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Genetic influences on heart rate variability

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ABSTRACT

Heart rate variability (HRV) is the variation of cardiac inter-beat intervals over time resulting largely from the interplay between the sympathetic and parasympathetic branches of the autonomic nervous system. Individual differences in HRV are associated with emotion regulation, personality, psychopathology, cardiovascular health, and mortality. Previous studies have shown significant heritability of HRV measures. Here we extend genetic research on HRV by investigating sex differences in genetic underpinnings of HRV, the degree of genetic overlap among different measurement domains of HRV, and phenotypic and genetic relationships between HRV and the resting heart rate (HR). We performed electrocardiogram (ECG) recordings in a large population-representative sample of young adult twins (n = 1060 individuals) and computed HRV measures from three domains: time, frequency, and nonlinear dynamics. Genetic and environmental influences on HRV measures were estimated using linear structural equation modeling of twin data. The results showed that variability of HRV and HR measures can be accounted for by additive genetic and non-shared environmental influences (AE model), with no evidence for significant shared environmental effects. Heritability estimates ranged from 47 to 64%, with little difference across HRV measurement domains. Genetic influences did not differ between genders for most variables except the square root of the mean squared differences between successive R-R intervals (RMSSD, higher heritability in males) and the ratio of low to high frequency power (LF/HF, distinct genetic factors operating in males and females). The results indicate high phenotypic and especially genetic correlations between HRV measures from different domains, suggesting that >90% of genetic influences are shared across measures. Finally, about 40% of genetic variance in HRV was shared with HR. In conclusion, both HR and HRV measures are highly heritable traits in the general population of young adults, with high degree of genetic overlap across different measurement domains.

1. Introduction

Heart rate variability (HRV) is the variation of cardiac inter-beat intervals over time which includes both periodic and aperiodic components. HRV results largely from the modulation of the heart rhythm by parasympathetic innervation to the cardiac sinoatrial node (reviewed in Berntson et al., 1997; Reyes del Paso et al., 2013). Experimental evidence from animal studies indicates that parasympathetic vagal stimulation leads to the steady-state increase in the inter-beat interval and, respectively, decrease in the heart rate, whereas sympathetic stimulation produces the opposite effect (reviewed in Berntson et al., 1997). Consequently, fluctuations of heart rate in the high frequency band (0.15–0.4 Hz) are generally viewed as an indicator of individual differences in parasympathetic cardiac autonomic function. The origins and functional meaning of the lower frequency cardiac rhythms (LF) have been more controversial. LF has often been assumed to index cardiac sympathetic control, and the LF/HF ratio has been proposed as an index of autonomic balance (e.g. Malliani et al., 1991). However, subsequent studies questioned the validity of LF power, with or without adjustment for HF or total power, as an index of sympathetic outflow to the heart (Goldstein et al., 2011), and the notion of sympathovagal balance has been disproven by a large body of research suggesting a more complex and often nonlinear relationship between the sympathetic and parasympathetic parts of the autonomic nervous system (Berntson et al., 1997; Billman, 2013; Eckberg, 1997; Goedhart et al., 2008). More recent evidence suggest that the HRV spectrum, including both HF and LF components, is predominantly determined by vagal control (Reyes del Paso et al., 2013) but LH can also reflect a modulation of cardiac autonomic outflow by baroreflexes (Goldstein et al., 2011).

Resting-state time and frequency domain measures of HRV show high test-retest reliability in both normal and clinical populations (Pitzalis et al., 1996; Schmidt et al., 2012). These stable, trait-like individual differences have been shown to be associated with individual variability in emotion regulation, personality, psychopathology, cardiovascular health, and mortality (reviewed in: Allen et al., 2007; Berntson et al., 1997; Chalmers et al., 2014; Kemp and Quintana, 2013; Rajendra Acharya et al., 2006; Thayer and Brosschot, 2005; Wulsin et al., 2015). It has been suggested that associations between negative affect and poor

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health outcomes may be mediated by autonomic imbalance resulting from decreased tonic activity of the parasympathetic branch of the ANS indicated by low HRV (Thayer and Brosschot, 2005; Wulsin et al., 2015).

Reduced time and frequency domain resting HRV presumably indicating lower vagal tone has been associated with anxiety disorders and related trait measures such as deficits in social approach behavior, impaired stress regulation, and behavioral inhibition (Alvares et al., 2013; Bleil et al., 2008; Chang et al., 2013; Scott and Weems, 2014). A recent meta-analysis of HRV studies in anxiety disorders showed significant HRV reductions in patients relative to controls with a small-to-moderate effect size (Chalmers et al., 2014). Evidence for an association between reduced HRV and major depression is more controversial. A meta-analysis of 18 studies concluded that depression is associated with reduced HRV (Kemp et al., 2010), however, this conclusion was subsequently challenged (Licht et al., 2011). Low HRV as indexed by increased LF/HF ratio has also been associated with increased risk for post-traumatic stress disorder (PTSD), both cross-sectionally (Minassian et al., 2014) and longitudinally (Minassian et al., 2015): lower HRV before combat deployment prospectively predicted higher prevalence of post-deployment PTSD in a large sample of active-duty marines. However, another study using latent variable modeling of multiple HRV indices suggested a possibility that the association between low HRV and PTSD may be partially mediated by tobacco and alcohol abuse associated with PTSD (Dennis et al., 2014).

A potential mechanism underlying the association between low HRV, anxiety, and exaggerated stress response may be related to impaired top-down prefrontal cortical modulation of autonomic activity (Gillie and Thayer, 2014; Thayer et al., 2009). It has been proposed that resting HRV may serve as a peripheral physiological index of self-regulatory capacity and integrity of CNS networks that support goal-directed behavior, in particular, the extent to which 'top–down' appraisals, mediated by cortical-subcortical pathways, can control brainstem activity and autonomic responses in the body (Park and Thayer, 2014; Thayer et al., 2012).

Thus, substantial body of research suggests that individual differences in autonomic regulation indexed by HRV represent important biomarkers of mental and physical health. Understanding genetic and environmental determinants of these individual differences can facilitate the development of prevention and treatment methods for psychosomatic disorders and lead to identification of targets for medication development.

Low HRV can potentially serve as an intermediate phenotype (endophenotype) for a broad range of dysfunctions involving physiological, affective, and cognitive dysregulation (Thayer and Lane, 2009). Emerging evidence from human and animal studies points to a possible genetic link between reduced HRV and susceptibility to anxiety disorders and stress. A clinical study showed familial aggregation of HRV and panic disorder: children of patients with panic disorder, who are at a heightened risk for developing anxiety disorders, had significantly lower nonlinear dynamical measure of HRV suggesting a relative decrease of cardiac vagal function, although no differences were observed in frequency domain HRV measures (Srinivasan et al., 2002). A preclinical study of inbred mice found that a strain characterized by fear overgeneralization to ambiguous contexts and cues, impaired context extinction, and impaired safety learning (a model of anxiety) showed a poor recovery of HRV suppression induced by fear, with HRV assessed using the square root of the mean squared differences between successive R-R intervals (RMSSD) (Camp et al., 2012). Taken together, these studies suggest that genetically transmitted abnormalities in vagal function may lead to impaired self-regulation of autonomic reactivity and associated anxiety symptoms and maladaptive stress response. Accordingly,

One of the key criteria for an endophenotype is heritability. Previous studies in twin samples have shown significant genetic influences on some of the HRV metrics. Our previous study of young adult female twins demonstrated significant genetic influences on HRV indices of the vagal tone (Anokhin et al., 2005). Two studies of middle-aged male twins (mean age > 50), one from the Vietnam Era Twin (VET) Registry (Su et al., 2010) and another from a population based-sample of Finnish twins (Uusitalo et al., 2007) showed significant heritability of both low- and high-frequency HRV power. Time domain measures of HRV showed heritability in a similar range (35–48%) (Kupper et al., 2004). Another twin study of time domain HRV measures based on 24-h ambulatory recordings yielded significant heritabilities of time domain variables ranging from 46 to 57% and indicated a substantial overlap of genetic influences on two time domain HRV measures, standard deviation of the R-R intervals (SDNN) and the RMSSD (Neijts et al., 2014). A study using a nonlinear dynamical measure of HRV (approximate entropy) showed only a modest heritability of 40% (Snieder et al., 2007).

Although previous studies have shown the importance of genetic factors in the etiology of individual differences in HRV, a number of important issues have not been fully addressed. First, it is not clear whether same or different genetic factors affect HRV measures from different domains (time, frequency, and nonlinear dynamics). For example, time- and frequency domain measures may reflect partially distinct physiological mechanisms that are influenced by distinct genetic factors. However, few studies focused on the genetic overlap across HRV measures using multivariate analyses. Second, sex differences in heritability and sex-specific genetic influences have not been investigated across measurements domains due to the fact that some studies included one gender only while others focused on a single measurement domain. Finally, it is not clear whether HRV and resting heart rate (HR) are influenced by same or different genetic factors. Although a negative correlation between HR and HRV is well known, the extent of genetic overlap between these functionally important measures has been little investigated. A question arises whether genetic variance in HRV measures can be largely accounted for by heritability of the HR (which would render HRV redundant as an index of genetic predisposition), or there is significant HRV-specific genetic variance. Answering this question is critical for the evaluation of HRV as an endophenotype.

Accordingly, the aims of the present study were: 1) To assess heritability of HRV measures in males and females and to test for gender-specific genetic influences using "sex limitation" genetic models; 2) To determine the degree of genetic overlap among HRV metrics from three different measurement domains – time, frequency, and nonlinear dynamics (i.e. whether they represent the same or distinct genetically transmitted differences); 3) To determine the extent to which genetic influences on HR contribute to individual differences in HRV and to determine, whether there is an HRV-specific genetic variance that is not shared with HR.

2. Method

2.1. Participants

The sample (n = 1103) consisted of young adult twins including 282 monozygotic (MZ) pairs (75 male and 207 female) and 229 dizygotic (DZ) pairs (58 male, 113 female, and 58 opposite-sex); 84.8% of participants were Caucasian, 12.7% Black, and 2.5% belonged to other ethnic groups. The age at assessment (Mean ± S.D.) was 20.8 ± 4.0 (range: 17 to 36 years). All participants were ascertained from the general population through state birth records. Exclusion criteria were minimal and included a history of head trauma with loss of consciousness for > 5 min, known history of epilepsy, current use of psychoactive medication, as well as hearing, visual and other physical and mental impairments that could prevent the subjects from understanding and following task instructions. To ensure that our sample is representative of the general population, no further exclusions for obesity, health conditions or medication were made. The study was approved by Washington University's