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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

Institutional Review Board, and a written informed consent was obtained from the participants.

2.2. Materials and procedure

The HRV assessment was performed as part of a broader psychophysiological assessment. During their lab visit, twins participated in a 1.5 to 2 h long psychophysiological recording session involving both EEG and ECG recording at rest and during tasks. At the beginning and at the end of this session, a 5-min resting recording was conducted, during which participants were seated in a comfortable recliner chair and asked to relax and avoid major body movements. Between these two resting periods, participants were administered a Continuous Performance Task (CPT, Go/No-Go version), a monetary gambling task, a flanker task, and a stop-signal task some participants. HRV indices were computed for both 5-min recording periods and averaged to obtain a single individual value. The mean interval between the two resting-state recordings was 105 min (range: 90 to 120 min). The ECG was recorded from two electrodes affixed to the left lower abdomen and the right mastoid using a Synamps 2 bioamplifier (Compumedics-Neuroscan) and digitized online with a sampling rate of 500 Hz (1000 Hz for approximately 35% of the sample).

2.3. ECG data analysis

The ECG channel was bandpass-filtered offline at 0.5–35 Hz before the detection of the QRS complex of the ECG as recommended in the literature (Hejjel and Kellenyi, 2005; Ruha et al., 1997). The detection of the R-peak, the most prominent component of the QRS complex, and all subsequent analyses were performed using Kubios HRV v.2.2 software developed by the Biosignal Analysis and Medical Imaging Group (BSAMIG), Department of Applied Physics, University of Eastern Finland (Niskanen et al., 2004; Tarvainen et al., 2014). The quality of R-peak detection was verified by visual inspection, and detection errors including skipped peaks or spurious beats (inter-beat interval of <150 ms) were corrected using the Kubios HRV software. The R-R interval series was detrended using smoothness priors regularization algorithm (Tarvainen et al., 2002), which was followed by the computation of HRV metrics.

Time domain measures included the mean of R-R intervals (R-R, ms), the mean heart rate (HR, beats/min), standard deviation of the R-R intervals (SDNN, ms), the square root of the mean squared differences between successive R-R intervals (RMSSD, ms), and the proportion of successive R-R interval pairs that differ by >50 ms relative to the total number of R-R intervals (PNN50, %).

Frequency domain analysis represents fluctuation of the heart rate as a spectrum density function by decomposing periodic fluctuations of the time domain signal (R-R interval time series) into its frequency components. Activity within a specific frequency band can be quantified as area under the curve of this function (spectral power). Frequency domain measures included low frequency band (LF, 0.04–0.15 Hz) and high frequency band (0.15–0.4 Hz) absolute power of R-R interval fluctuations computed using the parametric auto regression method (LF and HF, respectively), as well as the ratio between LF and HF band powers (LF/HF). Although functional meaning of the latter measure has been a matter of debate and its interpretation as a measure of "sympathovagal balance" has been largely disproven (Berntson et al., 1997; Billman, 2013; Eckberg, 1997), we included it because of its widespread use in HRV research.

The third class of HRV metrics is represented by measures derived from chaos theory-based approach that regards HRV as a manifestation of a nonlinear dynamical system. One such approach is based on plotting individual R-R intervals against the subsequent R-R intervals (Poincaré plot). The width of the Poincaré plot is a function of the sum of the low- and high-frequency amplitudes, with each amplitude weighted by the respective angular frequency. As a result of this weighting, the relative contribution of HF components to the plot width is larger than that of LF components (Khandoker et al., 2013). To characterize the geometry of the resulting distribution, we used the standard deviation of the Poincaré plot perpendicular to (width) and along the diagonal (length) computed using the Kubios HRV software (SD1 and SD2, respectively) (Brennan et al., 2001; Carrasco et al., 2001).

Since frequency domain (LF, HF, LF/HF) and nonlinear dynamical (SD1, SD2) measures showed a skewed distribution, a natural logarithm transformation was applied.

2.4. Statistical analyses

To estimate heritability, i.e. the relative contribution of genetic and environmental sources to the total phenotypic variance of HRV measures, we performed a biometrical genetic analysis using model fitting, a standard approach in twin genetic research (Neale and Cardon, 1992; Rijsdijk and Sham, 2002). Linear structural equation models were fitted using the Mx package specifically developed to model genetically informative data (Neale et al., 2002). These models assume that phenotypic variance arises from the following factors: additive genetic influences (A, for which identical twins share 100% and fraternal twins share 50%), non-additive genetic influences (D, for which identical twins share 100% and fraternal twins share 25%), environmental influences shared by family members (C, for which identical and fraternal twins share 100%), and individually unique (unshared) environmental influences (E). It is important to note that A, D, and C increase, whereas E decreases, intrapair twin similarity. In a sample containing only twins reared together, it is not possible to test for both D and C, and a decision about which to include is made based upon the twin-pair correlations; non-additive genetic influences are indicated when the rMZ > 2× rDZ whereas shared environmental influences are suggested when rDZ > 0.5 rMZ). Based on the correlations observed, we used either an ADE or an ACE model as the base model.

Since our sample included both male and female twins and preliminary analyses showed differences between male and female twin correlations, we investigated potential sex differences in genetic and environmental effects on ERP variables by fitting "sex-limitation" models to raw data from five zygosity groups (Neale et al., 2006). The sex-limitation model allows the magnitude of genetic and environmental effects to vary independently in males and females and includes sex-specific genetic influences accounting for the possibility that the set of genes which influences a trait in males is not identical to that which influences a trait in females. Both kinds of sex differences in genetic effects can be tested by fitting sub-models of the general sex-limitation model. The significance of sex-specific influences can be tested by fitting a reduced common effects model that does not include sex-specific genetic effects and assumes that phenotypic variances and covariances are influenced only by the genetic effects that are common to both males and females, but the magnitude of these effects is allowed to differ across sexes. A scalar model can then be used to test whether the proportion of variance attributable to genetic effects is equivalent across men and women, with the total variance allowed to differ across gender by a scalar multiple. The most restrictive model is one in which the total variance is equated across gender, yielding identical genetic and environmental contributions and total variability in males and females.

Path coefficients corresponding to these factors were estimated using a maximum likelihood method, and the goodness of model fit was indicated by a −2LL (log likelihood). Then different submodels were tested by dropping individual paths from the full model. The significance of individual paths was tested by comparing the goodness of fit of the restricted submodel with the goodness of fit of the more general model using a χ^2 test of −2LL difference with degrees of freedom corresponding to the difference in the degrees of freedom between two models (e.g., df = 1 if only one parameter is dropped in the restricted model). If dropping a path significantly reduced the goodness of fit (the χ^2 difference is significant), the path was retained in the model,

otherwise the more parsimonious restricted model was chosen (i.e. the one that accounted for the variance equally well, but with a fewer number of parameters). Heritability was estimated as the percentage of the total variance of the trait attributed to genetic factors; in addition, 95% confidence intervals of the estimates were computed.

To examine the extent to which different HRV measures are influences by the common versus independent genetic factors, we fit bivariate Cholesky models (see example on Fig. 1). These models allowed us to estimate the degree of overlap among genetic and environmental influences on different variables by computing genetic (rG) and environmental (rE) correlations, respectively, as well as to assess variable-specific genetic and environmental influences. A detailed description of the model fitting approach and assessment of heritability can be found elsewhere (Neale and Cardon, 1992; Rijsdijk and Sham, 2002).

3. Results

3.1. Twin correlations and heritability

Observed intra-pair twin correlations for HRV measures are presented in Table 1 separately for male, female and opposite-sex twin pairs. As expected, MZ correlations are high and significant (ranging from 0.40 to 0.71), whereas DZ correlations are substantially lower (from 0.11 to 0.42), with many of them being non-significant. Importantly, there was little difference in the size of twin correlations across the three measurement domains. For most measures, DZ correlations were less than half of MZ correlations, suggesting that the role of shared environmental factors is negligible and twin resemblance results from genetic factors.

A separate analysis of the two five-minute resting periods revealed significant differences with respect to several HRV measures including the RR interval, SDNN, RMSSD, LF power, LF/HF ratio, and SD measures, suggesting a slight increase in HRV in the course of the session, primarily in the low-frequency range. However, there was no significant difference in mean HR and HF power. Twin correlations computed separately for the two resting periods were extremely similar, with no evidence for a systematic trend. Since separate genetic modeling of the two resting recordings was not warranted by these data, HRV values were averaged across the two resting conditions in order to obtain a more generalized individual estimate.

Several HRV metrics showed significant sex differences indicating larger HRV in males: mean RR interval ($F[1,1058] = 81.02$, $p < 0.001$), SDNN (($F[1,1058] = 9.77$, $p < 0.01$), LF ($F[1,1058] = 31.65$, $p < 0.001$), and LH/HF ratio ($F[1,1058] = 45.30$, $p < 0.001$). Furthermore, resting heart rate was slower in males compared with females (65.5 and 71.7, respectively, $F[1,1058] = 81.02$, $p < 0.001$). Therefore, to account for possible sex differences in heritability and sex-specific genetic influences genetic model fitting included sex-limitation models (described below).

The results of structural equation modeling indicated that best-fitting univariate models for all HRV measures included additive genetic influences and non-shared environmental influences (AE model, Supplementary Table 1). Consistent with the pattern of twin correlations, we did not find evidence for significant shared environmental effects. For most HRV measures, no significant sex-specific genetic influences or sex differences in heritability were detected. Sex-limitation model allowing for sex differences in heritability and/or sex-specific genetic influences could be dropped in favor of models with no sex effects (HR, SDNN, PNN50, SD1) or scalar models allowing for sex differences in

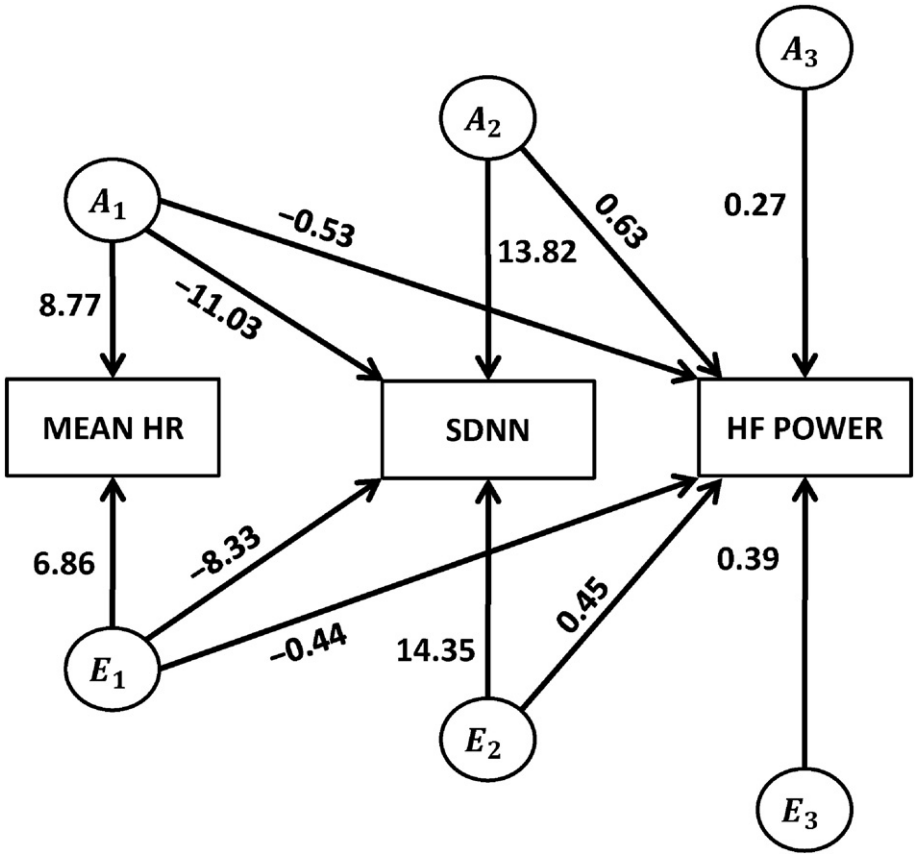

Fig. 1. A. Trivariate genetic model. In this triangular decomposition (Cholesky) model, rectangles represent the observed phenotypes (HR, SDNN, HF), and circles represent latent genetic and non-shared environmental variables (A and E, respectively). Paths from latent factors to observed phenotypes represent unique and shared influences (e.g. A1 to HR and A1 to SDNN, respectively). Unstandardized path coefficients are indicated next to each path.

Table 1
Twin-pair correlations (with 95% confidence intervals) for measures of heart rate variability.

Measure	Zygosity groups				
	MZF ($N = 207$ prs)	MZM ($N = 75$ prs)	DZF ($N = 113$ prs)	DZM ($N = 58$ prs)	DZO ($N = 58$ prs)
Time domain measures					
R-R	0.59* (0.49–0.67)	0.76* (0.64–0.84)	0.42* (0.26–0.56)	0.25 (−0.01–0.48)	0.25 (−0.02–0.47)
SDNN	0.55* (0.45–0.64)	0.57* (0.39–0.70)	0.22* (0.03–0.39)	0.19 (−0.07–0.43)	0.11 (−0.16–0.36)
HR	0.56* (0.46–0.65)	0.71* (0.58–0.81)	0.41* (0.25–0.56)	0.27* (0.01–0.49)	0.29* (0.03–0.51)
RMSSD	0.54* (0.44–0.63)	0.67* (0.51–0.77)	0.24* (0.06–0.41)	0.27 (0.00–0.49)	0.15 (−0.11–0.40)
PNN50	0.65* (0.46–0.65	0.70* (0.56–0.80)	0.25* (0.07–0.41)	0.36* (0.11–0.56)	0.23 (−0.03–0.46)
Frequency domain measures					
LF	0.47* (0.36–0.57)	0.47* (0.27–0.63	0.18 (−0.00–0.35)	0.10 (−0.16–0.35	0.30* (0.04–0.51)
HF	0.56* (0.46–0.65)	0.65* (0.49–0.76)	0.21* (0.02–0.38	0.28* (0.03–0.50)	0.26 (0.00–0.49)
LF/HF	0.40* (0.28–0.51)	0.55* (0.37–0.69)	0.28* (0.10–0.44)	0.42* (0.18–0.61)	0.30* (0.04–0.52)
Nonlinear dynamics measures					
SD1	0.57* (0.47–0.66)	0.69* (0.55–0.79)	0.28* (0.10–0.44)	0.26 (−0.01–0.48)	0.27* (0.01–0.49)
SD2	0.57* (0.47–0.66)	0.56* (0.38–0.70)	0.23* (0.04–0.39)	0.16 (−0.11–0.40)	0.26 (−0.00–0.48)

MZF = monozygotic female, MZM = monozygotic male, DZF = dizygotic female, DZM = dizygotic male, DZO = dizygotic unlike-sex.
* Indicates significant at $p < 0.05$.

the total variance only (LF, HF, SD2). However, there were two notable exceptions. For RMSSD additive genetic paths could not be equated for males and females, and the best-fitting model was the common effects model allowing for common genetic influences but different heritability estimates for males and females (64% and 52%, respectively). The second exception was the LF/HF ratio, for which a sex-limitation model showed the best fit. Although the common effects model fit was not significantly poorer than the sex-limitation model, the male parameters for the common effects model did not fit the correlation pattern observed (it suggested no A and substantial C, a pattern also not observed with either the sex-limitation or the scalar models). The common effects model was rejected based on interpretability. The scalar model was rejected based on change in Chi-square. Under the sex-limitation model, LH/HR ratio showed comparable heritability in males and females (57% and 64%, respectively) but was due to distinct genetic factors.

Overall, heritability estimates for HRV measures (Table 2) suggest that 50–60% of the observed individual differences in HRV can be attributed to additive genetic factors.

3.2. Correlations among HRV measures

Analysis of phenotypic correlations revealed strong relationships among HRV measures, both within and across measurement domains. Correlations among time domain variables ranged from 0.87 to 0.95, the correlation among frequency domain measures (low- and high-frequency power) was 0.75, and the correlation between two dimensions of Poincaré plot was 0.79. Correlations across time, frequency, and nonlinear dynamics domains ranged from 0.71 to 0.96. These generally high correlations suggested that at least 50% of variance was shared among HRV variables. The LF/HF ratio showed smaller-size correlations with other variables (0 to 0.63). Furthermore, this analysis also revealed that HRV measurements from all three domains showed significant correlations with mean HR (ranging from −0.38 to −0.72) and its inverse measure, the mean inter-beat (R-R) interval, suggesting that a substantial proportion of variance in HRV measures (up to 50%) is shared with the mean HR. These results warranted the investigation of genetic and environmental origins of this shared variance among different HRV measures, as well as between HRV and HR.

3.3. Genetic overlap among HRV measurement domains

Phenotypic correlations between variables can arise when these variables are influenced by common (overlapping) genetic or environmental factors, or both. To examine the overlap between genetic and environmental contributions to the phenotypic correlations between HR and HRV variables (SDNN and HF), we fit a trivariate genetic model (Fig. 2). As in univariate analyses, the AE model provided the best fit (AE model −2 times the log-likelihood = 18660.034 with 18 estimated parameters; $\Delta\chi^2(6) = 3.963$, $p = 0.68$ compared to the full ADE model). Proportions of variance attributable to genetic factors (heritability) and non-shared environmental factors (shown in Table 3) were consistent with univariate analyses (Table 2). Table 4 shows genetic (r_A) and non-shared environmental (r_E) correlations among the three variables. HR showed significant genetic correlations with both HRV measures, suggesting that about 38% of the genetic influences on HR overlapped with HRV measures (0.62 squared), and that 25–30% of the non-shared environmental influences were overlapping across HR and HRV measures.

Both genetic and non-shared environmental correlations between the time and frequency domain measures (SDNN and HF, respectively) were very high ($r_A = 0.95$, $r_E = 0.83$), suggesting that heritability of both measures is largely due to the same genetic factors. Individual-specific environmental influences also contribute significantly to observed covariation between these measures of HRV (but not to twin resemblance). Despite the strong genetic overlap, both measures of heart rate variability also had significant measure-specific genetic influences: 61% (95% CI: 50–72%) of the genetic influences on SDNN were independent of those on mean heart rate, 53% (95% CI: 43–63%) of the genetic influences on HF were independent of mean heart rate but overlapping with SDNN, but only 9% (95% CI: 5–14%) of the genetic influences on HF were specific to HF, i.e. not overlapping with either HR or SDNN.

Table 2
Proportions of variance attributable to genetic and non-shared environmental influences for the best fitting univariate models from selected measures of heart rate variability.

Measure	Best fitting model[a]	A_F	E_F	A_M	E_M	A'_M	k
Time domain							
R-R	Scalar AE	0.64* (0.58–0.70)	0.36* (0.30–0.42)	$=A_F$	$=E_F$	–	1.17* (1.07–1.29)
SDNN	No sex-effects AE	0.54* (0.45–0.61)	0.46* (0.39–0.55)	$=A_F$	$=E_F$	–	–
HR	No sex-effects AE	0.62* (0.55–0.68)	0.38* (0.32–0.45)	$=A_F$	$=E_F$	–	–
RMSSD	Common effects AE	0.52* (0.42–0.60)	0.48* (0.49–0.58)	0.64* (0.50–0.74)	0.36* (0.26–0.50)	–	–
PNN50	No sex-effects AE	0.59* (0.51–0.65)	0.41* (0.35–0.49)	$=A_F$	$=E_F$	–	–
Frequency domain							
LF	Scalar AE	0.47* (0.38–0.55)	0.53* (0.45–0.62)	$=A_F$	$=E_F$	–	1.15* (1.05–1.26)
HF	Scalar AE	0.58* (0.50–0.65)	0.42* (0.35–0.50)	$=A_F$	$=E_F$	–	1.11* (1.01–1.22)
LF/HF	Sex-limitation AE	0.64* (0.58–0.70)	0.36* (0.30–0.42)	0.00 (0.00–0.39)	0.43* (0.32–0.58)	0.57* (0.18–0.68)	–
Nonlinear dynamics domain							
SD1	No sex-effects AE	0.60* (0.53–0.66)	0.40* (0.34–0.47)	$=A_F$	$=E_F$	–	–
SD2	Scalar AE	0.55* (0.47–0.62)	0.45* (0.38–0.53)	$=A_F$	$=E_F$	–	1.11* (1.01–1.21)

[a] The sex-limitation model allows for genetic (A) and environmental (E) influences that are shared across females and males, but also allows for male-specific influences (A'_M; only one parameter can be gender-specific in a given model). The common effects model removes the male-specific path, A (heritability) and E (environmental influences are common across gender, although the proportions of variance attributable to each effect can vary across gender. The scalar model equates the proportions of variance across gender, but allows for differences in the absolute variance across gender. The no sex-effects model has no sex-differences. A_F = additive genetic influences for females, E_F = non-shared environmental influences for females, A_M = additive genetic influences for males that are common with those for females, E_M = non-shared environmental influences for males that are common with those for females, A'_M = male-specific additive genetic influences, k = scalar multiplier for the male variance.

* Indicates significant at $p < 0.05$.

Overall, 63% (95% CI: 52–72%) of the phenotypic correlation between HR and SDNN was attributable to overlapping genetic influences, 61% (95% CI: 51–70%) of the phenotypic correlation between HR and HFPOWER was attributable to overlapping genetic influences, and 59% (95% CI: 51–66%) of the phenotypic correlation between SDNN and HF was attributable to overlapping genetic influences (see Fig. 2).

As shown in Supplementary Table 3, additional bivariate models were tested to examine the overlap of a nonlinear dynamic measure (SD1) with the measures of heart rate variability (SDNN and HF; see Supplementary Table 2 showing that the AE model was the best-fitting in all cases). Heritability estimates based on bivariate models were consistent with estimates obtained in univariate analyses of the same variables and showed significant genetic correlations (r_A), ranging from 0.95 to 0.98, suggesting that >90% of genetic variance is shared across time domain, frequency domain, and nonlinear dynamical measures. Environmental correlations (r_E) were also significant, ranging from 0.85–0.96, suggesting that individually specific environmental influences also contribute significantly to observed covariation between these measures.

4. Discussion

The results of the present study using a large, population-based sample of young adult twins showed substantial heritability of HRV, suggesting that 50–60% of the observed individual differences in HRV measures can be attributed to additive genetic factors. Importantly, high heritability was observed across different domains of HRV measurement including time domain, frequency domain, and nonlinear dynamical measures. The present results are consistent with previous studies that varied with respect to age, gender, HRV measures used, and the duration of the ECG recording available for HRV assessment. Despite this variability across studies, results are generally convergent suggesting that HRV measures represent robust, trait-like individual differences in cardiac functioning. One important implication from this and previous studies is that a short, five-minute resting-state ECG recording is sufficient for capturing genetically transmitted variance in HRV.

The present results also suggest that most of these genetic influences are common to males and females. A notable exception is the LF/HF ratio, for which we could not reliably differentiate between the sex-limitation model and the common effects model. Under the sex-limitation model, LF/HF was highly heritable in both genders, but this heritability arose from distinct genetic influences in males and females.

Table 3
Standardized proportions of variance [95% Confidence Intervals] attributable to additive genetic (heritability) and non-shared environmental influences in the best-fitting trivariate model.

Variable	Additive genetic	Non-shared environment
HR	0.62 (0.55–0.68)	0.38 (0.32–0.45)
SDNN	0.53 (0.45–0.60)	0.47 (0.40–0.55)
HF	0.58 (0.50–0.65)	0.42 (0.35–0.50)

Note: All variance components significant at $p < 0.05$.

Table 4
Genetic and non-shared environmental correlations[a] between mean heart rate, SDNN, and HFPOWER from the best-fitting model examining the genetic and environmental contributions to the associations between the measures of heart rate variability.

	Mean heart rate	SDNN	HFPOWER LN
Mean heart rate	–	−0.62 (−0.70–−0.53)	−0.62 (−0.69–−0.53)
SDNN	−0.50 (−0.58–−0.41)	–	0.95 (0.93–0.97)
HFPOWER LN	−0.59 (−0.66–−0.51)	0.83 (0.79–0.86)	–

Note: A = additive genetic influences, E = non-shared environmental influences. All correlations significant at $p < 0.05$.

[a] Genetic correlations are above the diagonal; non-shared environmental correlations are below the diagonal.

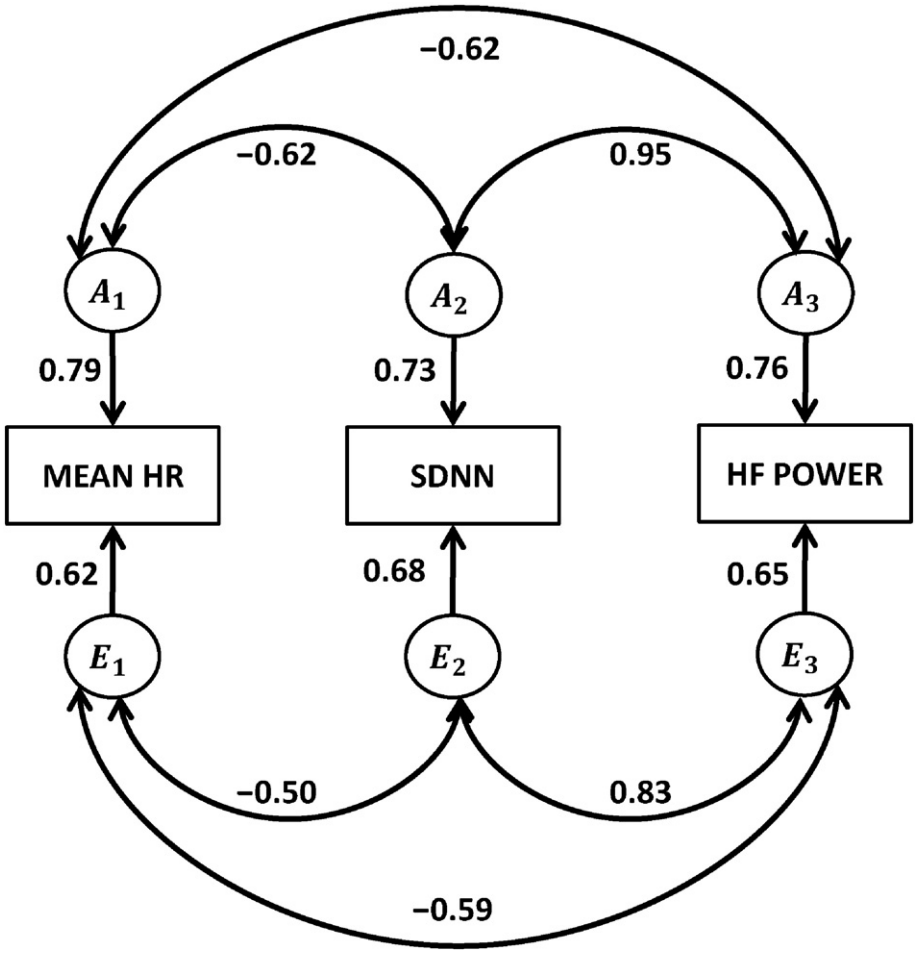

Fig. 2. Genetic and environmental correlations among HR and HRV variables. The upper part of the diagram shows the overlap between genetic factors influencing the phenotypes, whereas the lower part shows the overlap between environmental factors affecting the same phenotypes.

Although this finding warrants further investigation, it raises the possibility that individual differences in LF/HF may be mediated and/or modulated by partially distinct physiological and neurobehavioral pathways in males and females. As discussed in the Introduction, HRV is a complex phenotype that is strongly affected by a range of factors (psychosocial, hormonal, etc.). Many of these factors show significant sex differences and may also play a different role in shaping autonomic balance in males and females. The LF/HF index is complexly determined, its validity as a measure of "sympathovagal balance" has been largely disproven, and its exact interpretation remains unclear.

Another important conclusion from the present study is that shared environmental factors (prenatal environment, family, neighborhood, school, etc.) do not make a substantial contribution to individual differences in HRV. This finding seems to contradict to evidence that a number of factors potentially influencing HRV such as level of psychosocial stress show substantial variation across families. There is a possibility, however, that environmental influences on cardiac autonomic regulation are modulated by the individual's genotype. This kind of gene by environment interaction, if not accounted explicitly using measured environmental influences, would contribute to the genetic component of variance (heritability). It remains to be determined in future studies whether and how specific environmental exposures interact with genotype to produce individual differences in HRV.

Multivariate genetic analyses showed substantial overlap among genetic influences on HRV measurements from different domains, suggesting that over 90% commonality in genes influencing time domain (SDNN), frequency domain (HF), and nonlinear dynamical (SD1) measures of vagally mediated parasympathetic tone. One important implication from this finding is that these measures capture essentially the same genetically transmitted variation and thus the use of multiple measures may be redundant in studies focused on the genetic underpinnings of autonomic functioning.

Finally, one important issue that received relatively little attention in previous literature is the correlation between HR and HRV. Our analysis revealed high phenotypic correlations between these measures that ranged from −0.5 to −0.7 (0.5 to 0.7 for the inverse measure of HR, the R-R interval), suggesting that 25 to 50% of phenotypic variance is shared between HR and HRV measures. Furthermore, multivariate genetic analysis showed a high genetic correlation (r_G) between HR and both time and frequency domain HRV ($r_G = 0.62$), suggesting that about 40% of genetic variance in HRV can be captured by resting HR measurement. However, the current analysis also revealed a significant HRV-specific genetic variance not shared with HR for each of the three HRV variables. An important implication from this finding is that genetic influences unique to HRV may be mediated by psychophysiological mechanisms that are distinct from those mediating genetic influences that are shared among HR and HRV. Therefore, it can be recommended that in studies interested in capturing HRV-unique genetic variance, variation shared with HR is removed statistically, i.e. by using residuals after regressing HRV on HR.

Several limitations of the present study need to be acknowledged. The present study was focused on genetic aspects and did not investigate physiological mechanisms underlying HRV or functional meaning of HRV measures. However, the present results indicate a very strong

genetic overlap among different HRV indices suggesting that genetic influences specific to particular measures (e.g. time versus frequency domain) are minimal. Another limitation is that HRV was assessed in the resting state only. It is possible that genetic influences on HRV measures may be different and more measure-specific under the conditions of physical, cognitive, or emotional challenge. Next, the present study evaluated heritability of HRV in young adults only and provided little information about developmental dynamics of genetic influences. An ongoing longitudinal twin study in our laboratory will investigate genetic influences on HRV in adolescents, including genetic influences on the trajectory of age-related changes, as well as prospective association between HRV and subsequent health-related behaviors and outcomes. Finally, the source of small but significant differences in some HRV measures between the first and the second resting period remains unclear. Although both five-minute recordings represent a resting state in which participants were instructed to sit back and relax, it is possible that there were subtle difference in their functional state such as relatively higher alertness at the beginning of the session or, conversely, greater fatigue or relaxation at the end of the session.

5. Conclusions

Genetic factors determine 50 to 60% of observed individual differences in HRV measures in young adults. There is little evidence for shared (familial, etc.) environmental influences on HRV. Heritability estimates are comparable across measurement domains of HRV including time, frequency, and nonlinear dynamical measures. Genetic influences did not differ between genders for most variables except RMSSD (higher heritability in males) and LF/HF ratio (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, although about 40% of genetic variance in HRV was shared with HR, HRV-unique genetic influences were highly significant. Taken in combination with previous research, these results further support the utility of future research examining HRV as an endophenotype for a range of dysfunctions involving physiological, affective, and cognitive dysregulation.

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