ANZJP

Australian & New Zealand Journal of Psychiatry
2016, Vol. 50(6) 511–519
DOI: 10.1177/0004867415622689

A literature review of heart rate variability in depressive and bipolar disorders

Darryl Bassett

Abstract

Objective: Autonomic nervous system dysfunction has the potential to adversely impact general medical health and is known to exist in a number of psychiatric disorders. It reflects alterations in the function of several regions of the central nervous system. Measurement of heart rate variability provides a non-invasive tool for studying autonomic function. While the literature relating to the technical process of heart rate variability and aspects of depressive disorders has been reviewed in the past, research relating to both depressive and bipolar disorders has not been comprehensively reviewed. This paper critically considers the published research in heart rate variability in both depressive and bipolar affective disorders.

Method: A literature search using Medline, EMBASE, PsycINFO, ProQuest Psychology and references included in published literature was conducted using the following keywords: '*heart rate variability and autonomic, combined with depression, depressive disorder, bipolar, mania and sleep*'.

Results: The evidence demonstrates that, using heart rate variability measures, significant distortions of autonomic function are evident in both depressive and bipolar disorders and from most of their pharmacological treatments.

Conclusion: The autonomic dysfunction evident in both unipolar and bipolar affective disorders, and many psychotropic medications, has significant implications for our understanding of the neurophysiology of these disorders, their treatment and associated general health.

Keywords

Heart rate variability, autonomic, depression, bipolar, neurophysiology

Introduction

Changes in autonomic nervous system (ANS) activity have been linked to a variety of mood disorders, including bipolar disorders, depressive disorders, anxiety disorders and schizophrenia (Alvares et al., 2015; Gorman and Sloan, 2000; Henry et al., 2010; Kemp et al., 2014a; Moon et al., 2013; Outhred et al., 2014; Valenza et al., 2014), and consequently a variety of cardiac disorders (Kemp and Quintana, 2013; Stapelberg et al., 2012; Stein and Kleiger, 1999) and other general medical disorders (Cygankiewicz and Zareba, 2013; Xhyheri et al., 2012). In addition, vagal nerve stimulation (VNS) has shown promise as a treatment for severe depressive disorders (Daban et al., 2008; George et al., 2007; Rizvi et al., 2011). Regulation of parasympathetic activity (identified as cardiac vagal tone) has also been connected to regulation of emotional reactivity, psychological flexibility and social engagement, as well as reduced prefrontal cortical activity (Geisler et al., 2013; McCraty and Childre, 2010; Porges, 2009; Sgoifo et al., 2015; Thayer et al., 2009, 2012; Thayer and Lane, 2000). This review examines the current literature which explores the associations of the ANS with both major depressive dis-

School of Medicine, University of Notre Dame, Notre Dame, Fremantle, Western Australia; School of Psychiatry and Clinical Neurosciences, University of Western Australia, Nedlands, WA, Australia

Corresponding author:
Darryl Bassett, School of Psychiatry and Clinical Neurosciences, University of Western Australia, Suite 25, Hollywood Specialist Centre, 95 Monash Avenue, Nedlands, WA 6009, Australia.
Email: dbassett@iinet.net.au

orders (MDDs) and bipolar disorders, using heart rate variability (HRV) as a tool.

Autonomic dysregulation and HRV

A useful, safe, convenient and non-invasive measure of autonomic activity is HRV. HRV can be measured as the variations in time between consecutive R waves on an electrocardiograph (ECG) ('*Time domain measures*') and decomposition of the wave form of ECG-RR intervals (interbeat intervals or RRIs) into frequency power bands using spectral analysis ('*Frequency domain measures*') (Rajendra Acharya et al., 2006; Voss et al., 2006). A number of parameters are used to measure HRV (Kleiger et al., 2005; Reyes del Paso et al., 2013; Shaffer et al., 2014; Xhyheri et al., 2012). While there is wide agreement about the interpretation of these measures, there remains some debate about the precise implications of each parameter (Heathers, 2014; Quintana and Heathers, 2014). The most commonly used time domain measures are the standard deviation of normal to normal RRIs (SDNN), the root mean square of normal to normal interval differences (RMSSD) and the proportion of RRIs of more than 50 millisecond (pNN50). The SDNN is predominantly (but not exclusively) indicative of sympathetic activity (increasingly with the duration of ECG recordings), while the RMSSD and pNN50 are indicative of parasympathetic activity. The most common frequency domain measures are the high-frequency (HF) power band (HF = 0.15–0.4 Hz) and low-frequency (LF) power band (LF = 0.04–0.15 Hz). The HF measure is indicative of parasympathetic activity and the LF measure of a mix of sympathetic and parasympathetic activity. Total power (TP) is a broad measure of autonomic activity. HRV varies inversely with the heart rate and directly with the interbeat interval.

HRV provides a convenient tool for investigating the activity of the ANS in the pathophysiology of major mood disorders, as well as the genesis of cardiovascular and other complications associated with mood disorders and their treatment (Hanson et al., 2013; Kaplan et al., 1991; Kemp et al., 2012; Kemp and Quintana, 2013; Soares-Miranda et al., 2014; Stapelberg et al., 2012). Measurement of HRV has the potential to offer a diagnostic tool through the identification of individuals suffering some forms of mental illness (Brunoni et al., 2013; Carney et al., 2000; Kemp et al., 2010; Moon et al., 2013; Stapelberg et al., 2012; Valenza et al., 2014). It may offer even more specificity for melancholic/somatic subtypes of depressive illness (Kemp et al., 2014b; Messerotti Benvenuti et al., 2015), but this requires further confirmation.

The activity of the ANS is sensitive to age and gender (Thayer et al., 1998; Voss et al., 2013), physical activity (Perini and Veicsteinas, 2003; Routledge et al., 2010), alcohol consumption (Kemp and Quintana, 2013; Romanowicz et al., 2011; Sagawa et al., 2011), nicotine (Munjal et al., 2009), food and water intake (Quintana and Heathers, 2014), circadian rhythm (Boudreau et al., 2013; Tobaldini et al., 2013), heart rate (prominently around 60 bpm or less) (Billman, 2013; Sacha and Pluta, 2008), blood pressure (Kleiger et al., 2005) and several medications (Hanson et al., 2013; Kemp et al., 2014a; Kemp and Quintana, 2013; O'Regan et al., 2014; Stapelberg et al., 2012). HRV is also highly sensitive to respiration, including respiratory rate, respiratory depth and respiratory sinus arrhythmia (RSA) (Heathers, 2014; Perakakis et al., 2009; Quintana and Heathers, 2014; Schafer and Vagedes, 2013; Shaffer et al., 2014). Regulating the frequency and depth of respiration reduces this contribution to HRV (Quintana and Heathers, 2014). However, the number and complexity of the confounding variables which contribute to HRV make the collection of data from this parameter difficult and interpretation open to question. Designing research methodology to minimize these confounding variables and analysing the data to adjust for unavoidable confounding variables are critically important challenges in this area of study.

The ANS functions in a non-linear fashion, with the parasympathetic system approaching chaotic activity (Voss et al., 2006). Non-linear measures offer, potentially, more valid interpretations of ANS activity than the linear measures discussed above and are less sensitive to confounding variables (Kaplan et al., 1991; Kemp et al., 2010; Voss et al., 2006).

HRV and bipolar disorder

Research into mania has revealed considerable evidence of reduction in many HRV parameters and particularly parasympathetic activity, although the findings are not fully consistent. Henry et al. (2010) studied HRV in 23 hospitalized subjects with current mania and 23 healthy controls, using brief ECG recordings. The severity of illness was considered to be '*moderate*', using the criteria of Leucht et al. (2005) and Lukasiewicz et al. (2013), and the age range was between 18 and 55 years, inclusive. Subjects with mania exhibited non-significantly higher mean heart rates but reductions in SDNN. In contrast, the HF score was significantly higher in the manic patients, although so was the LF/HF ratio. Measures of the RMSSD and pNN50 were lower in the manic patients compared with the controls. Apart from a small decrease in LF/HF ratio with lithium use, there were no significant differences in measures related to mood stabilizer or antipsychotic use. Similarly, Moon et al. (2013) studied HRV in 41 subjects with bipolar affective disorder (manic phase), 34 with MDD, 35 with schizophrenia and 27 healthy control subjects. The manic subjects were reported to have Young Mania Rating Scale (YMRS) mean scores of 19.15 ± 8.58. They were all taking mood stabilizers and/or atypical antipsychotic medications. A brief ECG was recorded and the SDNN, RMSSD, TP, LF and HF measures were all lower in the manic subjects.

Only the HF scores were reduced in MDD. There were no significant differences in Approximate Entropy in either group. The authors suggested that the relatively '*extreme affective lability*' in the bipolar patients may have contributed to the changes in HRV reported. In 2014, Chang et al. (2014) found that 61 unmedicated patients with mania, compared with 183 healthy control subjects, exhibited lower mean and variance of RRIs (similar in significance to the SDNN) and lower LF and HF spectral power. However, the LF/HF ratios were higher, and both YMRS total scores were positively correlated with LF/HF ratio and negatively correlated with HF measures. These observations suggest that during unmedicated mania, HRV was significantly disrupted and the trend was towards higher sympathetic and lower parasympathetic activity.

Chang et al. (2015) examined HRV using 5-minute, supine ECG recordings (with standardized respiratory rate) in 116 unmedicated subjects with bipolar II disorder (currently depressed), 591 with MDD (also unmedicated) and 421 control subjects. The bipolar and unipolar depressed subjects were significantly older than the controls. The measures of HRV revealed that the bipolar subjects exhibited lower total variance, HF, LF and very-low-frequency (VLF) scores than the depressed subjects, and both were lower than the control subjects. They suggested that HRV measures might assist separation of unipolar and bipolar depression, but these findings await confirmation.

Outhred et al. (2014) summarized the association of bipolar spectrum disorder with disturbances in prefrontal and limbic network neural activity, early neural processing and ANS dysregulation. They commented upon the significant technical variations and limitations in the research they reviewed, as well as the diagnostic heterogeneity and medication use, but noted significant evidence of reduced autonomic activity in these disorders. Quintana et al. (2015) found significant reduction in 33 subjects suffering from bipolar disorders and 47 suffering from schizophrenia, with varying severity of symptoms, compared with 212 healthy controls.

HRV and euthymia in bipolar disorders

Cohen et al. (2003) recorded HRV using brief ECG recordings in 39 euthymic bipolar I and 39 healthy control subjects. The SDNN, TP and LF/HF ratios were significantly lower in the bipolar subjects than controls, and HF power was higher, suggesting a reduction in the sympathovagal ratio. Re-analysis of the data using non-linear mathematical procedures found no significant differences between the groups (Todder et al., 2005).

Gruber et al. (2011) recorded parasympathetic activity using HF scores in 23 euthymic bipolar subjects, compared with 24 controls, and reported a significant difference. The data showed identical mean values but with large variations. Latalova et al. (2013) reported in a '*Letter to the Editor*' a study of HRV in 23 subjects with remitted bipolar affective disorder (subtype unspecified). Brief ECG recordings were collected and HRV analysis included calculation of time domain variables, frequency domain variables and '*non-linear analyses*'. A reduction in '*most*' (unspecified) parameters of ANS function was reported, but multiple methodological deficiencies left this report difficult to interpret.

Lee et al. (2012) addressed the association of '*sub-syndromal*' bipolar depression and HRV. HRV measures from brief ECG recordings in bipolar subjects (10 males and 23 females) and healthy controls (23 males and 36 females) were employed. The Montgomery–Asberg Depression Rating Scale (MADRS) score in bipolar subjects was 3.8 ± 3.7 (mean $\pm$ standard deviation), and the Clinical Global Impression–Severity Scale (CGI-S) score was 1.6 ± 0.7 (very low). The bipolar patients were found to have lower HRV measures using the SDNN, pNN50 and log TP. Negative correlations were found between the CGI-S score and SDNN, RMSSD, pNN50, LF and HF powers. They concluded that sub-syndromal bipolar depression (not full remission) was accompanied by reduced HRV.

More recently, Voggt et al. (2015) used 30-minute ECG recordings in 90 predominantly medicated bipolar I and II subjects combined, deemed '*clinically stable*', and 62 healthy control subjects, to measure differences in HRV. They found that the SDNN, LF and HF parameters were lower in the bipolar subjects. The contribution by medication use (a very significant confounding variable) was not included in their multivariate analysis (multi-linear regression).

HRV and depressive disorder

The research on HRV in depressive disorders has already been reviewed by a number of authors, but it is helpful to summarize those findings and update the literature since their publication. The evidence for parasympathetic dysregulation in depressive disorders was critically assessed by Rottenberg (2007) in a meta-analysis of 13 cross-sectional studies. He concluded that depression only contributed a small to medium effect size impact upon cardiac vagal control, and only explained about 2% of the variance, with a '*small to medium*' overall effect size (Cohen's $d = 0.332$). However, the overall difference between depressed subjects and healthy controls was significant ($t = 4.26$ and $p < 0.001$) and the range of Cohen's d for individual studies was from 0.83 to −0.078. Subsequently, Kemp et al. (2010) performed a meta-analysis of 18 studies, which examined HRV in 673 patients with MDD and 407 healthy control subjects. Those with depression had lower HRV time-based measures, higher '*high-frequency*' power measures and higher Valsalva ratios than controls. Non-linear measures (probably more reliable than linear measures) indicated a negative correlation of depression

severity and HRV. Tricyclic antidepressants were associated with decreased HRV, while selective serotonin reuptake inhibitors (SSRIs), mirtazapine and nefazodone, had no significant effects. In 2012, Stapelberg et al. (2012) reviewed the literature relating to HRV in MDD and found further evidence consistent with reduced parasympathetic activity, although they noted that the results were confounded by the use of medications.

Kemp et al. (2012) used brief ECG sampling in non-medicated depressed subjects, including 24 without anxiety, 24 with generalized anxiety disorder and 14 with panic disorder or post-traumatic stress disorder, compared with 94 age- and sex-matched control subjects. They found significantly reduced RMSSD and HF measures in the depressed subjects with comorbid generalized anxiety. The LF/HF ratios were higher in those subjects, but this is of uncertain significance (Billman, 2013; Reyes del Paso et al., 2013; Shaffer et al., 2014).

Wang et al. (2013), in a carefully designed study, examined a number of HRV variables in 53 MDD subjects (of at least moderate severity) and 53 healthy subjects, matched for age and sex. Using 24-hour ECG recordings, they found SDNN, SDANN (standard deviation of the average normal to normal intervals), RMSSD and pNN50 measures, as well as HF power, were all significantly lower in the depressed subjects. The LF/HF ratios positively correlated with severity of depression, but, as noted above, this ratio is of uncertain significance. Brunoni et al. (2013) observed the effects of treatment for depression using sertraline or direct electric current therapy (tDCS) upon HRV, with 118 moderately depressed subjects and matched controls. The lower HRV measures in their depressed subjects did not change with positive clinical response to either treatment modality. They suggested that reduction in HRV in depressive disorder may be a biomarker of depression. Sgoifo et al. (2015) came to a similar conclusion in their review of the literature regarding autonomic dysregulation and depressive disorders. These conclusions await further confirmation.

Ahrens et al. (2008) found no differences in HRV measures (mainly frequency) in 22 recurrently depressed female subjects, in remission, compared with 20 control subjects (aged 51 ± 1.7 years). The ECG recordings were very brief and HRV measures limited to frequency data. The results are therefore limited in significance. However, Ha et al. (2015a) in a study of 30 predominantly female, '*newly*' depressed and medication-free subjects (mean age: 65 ± 5 years) exhibited lower high, low and total frequency HRV measures, as well as lower SDNN, RMSSD and pNN50, than 30 matched controls.

Shinba (2013) also studied the reactivity of HRV during depressive episodes in a group of 22 unmedicated depressed subjects, compared with 47 age- and gender-matched control subjects, during a cognitive challenge task. They found an increase in HF power and LF/HF ratio during and after the challenge, suggesting increased parasympathetic and possibly increased sympathetic activity in depressed subjects during a cognitive stress. However, the number of depressed subjects was small and the use of a cognitive challenge makes this study significantly different from those performed at rest.

In a study using 15,105 subjects and carefully considered methodology, Kemp et al. (2014a) found that depressive illness was not associated with reduction in measures of HRV, but recognized that the study population was heterogeneous and confounding variables may have distorted their findings in this group. Subsequently, Kemp et al. (2014b) confirmed the significance of the heterogeneity by finding lower HRV (measured as RMSSD) in subjects suffering from MDD with melancholia ($n=40$) than in a non-melancholic cohort ($n=32$). Messerotti Benvenuti et al. (2015) found a significant association between somatic symptoms of depression (using the Beck Depression Inventory II) and reduced HRV, measured by SDNN, NN50 and TP (but not RMSSD). However, their study population consisted of 62 healthy college students, and only the 25 students deemed to suffer dysphoric symptoms exhibited this association. Cognitive and affective symptoms of depression were not associated with changes in HRV. Their findings are of interest as they confirm an association of reduced HRV with somatic symptoms of depression (some similarities to melancholia) but are limited by the absence of actual depressive disorders in their subject cohort.

Ha et al. (2015b) reported that in 30 antidepressant-free subjects aged more than 60 years, compared with 30 healthy age- and sex-matched subjects, recently diagnosed depression was associated with reduced LF and HF power, TP, VLF power, SDNN, RMSSD and pNN50 measures. The severity of depression was moderate, with MADRS scores of 24.6 ± 5.

HRV, sleep and mood disorders

As disruption of sleep is highly significant in major mood disorders, promotes relapse, contributes significantly to impaired function (Boland and Alloy, 2013; Boudebesse et al., 2014; Goodwin et al., 2007; Harvey et al., 2005; Murray and Harvey, 2010; Pandi-Perumal and Kramer, 2010; Paykel et al., 1995; St-Amand et al., 2013; Yatham and Maj, 2010) and HRV exhibits a circadian rhythm (Boudreau et al., 2011, 2012, 2013), the associations of HRV with sleep and mood disorders are considered.

In healthy sleep, the sympathovagal balance is tipped towards parasympathetic activity around sleep onset and during sleep stages I, II, III and IV (Bianchi and Mendez, 2013; Busek et al., 2005; Cabiddu et al., 2012; Chouchou and Desseilles, 2014). Conversely, the sympathovagal balance is reversed during rapid eye movement (REM) sleep (Busek et al., 2005; Chouchou and Desseilles, 2014). All autonomic activity falls during stages III and IV, but perhaps with a greater fall in sympathetic than parasympathetic activity (Boudreau et al., 2013; Goldberger et al., 2001).

The sympathovagal imbalance reported in patients with mood disorders during 24-hour, bedtime and sleep studies may in part be related to the relative increase in REM-stage sleep duration reported in these disorders (Palagini et al., 2013; Pandi-Perumal and Kramer, 2010; Paykel et al., 1995). Yang et al. (2011) reported a study of ambulant 24-hour HRV measures (including multiscale entropy) in 52 non-medicated patients with MDD, 47 non-medicated patients with primary insomnia and 88 matched control subjects. The '*sleep*' process was included in the ECG record of the '*bedtime*' period. Subjects with current MDD and primary insomnia exhibited significant reductions in HRV indices (consistent with reduced parasympathetic activity) and reduced physiologic complexity, compared with the control subjects. The differences in HRV measures also correlated with poor sleep quality (Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale), but not with the measures of depressive symptoms (Beck Depression Inventory and Hamilton Depression Rating Scale). This confirmed that insomnia contributed to adverse changes in autonomic function, independent of depressive symptoms.

Migliorini et al. (2011) reported a study of HRV during sleep in one subject with bipolar affective disorder (aged 37 years, type I disorder) and eight healthy control subjects (aged 18–45 years). The study followed a complex design, with the bipolar subject observed over four nights and the control subjects for one night each. The bipolar subject's mean heart rate, SDNN and RMSSD were lower than the mean of all control values. In addition, the percentage of REM sleep was consistently increased, as would be expected from previous research (Palagini et al., 2013; Paykel et al., 1995; Steiger and Kimura, 2010). These findings were consistent with previous findings of reduced autonomic activity and increased REM sleep in bipolar subjects, but the research design and small numbers limited their significance.

Mariani et al. (2012) reported a '*bedtime*' HRV study of 12 patients suffering from bipolar disorders, aged between 18 and 65 years, in clinical states defined as euthymic, depressed, hypomanic or mixed. They were compared with 102 healthy control subjects. They found that '*most*' (unspecified) RMSSD scores and measures of Sample Entropy for bipolar subjects were below the first quartile and/or median value of the control group. This study is very difficult to interpret because of the small number of bipolar subjects, the mixture of mental states being assessed, the heterogeneous nature of the bipolar diagnoses, the lack of data regarding medication use, the lack of detail regarding results and the uncertain comparability of multiple observations from a number of subjects. However, the trend in these findings was again towards a reduction in HRV in subjects suffering from bipolar mood disorders, during the '*bedtime*' period.

Medication effects in HRV

Research has provided considerable evidence that antidepressant medications can exert significant effects upon HRV, but the differences between antidepressants are noteworthy. The effects of antipsychotic, anticonvulsant medications, lithium and benzodiazepines appear less intense than antidepressants, but the research findings exhibit significant variation.

Antidepressant medications

Davidson et al. (2005) found that venlafaxine was associated with a greater fall in HRV indices than paroxetine, while Van Zyl et al. (2008) found tricyclic antidepressants were associated with reductions in HRV indices over short recordings (2–40 minutes) but not long recordings (24 hours). SSRIs appeared to have minimal effects on HRV in both groups of recordings. Agelink et al. (2002) observed that reboxetine did not cause any significant changes in vagally mediated HRV indices, while Siepmann et al. (2004) found that moclobemide did not alter measures of HRV in 12 male volunteers (aged 22–29 years), compared with healthy volunteers.

Kemp et al. (2010, 2011) found that tricyclic antidepressants were associated with decreased HRV, while SSRIs, mirtazapine and nefazodone had no significant effects. Subsequently, Kemp et al. (2013) reported that escitalopram administered to 44 healthy subjects over the age of 25 years increased the HF (prominently parasympathetic) component of HRV, both at rest and during a period of psychological stress. Those subjects under 25 years did not exhibit any change, suggesting that differences in prefrontal maturation may be significant in this process.

Udupa et al. (2011), using brief ECG recordings, examined HRV parameters in subjects taking tricyclic antidepressants ($n=32$) or SSRIs ($n=32$). They found reductions in time and frequency measures with the use of tricyclic antidepressants but no change with SSRIs.

More recently, Chappell et al. (2013) performed a randomized, controlled, subject-blind, two-period, cross-over study with 26 healthy subjects aged 50–65 years (to minimize gender effects) (Umetani et al., 1998; Voss et al., 2013), using a placebo, duloxetine or escitalopram. They were sequentially exposed to escitalopram 20 mg daily or duloxetine 60 mg daily, each for 11 days, separated by 2 days of '*washout*'. Twenty-four-hour ECG recordings were collected, and analysis revealed that time-based and frequency-based HRV measures were not significantly different between the baseline recordings and each of the medication exposed days. Terhardt et al. (2013) measured time and frequency dimension HRV parameters during brief observation in 28 healthy controls and 41 moderately depressed subjects, both during a drug-free period, and after 14 and 28 days of treatment with venlafaxine or mirtazapine. They found that HRV measures declined during treatment with either medication, while heart rate increased.

In a study of a very large cohort, Kemp et al. (2014a) found that a large range of antidepressant medications (tricyclic antidepressants, serotonin and noradrenaline reuptake

inhibitors, SSRIs and a number of unspecified '*other antidepressants*') all significantly suppressed HRV (measured as RMSSD and HF). The effect of the tricyclics was the greatest (Cohen's *d* for RMSSD = 0.81 and HF = 0.73) and the SSRIs the least (RMSSD = 0.28 and HF = 0.25).

Lithium, antipsychotic and anticonvulsant medications

The research into the effects of lithium and anticonvulsant medications (the latter used in the treatment of mood disorders) suggests absence of effect upon HRV. The findings for antipsychotic medications are more heterogeneous, and there is evidence that prolonged use of antipsychotic medications may result in a normalization of reduced HRV provoked by the relevant medications.

Cohen et al. (2003) examined HRV in subjects taking lithium alone or combinations of lithium, sodium valproate, carbamazepine or olanzapine. They concluded that there was no medication effect upon the SDNN measure of HRV, including with lithium. Similarly, Lotufo et al. (2012), in their meta-analysis, reported only very limited evidence of an effect of anticonvulsant medications upon HRV. Stefani et al. (2013) found that withdrawal of anticonvulsant medications was not associated with changes in HRV, and Henry et al. (2010) found that mood stabilizer or antipsychotic use had no significant effect upon HRV measures.

Agelink et al. (2001) examined the effect of amisulpride, olanzapine, sertindole and clozapine upon HRV in subjects with schizophrenia, compared with control subjects. They found that only clozapine significantly reduced RMSSD, but the variation in all parameters measured was very large.

Iwamoto et al. (2012) measured the effects of chlorpromazine and mepromazine (with 72% receiving both) upon HRV in 211 subjects suffering from schizophrenia and 44 control subjects. An ECG was recorded for 5 minutes under standardized conditions, with regularly paced breathing. They reported that the LF and HF powers were lower, but LF/HF ratios the same, in the schizophrenia subjects. This suggested a reduction in overall autonomic activity, without an alteration in sympathetic/parasympathetic balance. A negative correlation of antipsychotic dose effect upon LF + HF power was noted. The muscarinic effects of mepromazine and chlorpromazine may have contributed to this effect (Huang et al., 2013).

Similarly, Linder et al. (2014), in a carefully executed study, measured HRV parameters in 55 young, predominantly female patients (mean age = 33 ± 7 years, 67% female) suffering from bipolar disorders (I and II), who were taking antipsychotic medications. Current use of second-generation antipsychotics, but not first-generation antipsychotics (the numbers were relatively small), was associated with a reduction in SDNN and RMSSD and strongly related to dopamine receptor 2 affinity (paradoxically, given high affinity in first-generation antipsychotics). However, extended use of antipsychotics (up to 5 years) and the use of lithium or anticholinergic medications were not associated with significantly reduced HRV measures.

Benzodiazepines

Khaspekova et al. (2005) found improvement of HRV in a study of clonazepam in the management of paroxysmal atrial fibrillation. Komatsu et al. (1995) reported evidence that midazolam reduced LF elements of HRV and increased elements of HF, during anaesthesia. A lack of clarity about the impact of benzodiazepines upon HRV remains.

Therapeutic interventions to enhance HRV

A number of treatment interventions have been considered to enhance HRV and thus inhibit the adverse effects of illness such as depressive and bipolar disorders. Exercise has shown promise (Soares-Miranda et al., 2014; Tonello et al., 2014), but varying efficacy and differences in effect between resistance exercise and aerobic exercise (Kingsley and Figueroa, 2014) and time of day leave the benefits of exercise uncertain. HRV biofeedback has shown some positive effects upon HRV (Prinsloo et al., 2014; Wheat and Larkin 2010), but the evidence is still limited. Acupuncture (Chung et al., 2014) has been employed with some encouraging but limited results, while the benefits of Yoga remain uncertain (Posadzki et al., 2015). Mindfulness may also enhance HRV, but this remains uncertain (Nijjar et al., 2014).

Conclusion

The ANS is central to physiological health and is regulated by central nervous system components which are fundamental to psychological functions. It is increasingly clear that major unipolar and bipolar mood disorders are associated with significant disruption of ANS activity. Whether these changes precede these disorders or persist during remission are important questions to be addressed. They also have implications for a variety of physiological functions such as cardiac function, energy regulation and gastrointestinal motility.

The changes in the operation of the ANS also offer a window into the neurophysiological changes which occur in the central ANS (insular cortex, cingulate cortex, medial and supraorbital prefrontal cortex, with links to hypothalamus, thalamus and periaqueductal grey). The ANS is heavily involved in the stress (or demand) response mechanisms and maintenance of optimal non-stress or vegetative functions. While sympathetic activity is essential for adequate responses to stress/demand, parasympathetic activity balances the potentially adverse effects of sympathetic drive (e.g. excessive arousal and reduced activity of non-essential functions) optimizing the physiological functioning of the ANS. As parasympathetic activity is more rapid and

flexible than sympathetic drive, this component of the ANS provides significant modulation of function. A variety of medications, including many psychotropic drugs, also appear to adversely impact autonomic function, but the degree of effect varies widely among medications.

HRV offers a relatively simple, well-tolerated, non-invasive and inexpensive method for studying some of these pathophysiological processes. The results of research into HRV and mood disorders suggest a clear trend towards evidence of a negative association and particularly the dysregulation of parasympathetic activity. However, there has been considerable variation in these results and concerns about the validity of the interpretations made of the variables derived, making definitive conclusions difficult. Careful attention to the management of confounding variables through more substantial sample sizes, careful subject selection (particularly subjects not taking relevant medications), use of non-linear measures, appropriate statistical analyses (such as Propensity Score Matching and Inverse Probability Weighting) (Hogan and Lancaster, 2004; Kemp et al., 2014a, 2014b; Pearl, 2000; Voss et al., 2006; Williamson and Forbes, 2014) and greater consistency in research methodology would facilitate our knowledge of major mood disorders and their adverse effects upon this critically important component of central nervous system function.

Despite these limitations, the study of HRV has already contributed meaningfully to our understanding of the pathophysiology of mood disorders, their adverse effects upon a variety of physiological functions and the adverse effects of psychotropic medications. When combined with clinical and other psychophysiological research techniques, HRV provides a valuable tool for expanding our knowledge and management of these common and disabling mental disorders.

Acknowledgements

The author gratefully acknowledges the contribution of Dr Sherylee Bassett in the preparation of this paper, through her critical comments upon drafts of this paper.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

References

Agelink MW, Majewski T, Wurthmann C, et al. (2001) Effects of newer atypical antipsychotics on autonomic neurocardiac function: A comparison between amisulpride, olanzapine, sertindole, and clozapine. *Journal of Clinical Psychopharmacology* 21: 8–13.

Agelink MW, Ullrich H, Baumann B, et al. (2002) Effects of reboxetine, a selective norepinephrine reuptake inhibitor, on sympathetic and parasympathetic outflow to the heart: Preliminary data. *Psychopharmacology* 163: 151–156.

Ahrens T, Deuschle M, Krumm B, et al. (2008) Pituitary-adrenal and sympathetic nervous system responses to stress in women remitted from recurrent major depression. *Psychosomatic Medicine* 70: 461–467.

Alvares GA, Quintana DS, Hickie IB, et al. (2015) Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: A systematic review and meta-analysis. *Journal of Psychiatry & Neuroscience* 40: 140217.

Bianchi AM and Mendez MO (2013) Methods for heart rate variability analysis during sleep. In: *2013 35th annual international conference of the IEEE engineering in medicine and biology society (EMBC)*, Osaka, Japan, 3–7 July 2013, pp. 6579–6582. New York: IEEE.

Billman GE (2013) The effect of heart rate on the heart rate variability response to autonomic interventions. *Frontiers in Physiology* 4: 222.

Boudreau P, Yeh WH, Dumont GA, et al. (2013) Circadian variation of heart rate variability across sleep stages. *Sleep* 36: 1919–1928.

Brunoni AR, Kemp AH, Dantas EM, et al. (2013) Heart rate variability is a trait marker of major depressive disorder: Evidence from the sertraline vs. electric current therapy to treat depression clinical study. *International Journal of Neuropsychopharmacology* 16: 1937–1949.

Busek P, Vankova J, Opavsky J, et al. (2005) Spectral analysis of the heart rate variability in sleep. *Physiological Research* 54: 369–376.

Cabiddu R, Cerutti S, Viardot G, et al. (2012) Modulation of the sympatho-vagal balance during sleep: frequency domain study of heart rate variability and respiration. *Frontiers in Physiology* 3: 45.

Carney RM, Freedland KE, Stein PK, et al. (2000) Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. *Psychosomatic Medicine* 62: 639–647.

Chang HA, Chang CC, Kuo TB, et al. (2015) Distinguishing bipolar II depression from unipolar major depressive disorder: Differences in heart rate variability. *The World Journal of Biological Psychiatry* 16: 351–360.

Chang HA, Chang CC, Tzeng NS, et al. (2014) Heart rate variability in unmedicated patients with bipolar disorder in the manic phase. *Psychiatry and Clinical Neurosciences* 68: 674–682.

Chappell JC, Kovacs R, Haber H, et al. (2013) Evaluation of the effects of duloxetine and escitalopram on 24-hour heart rate variability: A mechanistic study using heart rate variability as a pharmacodynamic measure. *Journal of Clinical Psychopharmacology* 33: 236–239.

Chouchou F and Desseilles M (2014) Heart rate variability: A tool to explore the sleeping brain? *Frontiers in Neuroscience* 8: 402.

Chung JW, Yan VC and Zhang H 2014. Effect of acupuncture on heart rate variability: A systematic review. *Evidence-Based Complementary and Alternative Medicine* 2014: 819–871.

Cohen H, Kaplan Z, Kotler M, et al. (2003) Impaired heart rate variability in euthymic bipolar patients. *Bipolar Disorders* 5: 138–143.

Cygankiewicz I and Zareba W (2013) Heart rate variability. *Handbook of Clinical Neurology* 117: 379–393.

Daban C, Martinez-Aran A, Cruz N, et al. (2008) Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression: A systematic review. *Journal of Affective Disorders* 110: 1–15.

Davidson J, Watkins L, Owens M, et al. (2005) Effects of paroxetine and venlafaxine Xr on heart rate variability in depression. *Journal of Clinical Psychopharmacology* 25: 480–484.

Geisler FC, Kubiak T, Siewert K, et al. (2013) Cardiac vagal tone is associated with social engagement and self-regulation. *Biological Psychology* 93: 279–286.

George MS, Nahas Z, Borckardt JJ, et al. (2007) Brain stimulation for the treatment of psychiatric disorders. *Current Opinion in Psychiatry* 20: 250–254 (discussion 247–249).

Goldberger JJ, Challapalli S, Tung R, et al. (2001) Relationship of heart rate variability to parasympathetic effect. *Circulation* 103: 1977–1983.

Gorman JM and Sloan RP (2000) Heart rate variability in depressive and anxiety disorders. *American Heart Journal* 140: 77–83.

Gruber J, Dutra S, Eidelman P, et al. (2011) Emotional and physiological responses to normative and idiographic positive stimuli in bipolar disorder. *Journal of Affective Disorders* 133: 437–442.

Ha JH, Park S, Yoon D, et al. (2015a) Short-term heart rate variability in older patients with newly diagnosed depression. *Psychiatry Research* 226: 484–488.

Ha JH, Park S, Yoon D, et al. (2015b) Short-term heart rate variability in older patients with newly diagnosed depression. *Psychiatry Research* 226: 484–488.

Hanson CS, Outhred T, Brunoni AR, et al. (2013) The impact of escitalopram on vagally mediated cardiovascular function to stress and the moderating effects of vigorous physical activity: A randomized controlled treatment study in healthy participants. *Frontiers in Physiology* 4: 259.

Heathers JA (2014) Everything Hertz: Methodological issues in short-term frequency-domain HRV. *Frontiers in Physiology* 5: 177.

Henry BL, Minassian A, Paulus MP, et al. (2010) Heart rate variability in bipolar mania and schizophrenia. *Journal of Psychiatric Research* 44: 168–176.

Hogan JW and Lancaster T (2004) Instrumental variables and inverse probability weighting for causal inference from longitudinal observational studies. *Statistical Methods in Medical Research* 13: 17–48.

Huang WL, Chang LR, Kuo TB, et al. (2013) Impact of antipsychotics and anticholinergics on autonomic modulation in patients with schizophrenia. *Journal of Clinical Psychopharmacology* 33: 170–177.

Iwamoto Y, Kawanishi C, Kishida I, et al. (2012) Dose-dependent effect of antipsychotic drugs on autonomic nervous system activity in schizophrenia. *BMC Psychiatry* 12: 199.

Kaplan DT, Furman MI, Pincus SM, et al. (1991) Aging and the complexity of cardiovascular dynamics. *Biophysical Journal* 59: 945–949.

Kemp AH and Quintana DS (2013) The relationship between mental and physical health: Insights from the study of heart rate variability. *International Journal of Psychophysiology* 89: 288–296.

Kemp AH, Brunoni AR, Santos IS, et al. (2014a) Effects of depression, anxiety, comorbidity, and antidepressants on resting-state heart rate and its variability: An ELSA-Brasil Cohort baseline study. *American Journal of Psychiatry* 171: 1328–1334.

Kemp AH, Outhred T, Saunders S, et al. (2013) Impact of escitalopram on vagally mediated cardiovascular function in healthy participants: Implications for understanding differential age-related, treatment emergent effects. *Psychopharmacology* 231: 2281–2290.

Kemp AH, Quintana DS and Malhi GS (2011) Effects of serotonin reuptake inhibitors on heart rate variability: Methodological issues, medical comorbidity, and clinical relevance. *Biological Psychiatry* 69: e25–e26 (author reply e27–e28).

Kemp AH, Quintana DS, Felmingham KL, et al. (2012) Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: Implications for cardiovascular risk. *PLoS ONE* 7: e30777.

Kemp AH, Quintana DS, Gray MA, et al. (2010) Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. *Biological Psychiatry* 67: 1067–1074.

Kemp AH, Quintana DS, Quinn CR, et al. (2014b) Major depressive disorder with melancholia displays robust alterations in resting state heart rate and its variability: Implications for future morbidity and mortality. *Frontiers in Psychology* 5: 1387.

Khaspekova NB, Solov'Eva AD, Nedostup AV, et al. (2005) Effect of clonazepam and antiarrhythmic drugs on heart rate variability in patients with paroxysmal atrial fibrillation. *Kardiologiia* 45: 35–40.

Kingsley JD and Figueroa A (2014) Acute and training effects of resistance exercise on heart rate variability. *Clinical Physiology and Functional Imaging*. Epub ahead of print 18 December. DOI: 10.1111/cpf.12223.

Kleiger RE, Stein PK and Bigger JT, Jr (2005) Heart rate variability: Measurement and clinical utility. *Annals of Noninvasive Electrocardiology* 10: 88–101.

Komatsu T, Singh PK, Kimura T, et al. (1995) Differential effects of ketamine and midazolam on heart rate variability. *Canadian Journal of Anaesthesia* 42: 1003–1009.

Latalova K, Prasko J, Kamaradova D, et al. (2013) Comorbidity bipolar disorder and personality disorders. *Neuroendocrinology Letters* 34: 1–8.

Lee JS, Kim B, Hong Y, et al. (2012) Heart rate variability in the subsyndromal depressive phase of bipolar disorder. *Psychiatry and Clinical Neurosciences* 66: 361–366.

Leucht S, Kane JM, Kissling W, et al. (2005) Clinical implications of brief psychiatric rating scale scores. *British Journal of Psychiatry* 187: 366–371.

Linder JR, Sodhi SK, Haynes WG, et al. (2014) Effects of antipsychotic drugs on cardiovascular variability in participants with bipolar disorder. *Human Psychopharmacology* 29: 145–151.

Lotufo PA, Valiengo L, Bensenor IM, et al. (2012) A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. *Epilepsia* 53: 272–282.

Lukasiewicz M, Gerard S, Besnard A, et al. (2013) Young Mania Rating Scale: How to interpret the numbers? Determination of a severity threshold and of the minimal clinically significant difference in the Emblem cohort. *International Journal of Methods in Psychiatric Research* 22: 46–58.

McCraty R and Childre D (2010) Coherence: Bridging personal, social, and global health. *Alternative Therapies in Health and Medicine* 16: 10–24.

Mariani S, Migliorini M, Tacchino G, et al. (2012) Clinical state assessment in bipolar patients by means of HRV features obtained with a sensorized T-shirt. *Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society* 2012: 2240–2243.

Messerotti Benvenuti S, Buodo G, Mennella R, et al. (2015) Somatic, but not cognitive-affective, symptoms are associated with reduced heart rate variability in individuals with dysphoria. *Frontiers in Psychology* 6: 599.

Migliorini M, Mendez MO and Bianchi AM (2011) Study of heart rate Variability in bipolar disorder: Linear and non-linear parameters during sleep. *Frontiers in Neuroengineering* 4: 22.

Moon E, Lee SH, Kim DH, et al. (2013) Comparative study of heart rate variability in patients with schizophrenia, bipolar disorder, post-traumatic stress disorder, or major depressive disorder. *Clinical Psychopharmacology and Neuroscience* 11: 137–143.

Munjal S, Koval T, Muhammad R, et al. (2009) Heart rate variability increases with reductions in cigarette smoke exposure after 3 days. *Journal of Cardiovascular Pharmacology and Therapeutics* 14: 192–198.

Nijjar PS, Puppala VK, Dickinson O, et al. (2014) Modulation of the autonomic nervous system assessed through heart rate variability by a mindfulness based stress reduction program. *International Journal of Cardiology* 177: 557–559.

O'Regan C, Kenny RA, Cronin H, et al. (2014) Antidepressants strongly influence the relationship between depression and heart rate variability: Findings from The Irish Longitudinal Study on Ageing (Tilda). *Psychological Medicine* 45: 623–636.

Outhred T, Kemp AH and Malhi GS (2014) Physiological correlates of bipolar spectrum disorders and their treatment. *Current Topics in Behavioural Neuroscience* 21: 47–102.

Palagini L, Baglioni C, Ciapparelli A, et al. (2013) REM sleep dysregulation in depression: State of the art. *Sleep Medicine Reviews* 17: 377–390.

Pandi-Perumal SR and Kramer M (2010) *Sleep and Mental Illness*. Cambridge: Cambridge University Press.

Paykel ES, Ramana R, Cooper Z, et al. (1995) Residual symptoms after partial remission: An important outcome in depression. *Psychological Medicine* 25: 1171–1180.

Pearl J (2000) *Causality: Models, Reasoning, and Inference*. Cambridge: Cambridge University Press.

Perakakis P, Taylor M, Martinez-Nieto E, et al. (2009) Breathing frequency bias in fractal analysis of heart rate variability. *Biological Psychology* 82: 82–88.

Perini R and Veicsteinas A (2003) Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. *European Journal of Applied Physiology* 90: 317–325.

Porges SW (2009) The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. *Cleveland Clinic Journal of Medicine* 76(Suppl. 2): S86–S90.

Posadzki P, Kuzdzal A, Lee MS, et al. (2015) Yoga for heart rate variability: A systematic review and meta-analysis of randomized clinical trials. *Applied Psychophysiology and Biofeedback* 40: 239–249.

Quintana DS and Heathers JA (2014) Considerations in the assessment of heart rate variability in biobehavioral research. *Frontiers in Psychology* 5: 805.

Quintana DS, Westlye LT, Kaufmann T, et al. (2015) Reduced heart rate variability in schizophrenia and bipolar disorder compared to healthy controls. *Acta Psychiatrica Scandinavica*. Epub ahead of print 15 September. DOI: 10.1111/acps.12498.

Rajendra Acharya U, Paul Joseph K, Kannathal N, et al. (2006) Heart rate variability: A review. *Medical & Biological Engineering & Computing* 44: 1031–1051.

Reyes del Paso GA, Langewitz W, Mulder LJ, et al. (2013) The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. *Psychophysiology* 50: 477–487.

Rizvi SJ, Donovan M, Giacobbe P, et al. (2011) Neurostimulation therapies for treatment resistant depression: A focus on vagus nerve stimulation and deep brain stimulation. *International Review of Psychiatry* 23: 424–436.

Romanowicz M, Schmidt JE, Bostwick JM, et al. (2011) Changes in heart rate variability associated with acute alcohol consumption: Current knowledge and implications for practice and research. *Alcoholism-Clinical and Experimental Research* 35: 1092–1105.

Rottenberg J (2007) Cardiac vagal control in depression: A critical analysis. *Biological Psychology* 74: 200–211.

Routledge FS, Campbell TS, Mcfetridge-Durdle JA, et al. (2010) Improvements in heart rate variability with exercise therapy. *Canadian Journal of Cardiology* 26: 303–312.

Sacha J and Pluta W (2008) Alterations of an average heart rate change heart rate variability due to mathematical reasons. *International Journal of Cardiology* 128: 444–447.

St-Amand J, Provencher MD, Belanger L et al. (2013) Sleep disturbance in bipolar disorder during remission. *Journal of Affective Disorders* 146: 112–119.

Sagawa Y, Kondo H, Matsubuchi N, et al. (2011) Alcohol has a dose-related effect on parasympathetic nerve activity during sleep. *Alcoholism-Clinical and Experimental Research* 35: 2093–2100.

Schafer A and Vagedes J (2013) How accurate is pulse rate variability as an estimate of heart rate variability? A review on studies comparing photoplethysmographic technology with an electrocardiogram. *International Journal of Cardiology* 166: 15–29.

Sgoifo A, Carnevali L, Pico Alfonso ML, et al. (2015) Autonomic dysfunction and heart rate variability in depression. *Stress* 18: 343–352.

Shaffer F, Mccraty R and Zerr CL (2014) A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. *Frontiers in Psychology* 5: 1040.

Shinba T (2013) Altered autonomic activity and reactivity in depression revealed by heart-rate variability measurement during rest and task conditions. *Psychiatry and Clinical Neurosciences* 68: 225–233.

Siepmann M, Handel J, Mueck-Weymann M, et al. (2004) The effects of moclobemide on autonomic and cognitive functions in healthy volunteers. *Pharmacopsychiatry* 37: 81–87.

Soares-Miranda L, Sattelmair J, Chaves P, et al. (2014) Physical activity and heart rate variability in older adults: The Cardiovascular Health Study. *Circulation* 129: 2100–2110.

Stapelberg NJ, Hamilton-Craig I, Neumann DL, et al. (2012) Mind and heart: Heart rate variability in major depressive disorder and coronary heart disease – a review and recommendations. *The Australian and New Zealand Journal of Psychiatry* 46: 946–957.

Stefani M, Arima H and Mohamed A (2013) Withdrawal of anti-epileptic medications during video EEG monitoring does not alter ECG parameters or HRV. *Epilepsy Research* 106: 222–229.

Steiger A and Kimura M (2010) Wake and sleep EEG provide biomarkers in depression. *Journal of Psychiatric Research* 44: 242–252.

Stein PK and Kleiger RE (1999) Insights from the study of heart rate variability. *Annual Review of Medicine* 50: 249–261.

Terhardt J, Lederbogen F, Feuerhack A, et al. (2013) Heart rate variability during antidepressant treatment with venlafaxine and mirtazapine. *Clinical Neuropharmacology* 36: 198–202.

Thayer JF, Ahs F, Fredrikson M, et al. (2012) A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews* 36: 747–756.

Thayer JF and Lane RD (2000) A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders* 61: 201–216.

Thayer JF, Hansen AL, Saus-Rose E, et al. (2009) Heart rate variability, prefrontal neural function, and cognitive performance: The neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavioral Medicine* 37: 141–153.

Thayer JF, Smith M, Rossy LA, et al. (1998) Heart period variability and depressive symptoms: Gender differences. *Biological Psychiatry* 44: 304–306.

Tobaldini E, Nobili L, Strada S, et al. (2013) Heart rate variability in normal and pathological sleep. *Frontiers in Physiology* 4: 294.

Todder D, Bersudsky Y and Cohen H (2005) Nonlinear analysis of RR interval in euthymic bipolar disorder. *Autonomic Neuroscience-Basic & Clinical* 117: 127–131.

Tonello L, Rodrigues FB, Souza JW, et al. (2014) The role of physical activity and heart rate variability for the control of work related stress. *Frontiers in Physiology* 5: 67.

Udupa K, Thirthalli J, Sathyaprabha TN, et al. (2011) Differential actions of antidepressant treatments on cardiac autonomic alterations in depression: A prospective comparison. *Asian Journal of Psychiatry* 4: 100–106.

Umetani K, Singer DH, Mccraty R, et al. (1998) Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. *Journal of the American College of Cardiology* 31: 593–601.

Valenza G, Nardelli M, Bertschy G, et al. (2014) Maximal-radius multiscale entropy of cardiovascular variability: A promising biomarker of pathological mood states in bipolar disorders. In: *2014 36th annual international conference of the IEEE engineering in medicine and biology society (EMBC)*, Chicago, IL, 26–30 August 2014, pp. 6663–6666. New York: IEEE.

Van Zyl LT, Hasegawa T and Nagata K (2008) Effects of antidepressant treatment on heart rate variability in major depression: A quantitative review. *BioPsychoSocial Medicine* 2: 12.

Voggt A, Berger M, Obermeier M, et al. (2015) Heart rate variability and Omega-3 Index in euthymic patients with bipolar disorders. *European Psychiatry* 30: 228–232.

Voss A, Baier V, Schulz S, et al. (2006) Linear and nonlinear methods for analyses of cardiovascular variability in bipolar disorders. *Bipolar Disorders* 8: 441–452.

Voss A, Schroeder R, Fischer C, et al. (2013) Influence of age and gender on complexity measures for short term heart rate variability analysis in healthy subjects. In: *2013 35th annual international conference of the IEEE engineering in medicine and biology society (EMBC)*, Osaka, Japan, 3–7 July 2013, pp. 5574–5577. New York: IEEE.

Wang Y, Zhao X, O'Neil A, et al. (2013) Altered cardiac autonomic nervous function in depression. *BMC Psychiatry* 13: 187.

Williamson EJ and Forbes A (2014) Introduction to propensity scores. *Respirology* 19: 625–635.

Xhyheri B, Manfrini O, Mazzolini M, et al. (2012) Heart rate variability today. *Progress in Cardiovascular Diseases* 55: 321–331.

Yang AC, Tsai SJ, Yang CH, et al. (2011) Reduced physiologic complexity is associated with poor sleep in patients with major depression and primary insomnia. *Journal of Affective Disorders* 131: 179–185.

Yatham LN, Maj M (2010) *Bipolar Disorder: Clinical and Neurobiological Foundations*. Chichester, West Sussex: Wiley-Blackwell.