Major depressive disorder with melancholia displays robust alterations in resting state heart rate and its variability: implications for future morbidity and mortality

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Background: Major depressive disorder (MDD) is associated with increased heart rate and reductions in its variability (heart rate variability, HRV) – markers of future morbidity and mortality – yet prior studies have reported contradictory effects. We hypothesized that increases in heart rate and reductions in HRV would be more robust in melancholia relative to controls, than in patients with non-melancholia.

Methods: A total of 72 patients with a primary diagnosis of MDD (age M: 36.26, SE: 1.34; 42 females) and 94 controls (age M: 35.69, SE: 1.16; 52 females) were included in this study. Heart rate and measures of its variability (HRV) were calculated from two 2-min electrocardiogram recordings during resting state. Propensity score matching controlled imbalance on potential confounds between patients with melancholia (n = 40) and non-melancholia (n = 32) including age, gender, disorder severity, and comorbid anxiety disorders.

Results: MDD patients with melancholia displayed significantly increased heart rate and lower resting-state HRV (including the square root of the mean squared differences between successive N–N intervals, the absolute power of high frequency and standard deviation of the Poincaré plot perpendicular to the line of identity measures of HRV) relative to controls, findings associated with a moderate effect size (Cohen's d’s = 0.56–0.58).

Patients with melancholia also displayed an increased heart rate relative to those with non-melancholia (Cohen's d = 0.20).

Conclusion: MDD patients with melancholia – but not non-melancholia – display robust increases in heart rate and decreases in HRV. These findings may underpin a variety of behavioral impairments in patients with melancholia including somatic symptoms, cognitive impairment, reduced responsiveness to the environment, and over the longer-term, morbidity and mortality.

Keywords: melancholia, non-melancholia, electrocardiogram, ECG, heart rate, heart rate variability, HRV, resting state

INTRODUCTION

Unfortunately, most researchers in psychiatry and psychology express little interest in the mapping of autonomic regulation as a “vulnerability” dimension for various disorders and behavioral problems, although visceral features are often symptoms of the disorders they are treating. –Porges (2011)

Major depressive disorder (MDD) is associated with reduced resting-state heart rate variability (HRV; Kemp et al., 2010, 2012; Brunoni et al., 2013; see Kemp and Quintana, 2013 for review), and these reductions are inversely associated with disorder severity (Kemp et al., 2010). Heart rate and its variability (HRV) are determined by a variety of physiological factors, although the most prominent of these is the autonomic system. A high level of parasympathetic (vagal) function is both desirable and beneficial as it reflects the capacity for an individual to respond, adapt and regulate responses when required. One can only imagine the consequences of buildings in Tokyo not being sufficiently flexible to withstand an earthquake. The ability to adapt quickly to change in the environment requires flexibility. Researchers (Kashdan and Rottenberg, 2010) have argued that a fundamental component of health is psychological flexibility and have suggested that HRV may provide the psychophysiological foundation for such flexibility (Friedman and Thayer, 1998; Kashdan and Rottenberg, 2010). By contrast, chronic reductions in HRV...
are associated with psychophysiological rigidity, dysregulation of a variety of allostatic systems, and increased risk for morbidity and mortality (see Kemp and Quintana, 2013 for review). The goal of the present paper is to determine whether specific subtypes of depression display more robust alterations in heart rate and commonly reported measures of HRV relative to controls.

In the resting state, the heart is under tonic inhibitory control by the vagus, yet measures of HRV are a more specific marker of vagal function than heart rate (Saul, 1990; Reyes Del Paso et al., 2013). That said, different measures of HRV provide information on different physiological control mechanisms (Reyes Del Paso et al., 2013). For instance, high frequency oscillations (0.15–0.4 Hz) relate to respiratory influences, while LF oscillations (0.04–0.15 Hz) reflect mechanisms relating to blood pressure control such as the baroreflex (Reyes Del Paso et al., 2013; see also Krygier et al., 2013).

Reduced HRV was first reported in depressed patients more than two-decades ago (Carney et al., 1988), and more recently, has been shown to predict adverse cardiovascular events over a follow-up period of 3–15 years (Hillebrand et al., 2013), highlighting the importance of continued research in this area. However, not all studies (Licht et al., 2008) — including our own (Kemp et al., 2014) — have reported reduced HRV in depressed patients highlighting the complexity of this issue. Recent debate has focused on whether the mood and anxiety disorders, or their treatments are associated with reductions in vagal function (Licht et al., 2011; Brunoni et al., 2012). Increases in heart rate are usually associated with decreases in HRV, and antidepressant medications clearly adversely affect heart rate and HRV (Licht et al., 2010; Kemp et al., 2014), yet uncertainty remains over whether unmedicated depressed patients display alterations in these psychophysiological markers (Kemp, 2011, 2012; Kemp et al., 2011, 2014; Licht et al., 2011; Brunoni et al., 2012).

One potential explanation for the contradictory findings is that distinct subtypes (e.g., melancholia; Gold and Chrousos, 2002; Malhi et al., 2005) may display more robust alterations in heart rate and HRV, yet studies are yet to determine whether this is the case. Melancholia is characterized by an over-active stress response, a line of evidence highlighting a major role for high heart rate and decreases in HRV after controlling for confounding variables using propensity scores (Kemp et al., 2014), a novel approach that allows for more appropriate control of confounders, and a technique we employ in the present study. Here we explore the impact of two major subtypes of depression – melancholia and non-melancholia – relative to controls, hypothesizing that patients with melancholic depression rather than non-melancholic depression will display robust decreases in HRV, relative to healthy controls, after controlling for major confounding variables including disorder severity (Kemp et al., 2010) and comorbid anxiety (Kemp et al., 2012; Alvares et al., 2013; Chalmers et al., 2014). Here we report on a variety of HRV measures to examine the which findings are robust across different measures. On the basis of parallel lines of evidence highlighting a major role for high heart rate in future morbidity and mortality (Fox et al., 2007; Lemogne et al., 2011; Åberg et al., 2014), we also examined the impact of depression on heart rate, expecting robust increases in heart rate in melancholia.

**MATERIALS AND METHODS**

**PARTICIPANTS**

A total of 72 patients with a primary diagnosis of MDD and 94 age- and sex-matched controls were included in this study. Participants in this study were recruited from the community as part of case-control study conducted in 2006 and 2007 (Kemp et al., 2012). Exclusion criteria included a history of brain injury (causing loss of consciousness for 10 min or more), neurological
disorder, other serious medical condition, or substance abuse or dependence for > 1 year. All participants were medication free for at least five half-lives. Our study was approved by the University of Sydney, Sydney West Area Health Service, University of Adelaide and Flinders University human research ethics committees, and written informed consent was obtained from participants in accordance with National Health and Medical Research Council guidelines.

**PROCEDURES**

Depressed participants were diagnosed with MDD and categorized with or without melancholic symptoms by trained and supervised research officers using the Mini International Neuropsychological Interview (MINI; Sheehan et al., 1998), a structured psychiatric interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Control participants were excluded if they self-reported a history or presence of psychiatric illness; they were also screened using the MINI. Depression severity was assessed using the 17-item structured interview guide for the Hamilton Depression Rating Scale (SIGH-D; Hamilton, 1960; Williams, 1988) and psychomotor disturbance was measured by the CORE assessment of psychomotor change (CORE; Hickie, 1996). The self-report, Depression, Anxiety and Stress Scale (DASS; Lovibond and Lovibond, 1995) was completed by Hickie et al. (2013). The CORE assessment of psychomotor change (CORE; Hickie, 1996) is a commonly reported, non-linear measure of short-term variability mainly caused by respiratory sinus arrhythmia (Tarvainen and Niskanen, 2008). All HRV measures were log transformed to normality.

**DATA PROCESSING AND STATISTICAL ANALYSIS**

All statistical analyses were performed using IBM SPSS Statistics, Version 21 with SPSS R Essentials plug-in and R statistics version 2.14.2. To avoid bias resulting from imbalance on disorder severity and comorbid anxiety – major confounding variables when seeking to compare patients with melancholia and non-melancholia – we conducted propensity score matching (PSM) using a custom designed plugin for IBM SPSS Statistics (Thoemmes, 2012). PSM involves producing a score (on the basis of entered covariates) for each participant that relates to the probability that the subject belongs to the melancholic versus non-melancholic grouping, and then matching patients in each grouping on this propensity score. If two participants have the same propensity score, then they are equally likely to have come from the same distribution (i.e., patient grouping). Therefore, selecting patients with non-melancholia that have the same propensity scores to those with melancholia, we avoid any bias resulting from an imbalance on covariates. The PSM procedure uses logistic regression to produce the propensity score, in which patient grouping is used as the outcome variable and selected covariates, as predictors. Covariates entered into PSM analysis included age, gender, depression, anxiety and stress DASS scores, SIGH-D, and MINI anxiety disorder status (yes, no). Cases with the closest score were then matched using a simple 1:1 nearest neighbor matching routine based on a ‘greedy’ matching algorithm. Balance statistics and associated graphs were inspected to confirm adequacy of the match.

As PSM requires a complete dataset without missing data, we first ran multiple imputation (MI) analysis (Schafer, 1999) in IBM SPSS Statistics to replace missing values using the automatic method. While a common approach to dealing with missing data
is deleting observations with missing values, and analyzing only those participants with a complete dataset, this listwise deletion approach is problematic for at least two reasons (Barzi and Woodward, 2004; van Ginkel and Kroonenberg, 2014). Firstly, it wastes data and reduces the power of analysis to determine an effect. Secondly, it may also produce biased estimates when loss of participants is systematic and not random. By contrast, MI yields estimates with good statistical properties. It uses all available data, makes less stringent assumptions about 'missingness' and pools plausible complete versions of an incomplete dataset into one analysis taking into account additional uncertainty due to missing data.

Data was missing for the following variables: depression (melancholia: 27.5%; non-melancholia: 37.5%), anxiety (melancholia: 22.5%; non-melancholia: 37.5%), and stress (melancholia: 22.5%; non-melancholia: 37.5%) from the DASS measure, MINI anxiety disorder status (yes, no; melancholia: no missing data; non-melancholia: 6.3%), and CORE total (melancholia: no missing data; non-melancholia: 3.1%) as predictors. MI procedures are appropriate for data in which up to 60% of values are missing (Barzi and Woodward, 2004). As recommended by others (Marshall et al., 2009), the imputation model used for missing data contained all variables to be subsequently analyzed including outcome variables (melancholic status in PSM, and heart rate and its variability in final analysis), variables to predict the missing data, and those variables to be imputed. Variables entered into MI analysis included: participant grouping, heart rate and HRV, depression, anxiety and stress from the DASS questionnaire, age, gender, SIGH-D, MINI anxiety disorder status and CORE total score.

Multiple imputation analysis produced 20 datasets relating to 72 MDD patients and PSM analysis was run on each of these datasets to obtain patients matched on propensity scores. The data for controls were then merged into each of the 20 datasets after which analyses were conducted on each dataset to examine group differences (MEL vs. NMEL vs. CTRL) on heart rate and HRV. As recommended previously (Hill, 2004), analysis of variance (ANOVA) analysis was carried out as a regression analysis using effect coding (Edwards, 1985; van Ginkel and Kroonenberg, 2014) so that results could then be combined according to Rubin's rules (van Ginkel and Kroonenberg, 2014). This approach has the advantage of averaging over the results from different groupings determined using PSM on the multiply imputed datasets (Hill, 2004). Guidelines and software for carrying out these procedures and combining results for pooled estimates and statistics are available here: http://www.socialsciences.leiden.edu/educationandchildstudies/childandfamilystudies/organisation/staffcfs/van-ginkel.html. One-tailed t-tests are reported given specific directional hypotheses. Effect size measures (Cohen’s d) were also determined and Cohen’s guidelines (Cohen, 1988) for interpreting Cohen’s d’s (small, d = 0.2; medium, d = 0.5; large, d = 0.8) were followed. Cohen’s d statistics were calculated using an online calculator available here: http://www.uccs.edu/~lbecker/

**RESULTS**

**PARTICIPANT CHARACTERISTICS**

Participant characteristics are reported in Table 1. No age or gender differences were observed, however, all groups differed on depression, anxiety and stress scales (Tukey’s HSD p < 0.05), highlighting the need for PSM of patients in melancholia and non-melancholia patient groupings.

**HEART RATE AND ITS VARIABILITY**

After application of PSM and pooling results according to Rubin’s rules, groups differed significantly on heart rate [F(2,108.25) = 3.664, p = 0.029], RMSSD [F(2,107.86) = 3.21, p = 0.044], HF (at trend levels) [F(2,102.76) = 2.966, p = 0.056], and PCSD1 [F(2,107.87) = 3.199, p = 0.045; Figure 1]. No significant differences on the combined overall test were observed for SDNN or LF. As hypothesized, heart rate was increased (by 7.85 beats per minute, BPM) in patients with melancholia – but not in those with non-melancholia – relative to controls (p = 0.004, one-tailed, d = 0.58). Also as hypothesized, HRV was decreased in patients with melancholia – but not in those with non-melancholia – relative to controls. More specifically, RMSSD (p = 0.01, one-tailed, d = 0.56), HF (p = 0.014, one-tailed, d = 0.57) and PCSD1 (p = 0.01, one-tailed, d = 0.56) were all decreased in patients with melancholia, relative to controls. No significant differences were observed between non-melancholia and controls. While patients with melancholia had higher heart rate than those with non-melancholia (by 6.75 BPM; p = 0.046, one-tailed, d = 0.20), no significant differences were observed between melancholia and non-melancholia.

| Table 1 | Participant characteristics: mean (M) ± standard error (SD).1 |
| --- | --- | --- | --- | --- |
| | CTL (M ± SE) | NMEL (M ± SE) | MEL (M ± SE) | p-value2 |
| Age | 35.69 ± 1.16 | 34.98 ± 1.56 | 37.28 ± 2.07 | 0.067 |
| Gender | 52F/42M | 17F/15M | 25F/15M | 0.675 |
| SIGH-D | n/a | 18.78 ± 0.68 | 21.50 ± 0.69 | 0.007 |
| DASS-D | 2.13 ± 0.25 | 2.170 ± 2.04 | 3.166 ± 1.39 | <0.0013 |
| DASS-A | 1.19 ± 0.19 | 9.30 ± 1.79 | 15.23 ± 2.15 | <0.0012 |
| DASS-S | 4.54 ± 0.47 | 19.00 ± 1.83 | 23.93 ± 1.88 | <0.0013 |
| CORE | n/a | 3.45 ± 0.53 | 7.18 ± 0.86 | <0.0013 |

1 M ± SE values based on original – not imputed data – data before propensity score matching of patient groupings; 2 p-value refers to that for omnibus ANOVA, or for SIGH-D and CORE, an independent-samples t-test; 3 post hoc tests revealed that all groups differ from each other, Tukey’s HSD p < 0.05.
on measures of HRV were observed between melancholia and non-melancholia.

**DISCUSSION**
The current study examined the impact of melancholia and non-melancholia on resting-state heart rate and HRV relative to controls, revealing robust alterations in patients with melancholia, but not in those with non-melancholia. These findings were associated with a moderate effect size across multiple measures (Cohens $d's = 0.56$–$0.58$), providing strong evidence for an impact of melancholia on vagally mediated, cardiac function. We also observed patients with melancholia to display a higher...
heart rate, relative to those with non-melancholia. We and others have demonstrated that HRV is inversely associated with disorder severity (Kemp et al., 2010) and that antidepressant medications – particularly tricyclic antidepressants and the serotonin and noradrenaline reuptake inhibitors often used in more severe depressions – have adverse effects on heart rate and HRV after controlling for disorder severity (Licht et al., 2010; Kemp et al., 2014). Together, these findings suggest that alterations in melancholic patients with severe depression treated with antidepressant medications would be stronger than those effects reported here, as our patients were all unmedicated.

Here we show that resting-state heart rate is increased – by almost eight beats per minute – and HRV, decreased in patients with melancholia relative to healthy controls, findings associated with a moderate effect size. An increased resting-state heart rate may reflect vagal withdrawal without necessarily, an increase in sympathetic nervous system activity (Porges, 2011; Kemp et al., 2014). This metabolically conservative response is usually observed during environmental challenge. We have suggested (Kemp et al., 2014) that this psychophysiological state may mirror the autonomic dysregulation observed in psychiatric illness during the resting-state, and the present study highlights that this may be the case for those with melancholia in particular. As noted above however, measures of HRV are more pure indicators of vagal activity (Saul, 1990) than heart rate, which also includes sympathetic input. Differences in heart rate were also observed between those with melancholia and non-melancholia, with those with melancholia displaying a higher heart rate, a difference of 6.75 BPM, a finding associated with a small effect size (Cohens $d = 0.20$). No differences however, were observed on measures of HRV. We suggest that this finding may reflect differences in a non-vagal (perhaps sympathetic) component of cardiac function. It is possible therefore that while vagal function distinguishes between patients and controls, non-vagal components of heart rate may further distinguish between disorder subtypes.

Critically, studies have reported strong evidence for a continuous increase in risk for cardiovascular and all-cause mortality in men and women with a resting heart rate above 60 beats/min, regardless of whether individuals have a history of cardiovascular disease (Fox et al., 2007; see also Cooney et al., 2010; Saxena et al., 2013). Here we observed patients with melancholia to display a higher resting, heart rate (78.48 BPM) relative to controls (70.63 BPM) and those with non-melancholia (71.73 BPM). Other studies (Lemogne et al., 2011; Åberg et al., 2014) have reported a relationship between high heart rate and suicide. In fact, 10 additional beats per minute has been shown to increase risk of suicide by 24 to 37% over a 9 year follow-up period in adjusted models (Lemogne et al., 2011). Another study on more than 1 million, 18-year-old participants with no prior mental illness (Åberg et al., 2014) reported that poor performance on cardiovascular fitness and cognitive tests was associated with a fivefold increased risk of suicide attempt or death over a 5- to 42-year follow-up period.

In addition to increases in heart rate, we also observed decreases in all measures of HRV except for SDNN and LF in patients with melancholia relative to controls. While SDNN reflects the ‘ebb and flow’ of a variety of factors including respiration, blood pressure control mechanisms, thermoregulation and kidney functioning, RMSSD is a more specific index of vagal function that correlates highly with the high-frequency component of HRV (Kleiger et al., 2005). Recent thinking also indicates that the low-frequency component of HRV reflects blood pressure control mechanisms such as the baroreflex (Goldstein et al., 2011; Reyes Del Paso et al., 2013). It is possible therefore that SDNN from short-term recordings is less sensitive than that extracted from 24-h long recordings, and that blood pressure control mechanisms are less involved in the differences observed here between patients with melancholia and controls.

A recent meta-analysis (Hillebrand et al., 2013) reported that HRV can predict the first cardiovascular event in individuals without known cardiovascular disease over a period of 3.5 to 15 years. Cardiovascular endpoints included hospitalization for angina pectoris, myocardial infarction, congestive heart failure, arterial peripheral vascular disease, coronary revascularization, stroke and cardiovascular death. This meta-analysis (Hillebrand et al., 2013) was based on eight studies with a total of 21,988 participants without known cardiovascular disease at baseline and reported pooled relative risks for a first cardiovascular event ranging from 1.35, 1.45, and 1.32 for SDNN, low-frequency or high-frequency HRV measures respectively. The authors proposed two possible mechanisms for their findings including vagal dysregulation activating inflammatory processes culminating in cardiovascular events. The other suggested mechanism was that individuals with low HRV already suffer from subclinical or silent CVD, highlighting that reduced HRV may be both a cause and consequence of ill health. Importantly, participants in the present study were free from serious medical conditions that may have otherwise impacted on the findings reported here.

It is important to note that our findings were obtained after accounting for a variety of confounding variables including severity of depression, anxiety and stress, and number of comorbid anxiety disorders. No significant differences were observed between patients with non-melancholia and controls, suggesting that heterogeneity in patient samples may underpin some of the past null findings that have been reported in the literature. Strengths of the present study include a medication free and physically healthy sample, and application of PSM to control for a variety of confounding variables across patient groupings. It is also important to acknowledge some limitations of our study. There are potential confounding factors that we did not control for here including physical activity (Rennie et al., 2003; Soares-Miranda et al., 2014), smoking status (Sjoberg and Saint, 2011; Harte and Meston, 2014), alcohol use (Quintana et al., 2013a,b), body mass index (Britton et al., 2007; Koenig et al., 2014), and biomarkers including fasting glucose (Stein et al., 2007) and cholesterol (Britton et al., 2007; Thayer and Fischer, 2013), all of which may impact on heart rate parameters. We refer interested readers to a recent review of the various issues that researchers should consider when collecting measures of HRV (Quintana and Heathers, 2014). Regardless, we note here that many of these factors known to impact on heart rate parameters are also observed in patients with mood disorders, highlighting the importance of cardiovascular risk reduction strategies in such patients, and on
the basis of the present study, those with melancholic symptoms in particular.

In conclusion, we report here that patients with melancholia – but not non-melancholia – display robust reductions in resting-state HRV relative to controls. This finding was observed even when applying PSM, a relatively novel technique to ensure that patient groupings did not differ on important confounds including age, gender, severity of depression, anxiety and stress, and comorbid anxiety disorders. Reduced vagal tone has important functional significance (e.g., impaired psychological flexibility; Thayer and Lane, 2006; Kashdan and Rottenberg, 2010), and over the longer-term may lead to significant morbidity and mortality from a host of conditions (Thayer et al., 2010; Kemp and Quintana, 2013). Our study therefore, has important implications for the health and wellbeing of patients with melancholic depression. Future studies are needed to further examine what particular behavioral features are most associated with the alterations in heart rate and HRV in patients with melancholia.

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