether such low doses also affect HRV.

rTMS is a method of brain stimulation whereby small magnetic impulses are directed to disrupt the polarity in selected regions of the cortex. rTMS localized to the dorsolateral prefrontal cortex has been suggested as a form of treatment for drug-resistant MDD (Pascual-Leone *et al.*, 1996). A meta-analytic study was conducted by Holtzheimer *et al.* (2001) to determine the efficacy of rTMS for treating depression. A total of twelve studies were selected containing 264 patients, which demonstrated a significant reduction in MDD symptom severity in comparison with sham trials, with the most significant results being from the dorsolateral prefrontal cortex rTMS subgroup ($n = 194$), in which 13.7% of participants showed a reduction in depressive scores of greater than 50%. Given this relationship, Udupa *et al.* (2007) sought to compare the effects of rTMS and SSRI treatments on HRV in drug-naive MDD patients. Although the antidepressant effects of both treatments were comparable, rTMS produced significantly greater improvements in HRV (SDNN), with nonsignificant improvements in LF, HF, LF/HF ratio, and RMSSD. Intriguingly, when rTMS was performed on healthy participants, no significant HRV alterations occurred (Vandermeeren *et al.*, 2010). Given the alterations in HRV in response to rTMS in patients with MDD, it has been suggested that rTMS may help 'correct' parasympathetic and sympathetic activity in these patients (Yoshida *et al.*, 2001). Interestingly, in a study with patients suffering from autism spectrum disorders, rTMS over the same brain regions significantly improved stereotypy and increased HRV in both the time (SDNN and pNN50) and HF frequency domain (Wang *et al.*, 2016).

Electroconvulsive therapy (ECT) has been developed and refined since its early use for treating a range of mental disorders. Modern ECT is conducted under general anesthetic and involves multiple administrations of targeted currents delivered over the course of 2–4 weeks. The use of ECT in treating MDD has proven to be effective, especially in treatment-resistant MDD. A meta-analysis by Dierckx *et al.* (2012) involving six studies ($n = 790$) examined the remission rates of MDD following treatments with ECT between 2001 and 2010. The overall remission rate was reported at 50.9%; however, because of the nature of this research, control participants were not used. This is a significant limitation, as early ECT research reported a significant placebo effect for ECT of depressive symptoms (Lambourn and Gill, 1978). Despite this confound, the success rates are greater than any previously discussed technique, and ECT has been shown to significantly alter HRV. Schultz *et al.* (1997) examined the impact of ECT on HRV in depressed patients. Counterintuitively, reduction in symptom severity significantly correlated with reduced HRV (SDNN) and reduced parasympathetic activity. However, opposite results have also been reported: Nahshoni *et al.* (2001) found an improvement in vagal modulation (HF), which was correlated with reductions in depressive symptoms in elderly patients. However, as we have seen in previous examples, this study also suffered from a low sample size. Moreover, as age is negatively related to all HRV parameters, the use of elderly patients may constitute an additional limitation to the generalization of the findings for the effect of ECT on HRV (Umetani *et al.*, 1998). Given the inconsistencies within the current literature, additional research is clearly warranted.

The vagus nerve and heart rate variability

One of the most direct links between HRV and depression comes from studies using vagus nerve stimulation. The vagus nerve, sometimes referred to as the pneumogastric nerve or the 10th cranial nerve, controls parasympathetic functioning, which, in turn, affects sympathetic functioning. Emerging from the medulla oblongata, the vagus nerve travels down through the torso connecting to all the major organs, finally terminating at the colon. Information from these organs is relayed to the CNS through the sensory branch, whereas the motor branch sends information from the CNS to the organs. With regard to HRV, the vagal nerve decreases heart rate, whereas at the same time increases HRV (mainly RMSSD and HF).

Recent medical advances have shown that our understanding of the vagus nerve is still limited, and that the importance of this nerve has been understated for decades. For instance, Corazzol *et al.* (2017) restored

consciousness to a patient who had been in a vegetative state for 15 years following traumatic brain injury. The patient was implanted with a direct vagus nerve stimulator, which is believed to have potentiated the spread of cortical signaling via re-establishing the thalamocortical network. This challenges the idea that the condition of patients in a vegetative state for over a year is irreversible (Giacino *et al.*, 2014). More important for our present discussion is that direct VNS has been shown to be beneficial for the treatment of treatment-resistant MDD. A surgical implant is inserted into the patient under general anesthesia. This implant contains a bipolar lead that is connected to the vagus nerve enclosed in the carotid sheath, while the generator is implanted subcutaneously near the left clavicle. Once the implant is turned on after postoperative recovery, impulses are sent that stimulate the vagal nerve repetitively. Stimulation thresholds are set individually, depending on the needs and thresholds of each patient.

Given the invasive nature of the implant, VNS has so far only been used in treatment-resistant cases of MDD. Sackeim *et al.* (2001) piloted this technique in 60 treatment-resistant MDD patients, to establish predictors of outcome and side effects, and to determine the response rate to this novel technique. The 10-week response rate ranged from 30.5 to 37.3% improvement, depending on which depression scale was used for the assessments, with relatively few side effects. On the basis of this finding, VNS was proposed as an effective technique to overcome mild to moderate treatment-resistant MDD. Marangell *et al.* (2002) conducted a 1-year follow-up of these patients to examine the chronic efficacy of VNS and reported that response rates were maintained, while remission rates had significantly increased. Finally, a 2-year follow-up was conducted by Nahas *et al.* (2005) who reported sustained response and remission rates, from which they suggested VNS as an effective treatment for resistant MDD or chronic recurrent MDD.

Although the neural mechanisms underlying the effects of VNS are still poorly understood, studies have shown a wide range of physiological and neurological changes in response to treatment with VNS. Two key hypotheses, the monoamine hypothesis and the neuroplasticity hypothesis, link the effects of VNS directly to the mode of actions of more traditional antidepressants. The vagal nerve is connected to the nucleus tractus solitarius located in the medulla oblongata. The nucleus tractus solitarius projections modulate the release of noradrenaline and serotonin, which in turn impacts the limbic system (Lulic *et al.*, 2009), and hence helps alleviate depressive symptoms (Delgado, 2000). Reduced neuroplasticity has been shown to be implicated in depression (Pittenger and Duman, 2008; Eyre and Baune, 2012; Player *et al.*, 2013), and while the exact mechanisms are beyond the scope of this paper, VNS, like antidepressants (D'sa and Duman, 2002), has been suggested to improve neuroplasticity in depressed individuals. Evidence to support this claim comes primarily from animal studies in which VNS has been used to improve recovery following traumatic brain injury and stroke (Naritoku, *et al.*, 2000; Khodaparast *et al.*, 2014).

Regardless of the underlying mechanisms, the vagal nerve is critically involved in the regulation of the autonomic nervous system and regulates the sympathetic/parasympathetic balance (Sackeim *et al.*, 2001; Nahas *et al.*, 2005; Nemeroff *et al.*, 2006). As a result, VNS directly affects HRV, and it has been suggested that reduced vagal tone underlies the reduced HRV seen in many depressed patients, and, consequently, VNS improves autonomic control and reverses the HRV deficit (Zhang *et al.*, 2009). Given this relationship, the normalization of HRV should be considered as a mechanism involved in the alleviation of treatment-resistant MDD.

Intriguingly, the relationship between depression and vagal tone/HRV may actually be bidirectional, a claim that emerges from studies investigating the impact on myocardial infarction and the increased prevalence of depressive symptoms. Although it is difficult to examine depressive symptoms before and after CVD to determine whether there is a clear causal relationship, a meta-analysis by Thombs *et al.* (2006), compiling 24 studies containing 14 326 patients, found that 45% of CVD patients were rated as having minor to major depression. Of these studies, only four assessed the development of depression symptom severity over time. Overall, depressive symptoms progressively increased with time following myocardial infarction during the stay in the hospital and persisted in later follow-up examinations after discharge. In accordance with these studies, Lippi *et al.* (2009) proposed a negative spiral relationship, whereby depressive symptoms increase the risk of CVD, while in turn, CVD increases the severity of depressive symptoms. Furthermore, there is some evidence to suggest that a reduction in vagal tone and subsequently in HRV may trigger an increase in depression. By severing the vagus nerve, its regulatory effects on heart rate are removed, which results in a decrease in HRV (Bogaert *et al.*, 2001). During a heart transplant procedure, the vagus nerve is routinely severed from the patient's heart but not reconnected to the donor heart upon transplantation. One study examining the effects of heart transplant surgery on mood disorders showed that MDD prevalence in the 3 years following surgery was 25.5%, whereas prevalence rates of all mood disorders assessed were at 38.3%. The occurrence of MDD and depressive episodes was more common during the first 12 months following transplantation, than when assessed at 36 months, which may in part be caused by the severed vagal nerve (Dew *et al.*, 2001). Furthermore, potential reinnervation, thus improved HRV has been observed at 20 months post-transplantation (Bernardi *et al.*, 1994). Finally, depression rates in this study were higher than what is observed in patients following renal transplantation,

where the cumulative prevalence rate is ~9.1% based on Medicare claims (Dobbels *et al.*, 2008). To fully understand the mechanisms underlying this potential bidirectional relationship between depression and CVD, further research should be conducted. However, considering the evidence, HRV abnormalities should not only be considered as a biomarker of current depression, but should also be used as a predictive biomarker to detect those at risk of experiencing a depressive episode in the future.

Future directions

Overall, although the literature overwhelmingly shows that MDD is associated with a reduction in HRV, implying that HRV should be considered as a mechanism underlying depression, as well as a predictive biomarker of depression, there remain substantial gaps in our understanding of this relationship.

As discussed, there are many parameters through which HRV can be examined, with reduced HF and RMSSD being the most cited in the depression literature. Although this is useful in identifying deficits within the parasympathetic modulation of HRV in depression, some key information may be lost through not reporting other, less frequently reported parameters, such as LF as reported in Loo *et al.* (2002), when examining the effects of agomelatine. Furthermore, the use of nonlinear methods of examining HRV is almost nonexistent within the field of depression. Nonlinear HRV analysis techniques can more accurately capture the complexity of ECG modulation and thus may be more sensitive to capturing subtle differences. For example, Young and Benton (2015) used both linear (SDNN, LF, HF, and LF : HF ratio) and nonlinear (entropy, DFA, recurrence quantification analysis) analyses of HRV during a range of behavioral tasks. The results suggested that nonlinear methods of examining HRV accounted for a greater amount of variance than seen in linear methods. Therefore, it is advisable to report all HRV parameters possible (including nonsignificant results), with a particular focus on nonlinear parameters. This is all the more important as reduced HRV, especially in RMSSD and HF, has been reported in many psychiatric disorders, including autism spectrum disorder (Ellenbroek and Hatic, 2017), schizophrenia (Clamor *et al.* 2016), and other disorders (Alvares *et al.* 2016). Although this may imply common underlying neurobiological deficits, further detailed, nonlinear analyses may reveal important differences in HRV dysregulation in these mental disorders. Furthermore, given the heterogeneous nature of depression, nonlinear HRV analyses may provide further insight into different manifestations of the disorder. In this respect, it is also important to investigate the relationship between HRV dysregulation and the symptoms of MDD. As mentioned above, HRV alterations have been related not only to emotional and cognitive symptoms, but also to coping strategies and personality traits. A more in-depth analysis, especially using sophisticated nonlinear techniques, may perhaps allow us to tease apart the relative contribution of each of these factors in HRV.

Given the association between depression and CVD, the majority of studies examining depression and HRV have involved patients suffering from CVD. Although studies investigating these patients are useful in examining the link between CVD and depression, they introduce a confound when trying to examine depression in the absence of CVD. Further investigations should examine the association between depression and HRV in participants who are not afflicted with CVD. This suggestion extends into studies on antidepressants, as CVD may confound the impacts of antidepressants on HRV. Most studies on antidepressants and the cardiac system have focussed on the side-effect potential of these drugs. However, as we discussed, some drugs, most notably the SSRIs seem to be able to reverse HRV in concert with an improvement of the symptoms. However, more extensive studies are certainly needed, as well as more pharmacological studies focussing on understanding of the basic neurobiological mechanisms involved in HRV regulation.

In this respect, it is surprising how small the contribution of animal research in our understanding of HRV has been so far. Although some basic studies have been performed (Sgoifo *et al.*, 2002; Stiedl *et al.*, 2005), to the best of our knowledge, no animal model for MDD, or indeed for other psychiatric disorders, has incorporated HRV as a potential symptom. The only possible exception being work carried out by Sgofio *et al.* (2002) on high and low anxiety animals. Given the fact that, like for instance prepulse inhibition in schizophrenia, HRV can be assessed in humans and animals with virtually identical techniques, and seems to be directly related to emotional control; further investigation of the usefulness of HRV as a functional parameter with translational validity is clearly warranted. Moreover, such animal research would allow to disentangle the effects of MDD from treatment and comorbid CVD. In addition, it would allow for a more thorough analysis of, for instance, the impact of a vagus nerve severance or stimulation and the above-mentioned hypothesis that the relationship between HRV and MDD is indeed bidirectional. Moreover, newer noninvasive technologies have been developed (Heier *et al.*, 2010) that allow recording of HR and HRV in rodent pups as young as 2 days of age, opening up the possibility of performing longitudinal recordings from birth to adulthood.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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