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Review article

Heart rate variability in bipolar disorder: A systematic review and meta-analysis

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ABSTRACT

Background: Heart rate variability (HRV) has been suggested reduced in bipolar disorder (BD) compared with healthy individuals (HC). This meta-analysis investigated: HRV differences in BD compared with HC, major depressive disorder or schizophrenia; HRV differences between affective states; HRV changes from mania/depression to euthymia; and HRV changes following interventions.
Methods: A systematic review and meta-analysis reported according to the PRISMA guidelines was conducted. MEDLINE, Embase, PsycINFO, The Cochrane Library and Scopus were searched. A total of 15 articles comprising 2534 individuals were included.
Results: HRV was reduced in BD compared to HC ($g = -1.77$, 95% CI: -2.46; -1.09, $P < 0.001$, 10 comparisons, $n = 1581$). More recent publication year, larger study and higher study quality were associated with a smaller difference in HRV. Large between-study heterogeneity, low study quality, and lack of consideration of confounding factors in individual studies were observed.
Conclusions: This first meta-analysis of HRV in BD suggests that HRV is reduced in BD compared to HC. Heterogeneity and methodological issues limit the evidence. Future studies employing strict methodology are warranted.

Contents

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1. Introduction

The autonomic nervous system links the central nervous system and the cardiovascular system (Lown and Verrier, 1976; Palma and Benarroch, 2014). This link is reflected by the central autonomic network (Benarroch, 1993, 2014) and the brain-heart axis (Manea et al., 2015). The heart rate is continuously modulated through complex interactions between both branches of the autonomic nervous system, the sympathetic nervous system and vagal systems (Palma and Benarroch, 2014; Sunagawa et al., 1998). Since the autonomic nervous system activity and heart rate are nonlinearly related, changes in sympathetic activity or vagal tone alone have the potential to alter the dynamic heart rate response to stimulation of either branch of the system (Sunagawa et al., 1998). Heart rate variability (HRV) reflects the oscillation in the time intervals between consecutive heartbeats, and is a validated measure of balance in the activity of the autonomic nervous system (Electrophysiology TF of the ES of C the NAS of P., 1996; Berntson et al., 2008; Billman, 2011). HRV can be assessed using readily available none-invasive methods, and is usually measured using either a time–domain or a frequency-domain approach (Electrophysiology TF of the ES of C the NAS of P., 1996). Time-domain analysis are based on the variation in intervals between consecutive heartbeats reflected by HRV (and/or variation in interval between R–R waves). Frequency-domain analysis assigns measures of beat-to-beat intervals to frequency bands, with analysis usually divided into three different bands: high frequency (0.15–0.40 Hz), low frequency (0.04–0.15 Hz), and very low frequency (0.0033–0.04 Hz) (Electrophysiology TF of the ES of C the NAS of P., 1996). High frequency HRV (HF) is suggested to estimate parasympathetic cardiac influence, whereas low frequency HRV (LF) most likely estimates a combination of parasympathetic and sympathetic cardiac influences (Berntson et al., 2008; Billman, 2013). The ratio of LF to HF (LF/HF) has been proposed to reflect the balance of the autonomic nervous system (Berntson et al., 2008; Billman, 2013).

The ability of the nervous system and heart rate to adapt to environmental changes is crucial, and healthy individuals exhibit higher HRV than individuals suffering from various medical conditions. Healthy life expectancy and risk of sudden cardiac death have been suggested to depend on intact autonomic functioning (Palma and Benarroch, 2014; Zulfiqar et al., 2010; Xhyheri et al., 2012). A reduced HRV has been found to be an important risk factor for coronary heart disease, atherosclerosis, heart failure, arrhythmias and mortality after an acute myocardial infarction (Algra et al., 1993; Rennie et al., 2003; Kleiger et al., 1987; van der Wall and van Gilst, 2013).

Several lines of evidence indicate autonomic dysfunction and central autonomic disturbances in bipolar disorder (Levy, 2013; Outhred et al., 2014; Wang et al., 2016). An increased risk of cardiovascular disease is found in bipolar disorder (Goldstein et al., 2015), and it is possible that a reduced HRV in bipolar disorder could predict sudden cardiac death in this population. In patients with bipolar disorder, a reduction in HRV compared with healthy control individuals has been found in individual studies (Cohen et al., 2003; Henry et al., 2010; Chang et al., 2015). However, studies investigating HRV in bipolar disorder have included patients in various affective states (Chang et al., 2015; Chang et al., 2014; Cohen et al., 2013; Lee et al., 2012), used small sample sizes (Gruber et al., 2015; Howells et al., 2013; Levy, 2014), did not address possible confounding issues that are known to affect HRV in the statistical analyses (Cohen et al., 2003; Chang et al., 2014; Gruber et al., 2015; Howells et al., 2013; Quintana et al., 2016a), and have showed large variation in study results. Thus, the role of HRV alterations in bipolar disorder is unclear.

Previous review articles on HRV have investigated differences in HRV in a variety of psychiatric disorders without separate analyses on bipolar disorder, and have not addressed issues regarding factors responsible for between-study heterogeneity (Alvares et al., 2015; Bassett, 2015; Montaquila et al., 2015; Clamor et al., 2016). Further, confounding issues and quality of included studies have not been evaluated systematically, and meta-analyses on patients with bipolar disorder in different affective states have not been done.

The objectives of the present systematic review and meta-analysis were to investigate the following; 1) HRV in adult patients with bipolar disorder compared with healthy control individuals, patients with major depressive disorder or schizophrenia; 2) differences in HRV between affective states (euthymia, depression, mania, and mixed state) in patients with bipolar disorder; 3) changes in HRV from mania, mixed state or depression to euthymia in patients with bipolar disorder; 4) changes in HRV following a treatment intervention for an acute affective episode in patients with bipolar disorder. Furthermore, in order to investigate possible clinical and methodological sources of heterogeneity across studies meta-regression was conducted.

This is the first systematic review and meta-analysis of HRV in bipolar disorder.

2. Methods

This systematic review and meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009). Methods of the review and eligibility criteria were established in advance and documented in a review protocol that can be retrieved from the authors upon request. No modifications were made to the review protocol during the review process.

2.1. Study selection

2.1.1. Eligibility criteria

Original studies reporting on HRV in patients with bipolar disorder (I, II, both or not specified), regardless of the affective state, were eligible for review. HRV was defined as the primary outcome for meta-analyses, but other reported HRV measures (HF, LF, LF/HF) were included as well. Further inclusion criteria were: 1) adults above 18 years of age 2) cross-sectional or longitudinal studies comparing HRV in adult patients with bipolar disorder a) with healthy control individuals or with patients with major depressive disorder