Published in final edited form as:

Behav Genet. 2018 September ; 48(5): 386–396. doi:10.1007/s10519-018-9915-1.

Resting Heart Rate Variability (HRV) in Adolescents and Young Adults from a Genetically-Informed Perspective

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Abstract

Reduced heart rate variability (HRV) is associated with cardiac morbidity, mortality, and negative psychopathology. Most research concerning genetic influences on HRV has focused on adult populations, with fewer studies investigating the developmental period of adolescence and emerging adulthood. The current study estimated the genetic and environmental contributions to resting HRV in a sample of twins using various HRV time domain metrics to assess autonomic function across two different time measurement intervals (2.5- and 10-min). Five metrics of resting HRV [mean interbeat interval (IBI), the standard deviation of normal IBIs (SDNN), root square mean of successive differences between IBIs (RMSSD), cardiac vagal index (CVI), and cardiac sympathetic index (CSI)] were assessed in 421 twin pairs aged 14–20 during a baseline electrocardiogram. This was done for four successive 2.5-min intervals as well as the overall 10-min interval. Heritability (h^2) appeared consistent across intervals within each metric with the following estimates (collapsed across time intervals): mean IBI ($h^2 = 0.36–0.46$), SDNN ($h^2 = 0.23–0.30$), RMSSD ($h^2 = 0.36–0.39$), CVI ($h^2 = 0.37–0.42$), CSI ($h^2 = 0.33–0.46$). Beyond additive genetic contributions, unique environment also was an important influence on HRV. Within each metric, a multivariate Cholesky decomposition further revealed evidence of genetic stability across the four successive 2.5-min intervals. The same models showed evidence for both genetic and environmental stability with some environmental attenuation and innovation. All measures of HRV were moderately heritable across time, with further analyses revealing consistent patterns of genetic and environmental influences over time. This study confirms that in

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Compliance with ethical standards

Conflict of interest Jessica L. Bourdon, Ashlee A. Moore, Meridith Eastman, Jeanne E. Savage, Laura Hazlett, Scott R. Vrana, John M. Hettema, Roxann Roberson-Nay declare that they have no conflict of interest.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10519-018-9915-1>) contains supplementary material, which is available to authorized users.

Informed consent Informed consent/assent was collected for all participants and procedures were approved the university's Institutional Review Board.

Human and animal rights All human subjects ethical standards were followed by all authors and research assistants who worked on the AYATS. Each individual involved in the project is up-to-date on Collaborative Institutional Training Initiative (CITI) and MATR training.

an adolescent sample, the time interval used (2.5- vs. 10-min) to measure HRV time domain metrics does not affect the relative proportions of genetic and environmental influences.

Keywords

Heart rate variability; Heritability; Time metrics; Time intervals; Adolescence; Psychophysiology

Introduction

Reduced heart rate variability (HRV) is associated with autonomic nervous system (ANS) disruption, cardiac morbidity and mortality, and psychopathology (Task Force for the European Society of Cardiology and the North American Society of Pacing Electrophysiology [Task Force] 1996). To date, most studies of resting HRV have relied on adult samples (Shahrestani et al. 2014), with fewer studies concentrating on adolescence and emerging adulthood. This developmental period is a key time for the surfacing of many mental health difficulties (e.g., depression, social anxiety, generalized anxiety) related to altered ANS function (Costello et al. 2003; Hankin et al. 1998; Lewisohn et al. 1998; de Lijster et al. 2017; Saluja et al. 2004). Thus, understanding the genetic architecture of HRV at this life stage may aid identification of at-risk populations (i.e., during screening processes) and also clarify whether risk of ANS disruption changes throughout development when compared to studies conducted in other age groups. The present study will extend what is currently known about HRV in adolescents and young adults by estimating the heritability and genetic and environmental stability of key HRV time domain metrics using two different measurement intervals (2.5- vs. 10-min) in a sample of adolescent and young adult twins.

Genetic influences of resting HRV in adolescents and young adults

The heritability of resting HRV has not been widely studied, although the heritability of heart rate and heart rate reactivity have been extensively examined (for meta-analyses, see Wang et al. 2015; Wu et al. 2010, respectively). In a mixed sample of adolescents and adults, the heritability of HRV across three environments over 24 h (sleeping, sitting, and normal activity) was found to range between 0.46 and 0.53 for the standard deviation of normal interbeat intervals (SDNN), 0.49–0.53 for the root mean square differences between interbeat intervals (RMSSD), and 0.48–0.57 for peak valley respiratory sinus arrhythmia (RSA; Neijts et al. 2014). In an adult-only sample, similar heritability estimates have been found to range from 0.43 to 0.63 across five frequency domain metrics (ultra low, very low, low, high, and total power) over 24 h (Su et al. 2010).

Only two studies have examined the heritability of resting HRV in a sample explicitly limited to adolescents and young adults. Both were drawn from the Georgia Cardiovascular Twin Study and included a mix of European- and African-American participants (Wang et al. 2005, 2009). Slightly different heritability estimates were found across these studies. First, the heritability was estimated to be 0.66 for SDNN, 0.71 for RMSSD, 0.45 for low-frequency (0.04–0.15 Hz), and 0.63 for high-frequency (0.15–0.40 Hz) components for roughly a 4-min time interval sampled from a 10-min rest period (Wang et al. 2005). The

later study found somewhat lower estimates across a 2-min interval collected during a 10-min rest period, specifically 0.48 for RMSSD and 0.50 for high-frequency. Estimate differences could be related to time interval assessed, size of the sample, or other factors.

A recent study by Golosheykin et al. (2017) investigated HRV in an older sample consisting of over 1000 twins aged 17–36 years. This study found significant shared genetic variance across multiple time- and frequency-domain measures of HRV. Furthermore, the results of this study suggested the possibility of sex-specific genetic effects for some measures of HRV, indicating increased HRV in males compared to females (Golosheykin et al. 2017). The present study attempts to replicate and expand extant research addressing the genetic influences on HRV in adolescents and young adults. To this aim, we assess a broad array of HRV time domain metrics and estimate their heritability and sources of stability using different time intervals.

Resting HRV time domain intervals and metrics

Traditionally, there have been two primary approaches to assess HRV from a time domain perspective: using short (5–15 min) or long (up to 24 h) recordings (Kleiger et al. 2005). Evidence is mixed as to whether ultra short (10–120 s) recordings are reliable and valid measures when compared to short or long intervals (Dekker et al. 1996; Munoz et al. 2015; Nussinovitch et al. 2011; Thong et al. 2003). Studies of ultra short intervals have primarily relied on SDNN and RMSSD, with RMSSD being a stronger index of HRV compared to SDNN. However, the evidence implies that even when assessing RMSSD, the longer end of the ultra short spectrum (60–120 s) is typically more valid and reproducible (Thong et al. 2003; Munoz et al. 2015; Nussinovitch et al. 2011). Thus, many studies (i.e., Dieleman et al. 2016; Wang et al. 2009) continue to rely on either short or long time interval lengths as was originally recommended (Task Force 1996). To address the appropriateness of short versus ultra short time intervals in assessing resting HRV, the present study will also examine the consistency of consecutive intervals that are 150 s in length from a genetically-informed perspective.

Past studies on time intervals used in HRV analyses suffer from two major limitations. First, they have been limited to adult samples, leaving questions regarding the utility and comparability of time intervals in other age groups. The knowledge gap is particularly important to address in adolescent/young adult samples, where lifestyle and medical interventions may be especially effective in reducing risk for later illnesses and psychopathology (i.e., school-based programs aimed at smoking, exercise, and other ANS-related behaviors; treatment adherence awareness; Williams et al. 2002). Second, the two main time domain metrics used in studies examining the effects of various intervals for indexing HRV and ANS disruption have been RMSSD and SDNN. Both of these metrics are derived from the mean interbeat interval (mean IBI) and assess both branches of the ANS [sympathetic (SNS) and parasympathetic (PNS)] simultaneously (Allen 2002; Task Force 1996). The current study includes two additional metrics that putatively assess mainly the PNS or SNS: the cardiac vagal index (CVI) and cardiac sympathetic index (CSI), respectively (Allen 2002; Toichi et al. 1997). CVI and CSI have been shown to be valid ways to geometrically analyze HRV (Allen et al. 2007; Toichi and Kamio 2003), a form of

analysis endorsed by the Task Force (1996). Calculations of these metrics are based on a Lorenz plot of each IBI against subsequent IBI separately for each point (Toichi et al. 1997). While CSI has been used more widely to index SNS (i.e., Farmer et al. 2015; Weinberg et al. 2009), CVI is an equally valid way to index PNS (Sugaya et al. 2015).

Research aims

To date, no study has assessed the stability of various consecutive time intervals from a genetically-informed perspective using a wide array of time domain metrics that tap into various aspects of the ANS during adolescence/emerging adulthood. The goals of the current study are to (1) estimate the heritability of an expanded set of resting time domain HRV metrics in an adolescent and young adult sample, and (2) assess the genetic and environmental stability of these metrics. Genetic stability reflects continuity of the influence of a genetic factor over time. Heritability estimates will be examined for a 10-min (short) resting period and the four successive 2.5-min (ultra-short) intervals that comprise the longer 10-min period while the genetic stability estimates will only be calculated from the successive 2.5-min intervals. Metrics examined include those that putatively tap different aspects of cardiac activity including (1) rate (mean IBI), (2) total HRV (SDNN, RMSSD), (3) parasympathetic influences (CVI), and (4) sympathetic influences (CSI).

Methods

Participants

Participants in the present, cross-sectional study were 842 twins [421 complete twin pairs; 157 monozygotic (MZ) pairs, 252 dizygotic (DZ) pairs; $M_{age} = 17$ years; female = 57%] participating in the first wave of a longitudinal twin study of risk for internalizing syndromes. In brief, twin participants aged 15–20 years were recruited through the Mid-Atlantic Twin Registry (MATR), a registry of twins, other higher-order multiples, and their family members (Lilley and Silberg 2013) to generate an epidemiological sample of twins (note that one DZ pair was aged 21, which is reflected in Table 1). The overall purpose of the parent study was to examine how negative valence system constructs contribute to internalizing disorders by recruiting a community sample of participants with varying degrees of symptomology. All twins were generally healthy and free of medications with psychotropic effects at the time of the study (for more details see, Cecilione et al. 2018). Following removal of outliers (defined as 3 standard deviations above or below the mean for a metric), the final analytical sample consisted of 784 participants with 2.5-min interval data (395 complete twin pairs; MZ = 152; DZ = 240; $M_{age} = 17$ years; female = 57%; Caucasian = 91%; Black = 4%; Hispanic = 4%) and 776 with 10-min interval data (388 complete twin pairs; MZ = 151; DZ = 237; $M_{age} = 17$ years; female = 56%; Caucasian = 92%; Black = 4%; Hispanic = 4%; see Table 1 for a complete demographic breakdown of participants in the final analytical sample). Zygosity was assessed based on parent- or self- (for participants age 18 or older) report of physical characteristics and similarities between twins and confirmed on a subset of the sample ($N = 82$) using a single nucleotide polymorphism (SNP) assay. There was a high degree of agreement between the two methods ($\kappa = 0.95$; confidence

interval [CI] 0.88–1.00), confirming prior established validity of the parent- and self-report method (Kasriel and Eaves 1976).

Procedures and recording

Resting electrocardiogram (EKG) was recorded for 10 min after participants completed numerous behavioral assessments but prior to a stress test. Participants sat in an upright position and were instructed to remain as still as possible. Cardiac response was acquired using the ECG100C amplifier (BIOPAC Systems, Inc. 2010) along with disposable adhesive electrodes (EL503) stippled with a small application of Signa gel. Electrodes were attached to the participant's right collarbone and left wrist. The raw EKG channel was filtered to a low frequency cutoff of 0.05 Hz and high frequency cutoff of 35 Hz with 8000 coefficients. QRS markers were then placed on the channel to locate R-spikes using the default function in *Acqknowledge* (BIOPAC Systems, Inc. 2010). Trained study personnel examined and scored each file individually, checking each QRS mark for incorrect or missing marks.

Once all R-spikes were identified, the time (milliseconds) between R-spikes was plotted to determine whether any R-spikes were clearly missed or whether a component of the QRS complex was erroneously counted as an R-spike. Once all R-spikes were correctly characterized, the time between each R-spike (i.e., IBI) was outputted, and HRV metrics were calculated using calculations described by Allen (2002), Allen and colleagues (2007), and Toichi et al. (1997) (see Supplemental Table I for details on metric calculations). Outliers above or below the mean by three standard deviations for each metric at each time interval were excluded from analyses ($N = 52$ excluded from the 10-min interval sample; $N = 60$ excluded from the 2.5-min interval sample) (Howell 1998). The 10-min IBI series was further divided into four 2.5-min intervals for a total of five time periods that were assessed in the current study.

Data analysis

All analyses were conducted in the R software package (version 1.0.136; R Development Core Team 2008) with heritability estimates calculated using the OpenMX package (Boker et al. 2011).

Data characteristics—Spearman correlations assessed the relationship between metrics for each time interval. The impact of potential covariates (sex, race/ethnicity, and age) were examined using univariate linear regressions where each metric at each time point was regressed onto each potential covariate. Bonferroni correction was implemented to correct for the fact that 15 regressions were run for each metric during this process; the threshold was set to $p = 0.003$ for these analyses. Significant covariates were included in the subsequent analyses.

Heritability and genetic stability estimates—Biometrical structural equation modeling (Neale and Cardon 1992) was used to decompose the variance in the observed time domain metrics into additive genetic (A), shared environmental (C) and unique, or non-shared, environmental (E) factors. Additive genetics (A) reflects the additive effect of individual alleles at genetic loci influencing a trait or behavior and contributes twice as

much to the MZ twin correlation as the DZ twin correlation (because MZ twins share 100% of their genes, whereas DZ twins share, on average, 50% of their genes by descent). Common environmental effects (C) reflect influences that make family members more alike compared to random pairs of individuals and contribute equally to the MZ and DZ correlations. Unique environmental effects (E) are uncorrelated between twins, and reflect aspects of the environment that are unique to each individual, plus measurement error.

For each of the observed time metrics (IBI, RMSSD, SDNN, CVI, and CSI), variance decomposition was performed across the four successive 2.5 min intervals and the overall 10-min interval to estimate heritability (25 total analyses). To examine genetic and environmental stability, a Cholesky decomposition was run for each time domain metric (five total analyses) that included cross paths between each of the four successive 2.5-min time intervals. Figure 1 displays the full Cholesky decomposition model used in these analyses with mean IBI as an example. For each analysis, the variance and/or covariance was first decomposed into latent A, C, and E factors (saturated model). The significance of covariates (included, where applicable, as definition variables on the means) in the saturated model was assessed by constraining the covariate parameter to zero to determine the best-fitting, most parsimonious model (i.e., ACE + Sex vs. ACE – Sex) via the Likelihood Ratio Test (LRT; Wilks 1938) and Akaike's Information Criteria statistic (AIC; Akaike 1987). The same process was followed to test the significance of individual parameters by comparing the saturated model (either with or without covariates) to nested sub-models (AE, CE, and E models) to determine the final model for each metric. For reference, genetic stability would appear as a single genetic factor accounting for the majority of variance at all four time intervals. Attenuation of genetic effects would be demonstrated by decreasing heritability magnitude over time while genetic innovation (new genetic influences coming “online”) would appear as additional significant genetic factors (in addition to the first factor).

Results

Data characteristics

Basic statistics—For each metric, the mean and standard deviations were calculated across time intervals (see Table 2).

Covariates—Potential covariates (sex, race/ethnicity, age) were regressed onto each time metric at each interval using univariate linear regression (see Supplemental Table II). Significant and mostly consistent effects were found for sex, with female sex predicting lower mean IBI ($\beta = -42.053$ to -33.371 , $p < 0.001$), SDNN ($\beta = -8.320$ to -7.346 , $p < 0.001$), and CVI ($\beta = -0.101$ to -0.097 , $p < 0.017$) at each time point except the second successive 2.5-min interval for SDNN. Age predicted increased RMSSD for the full 10-min interval ($\beta = 0.470$, $p = 0.001$). These covariates were subsequently included in their respective heritability analyses.

Phenotypic correlations—All time metrics were highly correlated (see Table 3), with the highest correlations between SDNN and RMSSD ($r = 0.96$ – 0.97 , $p < 0.001$) at each time interval. The lowest correlations were consistently between CSI and SDNN across time points ($r = -0.47$ to -0.34 , $p < 0.001$). CSI is negatively correlated with all metrics across

time intervals, consistent with the idea that CSI is thought to reflect primarily SNS activity (Allen 2002; Farmer et al. 2015; Toichi et al. 1997; Weinberg et al. 2009) while the other metrics reflect predominantly PNS activity (CVI; Allen 2002; Allen et al. 2007; Toichi et al. 1997; Toichi and Kamio 2003; Sugaya et al. 2015) or both PNS and SNS activity (mean IBI, SDNN, RMSSD; Allen 2002; Task Force 1996).

Heritability estimates

Correlations for MZ and DZ twin pairs implied significant contributions of additive genetic factors to each metric at all intervals ($r_{DZ} < r_{MZ}$), as well as common environment ($r_{DZ} > \text{half } r_{MZ}$) for many time points and unique environment ($r_{MZ} < 1$) for all time points (see Table 4). Several time points indicated possible dominance effects ($r_{DZ} < \text{half } r_{MZ}$) in which effects of alleles are multiplicative/non-additive, but there was insufficient power in the current sample to discriminate between non-additive genetic variance components (Martin et al. 1978).

For each heritability analysis, covariates were included in the saturated models where applicable as noted above. Before assessing sub-models, saturated models with and without covariates were compared, with the lowest AIC value indicating the best-fitting, most parsimonious model (Williams and Holahan 1994). It was found that covariates could be eliminated from all models (see Supplemental Tables III–VII) and were not included in the subsequent Cholesky decomposition models. Next, sub-models (AE, CE, and E models) were compared to the full model (ACE model without covariates; see Table 5 for final standardized, squared estimates and Supplemental Tables III–VII for detailed fit statistics). Heritability estimates (i.e., additive genetic component, A) across all metrics and time intervals were moderate and quite comparable in terms of relative proportions of genetic and environmental influences. Final estimates were as follows: mean IBI ($h^2 = 0.36\text{--}0.46$), SDNN ($h^2 = 0.23\text{--}0.30$), RMSSD ($h^2 = 0.36\text{--}0.38$), CVI ($h^2 = 0.37\text{--}0.42$), and CSI ($h^2 = 0.34\text{--}0.46$). Within each metric, the confidence intervals were overlapping across time points. Common environment was not a significant contribution to any model, with all remaining variance accounted for by unique environment, which includes measurement error.

Stability of genetic and environmental sources of variance

For each time domain metric, a full Cholesky decomposition (ACE) model, without covariates, for the four successive 2.5 min intervals were computed. These decompositions were compared to a series of sub-models where all effects of A and C were individually and jointly dropped. After the overall structure of the final model was determined based on AIC, all remaining parameter estimates > 0.03 were tested for significance (see Table 6 for final standardized, squared estimates, and Supplemental Tables VIII–XII for detailed fit statistics). Across all HRV metrics, there was evidence for genetic stability as well as environmental stability and innovation. Specifically, mean IBI showed genetic stability, with a single factor accounting for the genetic variance at all time intervals ($A = 0.51\text{--}0.59$). This pattern of genetic stability across the four successive 2.5 min intervals was also observed for SDNN ($A = 0.37\text{--}0.44$), RMSSD ($A = 0.44\text{--}0.50$), and CVI ($A = 0.47\text{--}0.50$). Genetic stability was also present for CSI, with one factor accounting for the majority of the genetic

variance across time intervals ($A = 0.34\text{--}0.43$). However, CSI also had one significant genetic innovation during the fourth 2.5-min interval, although the percent of variance accounted for by this innovation was small (0.05). Similar to the genetic stability results, environmental influences at all four time intervals were primarily due to a single environmental factor (environmental stability with some attenuation); however, there were consistently small to moderate environmental innovations at each of the four time intervals. These environmental innovations may reflect slightly different environmental circumstances and/or differences in measurement error at each of the four intervals.

Discussion

The current study contributes to the literature by examining the heritability and sources of stability of a range of resting HRV time domain metrics across multiple time intervals in a sample of adolescents and young adults (ages 14–20). The study was designed to provide greater insight into the comparability of genetic and environmental influences on resting HRV across short and ultra-short time intervals (2.5-min or 10-min). Specifically, characteristics and heritability estimates were assessed across five time intervals for five metrics including a metric of rate (mean IBI), total heart rate variability influenced by the SNS and PNS (SDNN, RMSSD), and putative PNS (CVI) and SNS (CSI) influences. Overall, regardless of time interval or HRV metric, the heritability was moderate and consistent, with the remaining non-genetic variance accounted for by unique environment. Genetic stability and environmental stability were also observed, although the latter influence attenuated slightly over time, with environmental innovations accounting for a moderate proportion of the environmental variance.

Despite the younger cohort, the means and standard deviations for all metrics for the full 10-min baseline time interval were within the normal range previously reported for adults (Allen 2002). Across each time interval, all of the metrics were highly and positively correlated with one another with the exception of CSI, which was moderately and negatively correlated with all other metrics. This is likely because CSI is believed to be influenced predominantly by the SNS. The weaker correlations between the other metrics (mean IBI, SDNN, RMSSD, CVI) and CSI suggest that the time metrics influenced by both branches of the ANS may be more parasympathetically than sympathetically influenced.

The final heritability estimates do not completely align with those found in comparable studies of adolescents (Wang et al. 2005, 2009). Only two of our included metrics, SDNN and RMSSD, were employed in these studies. The current findings for SDNN are lower than those found by Wang et al. (2005), with non-overlapping confidence intervals for all but one time point. There is more consistency across studies for RMSSD, with the current study finding lower estimates but with overlapping confidence intervals (Wang et al. 2009). The slightly inconsistent heritability estimates between these studies may be due to sample size, specific data collection procedures, or analysis techniques. However, the comparability of the heritability estimates from our data implies that inconsistencies between estimates are likely not due to the measurement time interval used. This is an important consideration for future research, especially in large-scale studies for which the collection of other variables, and therefore time, are at a premium.

Another consideration in large-scale studies is which HRV metrics to include. By examining HRV metrics that assess a wider array of underlying biological mechanisms, the current study provides unique insight into the genetic and environmental stability of these metrics across four ultra short (2.5 min) time intervals. Specifically, mean IBI, SDNN, RMSSD, CVI, and CSI were influenced by a single genetic factor across all four successive 2.5 min intervals. Furthermore, this genetic influence is of comparable magnitude across time intervals, indicating that an ultra short (2.5-min) interval provides the same information regarding underlying genetic influences as a longer (10-min) interval. The environmental influences across the four 2.5-min intervals were somewhat less stable. Although one factor did contribute substantially to the environmental variance over time, the magnitude of this influence modestly attenuated over the full 10-min interval. For each metric, environmental influences unique to each 2.5-min interval were significant contributors to the overall variance, reflecting environmental innovations. These findings complement the recent findings by Goloskeykin and colleagues (2017). They fit a multivariate model across multiple HRV domains (time, frequency, and non-linear) to examine shared genetic and environmental factors across metrics. Here, we examined similar metrics but focused on their genetic stability over time. Together, these studies shed additional light on the genetic underpinnings of HRV from multiple perspectives.

The current study has several strengths. First, it adds to the current literature assessing resting HRV in adolescence and emerging adulthood. It is important to study heritability across the lifespan, as developmental factors are known to influence both genetic and environmental risk (Kendler et al. 2008). A clear understanding of genetic and environmental influences on HRV during the adolescent and young adult years will inform our understanding of autonomic regulation during this developmental period. Second, use of data from the 2.5-min intervals expands past work on ultra short time intervals which suggests that time periods around 120 s generate reliable and valid outcomes (Thong et al. 2003; Munoz et al. 2015; Nussinovitch et al. 2011). Yet, most studies continue to use short time periods in their analyses (5–15 min). Our findings add a genetically-informed perspective and indicate that resting HRV metrics are quite comparable and stable across 2.5-min (150 s) as well as longer 10-min time periods. Perhaps this relieves some pressure on researchers when debating what time interval to use. Finally, current findings provide additional rationale for the inclusion of CVI and CSI in future studies.

Despite the significant strengths of the current study, the results should be interpreted in light of several limitations. First, our sample was mostly Caucasian, and therefore may not generalize to other races and ethnicities, though previous studies have not found significant differences in heritability between ethnic groups (Wang et al. 2005, 2009). Second, the current study only examined time domain metrics; it is possible that the genetic influences on HRV may differ for frequency domain metrics. However, as frequency domain metrics are based on Fourier transformations of the IBI series (a time metric), significant differences are not expected. Third, the current multivariate analysis used to examine genetic stability was a Cholesky decomposition, which is atheoretical in nature. While informative on broad patterns of stability (including attenuation and innovation), latent growth or autoregressive models may better capture the nuances of such changes over time. Thus, future studies may wish to compare such models. Lastly, although our twin sample is the largest to date to

examine a number of different HRV metrics in this age range, it does not have adequate power to test for qualitative and quantitative sex effects on proportions of variance (Neale and Cardon 1992; Verhulst 2017). Our sample size also limits our power to detect non-additive (dominant) genetic effects (Martin et al. 1978), which may play a role HRV time domain metrics, especially given the patterns of twin correlations observed in the current study.

Moving forward, genetic covariance with other psychiatric phenotypes should be considered in future studies, particularly those associated with increased cardiac morbidity (e.g., major depression, panic disorder) (Hovland et al. 2012; Vasquez et al. 2016). For example, a gene-by-stress interaction has been found when assessing heart rate at rest and during stressful periods in a sample aged 13–63 years (De Geus et al. 2007). Stress was shown to increase the genetic heritability across various heart rate metrics. Also, a genetic correlation between depression and HRV frequency domain metrics in adults (aged 47–60 years) has been found (Su et al. 2010). Relatedly, the search for molecular genetic mechanisms underlying HRV is underway (Nolte et al. 2017) and future research, with increasingly larger sample sizes, will be needed to explain the genetic variance estimated in heritability studies. It also appears that much of the variance of HRV is accounted for by individual environment, some of which changes between even ultra short (2.5-min) intervals, and therefore specific environmental factors (e.g., early life stressors) affecting autonomic health and overall cardiac health in adolescents should be explored. Finally, longitudinal investigations of heritability over longer periods of time are needed to assess the impact of development on genetic and environmental influences to HRV and the contribution of HRV to temporally measured physical and mental health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank the participants from the Adolescent and Young Adult Twin Study (AYATS), as well as the many VCU students who contributed to execution of the project, particularly Jason Burchett. We would also like to thank Audrey Anderson for her assistance collecting and processing the data and Shannon Hahn and Jennifer Cecilione for their work as project coordinators.

Funding

The AYATS is funded by NIMH R01MH101518 (PI: RRN). AAM is supported by NIMH F31MH111229. JLB, MLE, and JES are supported by NIMH T32MH020030. LH is supported by NIMH R01MH101518. JMH is supported by NIMH R01MH098055.

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Fig. 1. Full Cholesky decomposition model tested for mean IBI. Upper panel represents effects of A and lower panel reflects effects of E

Table 1

Demographic characteristics of the final analytical sample

	Female		Male	
	MZ (%)	DZ (%)	MZ (%)	DZ (%)
2.5-min interval				
Total	41	59	36	64
Age 15–16	56	51	52	61
Age 17–18	27	33	35	28
Age 19–20	18	16	13	11
Age 21	0	0.39	0	0.46
10-min interval				
Total	41	59	37	63
Age 15–16	56	52	52	61
Age 17–18	26	33	35	28
Age 19–20	18	15	13	11
Age 21	0	0.39	0	0.47

Table 2

Mean ($\pm SD$) of each metric (milliseconds [ms])

Metric	2.5-min intervals			10-min interval		
	1st	2nd	3rd	4th		
Mean IBI	832.97 (132.84)	829.29 (130.00)	826.67 (128.85)	824.79 (126.61)	828.04 (127.83)	
SDNN	70.84 (29.61)	68.47 (29.26)	68.46 (29.45)	69.32 (28.34)	72.49 (28.22)	
RMSSD	62.02 (36.79)	60.35 (36.76)	59.16 (35.90)	59.05 (34.21)	60.83 (35.38)	
CVI	4.70 (0.42)	4.67 (0.42)	4.66 (0.42)	4.68 (0.42)	4.71 (0.40)	
CSI	2.31 (0.80)	2.32 (0.81)	2.37 (0.83)	2.38 (0.82)	2.46 (0.80)	

Table 3

Correlations between each time domain metric for each interval

Measure	1	2	3	4	5
1st 2.5 min interval (minutes 0–2.5)					
1. Mean IBI	–	0.65 *	0.73 *	0.70 *	–0.52 *
2. SDNN		–	0.88 *	0.97 *	–0.38 *
3. RMSSD			–	0.97 *	–0.74 *
4. CVI				–	–0.57 *
5. CSI					–
2nd 2.5 min interval (minutes 2.5–5.0)					
1. Mean IBI	–	0.66 *	0.73 *	0.71 *	–0.51 *
2. SDNN		–	0.88 *	0.97 *	–0.37 *
3. RMSSD			–	0.96 *	–0.74 *
4. CVI				–	–0.55 *
5. CSI					–
3rd 2.5 min interval (minutes 5.0–7.5)					
1. Mean IBI	–	0.65 *	0.72 *	0.71 *	–0.54 *
2. SDNN		–	0.87 *	0.97 *	–0.34 *
3. RMSSD			–	0.96 *	–0.72 *
4. CVI				–	–0.53 *
5. CSI					–
4th 2.5 min interval (minutes 7.5–10)					
1. Mean IBI	–	0.66 *	0.73 *	0.70 *	–0.51 *
2. SDNN		–	0.88 *	0.97 *	–0.38 *
3. RMSSD			–	0.97 *	–0.73 *
4. CVI				–	–0.56 *
5. CSI					–
Full 10 min interval (minutes 0–10)					
1. Mean IBI	–	0.70 *	0.74 *	0.74 *	–0.53 *
2. SDNN		–	0.90 *	0.97 *	–0.47 *
3. RMSSD			–	0.97 *	–0.80 *
4. CVI				–	–0.65 *
5. CSI					–

*
 $p < 0.001$

Table 4

Genetic correlations among MZ and DZ twins

Metric	rMZ	rDZ
First 2.5 min interval (minutes 0–2.5)		
Mean IBI	0.53 **	0.26 **
SDNN	0.44 **	0.12
RMSSD	0.48 **	0.19 *
CVI	0.51 **	0.18 *
CSI	0.40 **	0.12
2nd 2.5 min interval (minutes 2.5–5.0)		
Mean IBI	0.57 **	0.26 **
SDNN	0.50 **	0.16 *
RMSSD	0.52 **	0.17 *
CVI	0.55 **	0.18 **
CSI	0.32 **	0.20 *
3rd 2.5 min interval (minutes 5.0–7.5)		
Mean IBI	0.61 **	0.26 **
SDNN	0.43 **	0.12
RMSSD	0.48 **	0.19 *
CVI	0.50 **	0.21 *
CSI	0.33 **	0.16 *
4th 2.5 min interval (minutes 7.5–10)		
Mean IBI	0.60 **	0.28 **
SDNN	0.42 **	0.19 *
RMSSD	0.51 **	0.21 *
CVI	0.52 **	0.25 **
CSI	0.45 **	0.24 **
Full 10 min interval (minutes 0–10)		
Mean IBI	0.59 **	0.27 **
SDNN	0.47 **	0.21 *
RMSSD	0.55 **	0.19 *
CVI	0.56 **	0.24 **
CSI	0.46 **	0.22 *

*
 $p < 0.05$;**
 $p < 0.001$

Table 5

Parameter estimates for best-fitting models for each metric at each time interval

Metric/time interval	A (95% CIs)	E (95% CIs)
Mean IBI		
1st 2.5 min	0.36 (0.21–0.49)	0.64 (0.51–0.79)
2nd 2.5 min	0.40 (0.25–0.53)	0.60 (0.48–0.75)
3rd 2.5 min	0.45 (0.30–0.57)	0.55 (0.43–0.70)
4th 2.5 min	0.46 (0.32–0.58)	0.54 (0.42–0.68)
Full 10 min	0.43 (0.28–0.55)	0.57 (0.45–0.72)
SDNN		
1st 2.5 min	0.28 (0.12–0.42)	0.72 (0.58–0.88)
2nd 2.5 min	0.30 (0.06–0.57)	0.70 (0.51–1.00)
3rd 2.5 min	0.23 (0.08–0.37)	0.77 (0.63–0.92)
4th 2.5 min	0.30 (0.14–0.44)	0.70 (0.56–0.86)
Full 10 min	0.29 (0.14–0.43)	0.71 (0.57–0.89)
RMSSD		
1st 2.5 min	0.36 (0.22–0.50)	0.64 (0.53–0.78)
2nd 2.5 min	0.38 (0.26–0.51)	0.62 (0.52–0.75)
3rd 2.5 min	0.36 (0.24–0.49)	0.64 (0.53–0.76)
4th 2.5 min	0.38 (0.25–0.52)	0.62 (0.51–0.75)
Full 10 min	0.38 (0.24–0.51)	0.62 (0.50–0.76)
CVI		
1st 2.5 min	0.37 (0.22–0.49)	0.63 (0.51–0.78)
2nd 2.5 min	0.39 (0.25–0.51)	0.61 (0.49–0.75)
3rd 2.5 min	0.37 (0.22–0.49)	0.63 (0.51–0.77)
4th 2.5 min	0.42 (0.27–0.54)	0.58 (0.46–0.73)
Full 10 min	0.41 (0.27–0.53)	0.59 (0.47–0.75)
CSI		
1st 2.5 min	0.34 (0.24–0.48)	0.66 (0.55–0.81)
2nd 2.5 min	0.34 (0.27–0.48)	0.66 (0.54–0.81)
3rd 2.5 min	0.33 (0.19–0.47)	0.67 (0.55–0.82)
4th 2.5 min	0.46 (0.32–0.60)	0.54 (0.44–0.67)
Full 10 min	0.46 (0.33–0.61)	0.54 (0.44–0.66)

Table 6
Parameter estimates (squared, standardized) for best-fitting multivariate model across all time domain metrics (confidence intervals)

Mean IBI		A22	A21	A33	A32	A31	A44	A43	A42	A41
A11										
0.51 (0.39–0.60)	–		0.54 (0.43–0.63)	–	–	0.57 (0.46–0.66)	–	–	–	0.59 (0.48–0.67)
E11	E22		E21	E33	E32	E31	E44	E43	E42	E41
0.49 (0.40–0.61)	0.05 (0.045–0.06)		0.41 (0.32–0.52)	0.05 (0.04–0.053)	0.03 (0.02–0.04)	0.36 (0.27–0.46)	0.04 (0.03–0.044)	0.02 (0.01–0.023)	0.02 (0.01–0.03)	0.34 (0.26–0.44)
SDNN										
A11	A22		A21	A33	A32	A31	A44	A43	A42	A41
0.42 (0.29–0.51)	–		0.44 (0.32–0.54)	–	–	0.37 (0.26–0.47)	–	–	–	0.43 (0.31–0.53)
E11	E22		E21	E33	E32	E31	E44	E43	E42	E41
0.59 (0.49–0.71)	0.28 (0.24–0.32)		0.29 (0.21–0.38)	0.27 (0.24–0.31)	0.07 (0.04–0.09)	0.29 (0.21–0.39)	0.23 (0.19–0.26)	0.07 (0.05–0.09)	0.05 (0.03–0.08)	0.23 (0.15–0.32)
RMSSD										
A11	A22		A21	A33	A32	A31	A44	A43	A42	A41
0.44 (0.33–0.54)	–		0.46 (0.35–0.55)	–	–	0.46 (0.35–0.55)	–	–	–	0.50 (0.39–0.60)
E11	E22		E21	E33	E32	E31	E44	E43	E42	E41
0.56 (0.46–0.67)	0.14 (0.12–0.17)		0.40 (0.31–0.50)	0.11 (0.10–0.13)	0.05 (0.04–0.07)	0.38 (0.29–0.48)	0.11 (0.09–0.13)	0.02 (0.016–0.04)	0.04 (0.03–0.06)	0.32 (0.24–0.43)
CVI										
A11	A22		A21	A33	A32	A31	A44	A43	A42	A41
0.47 (0.36–0.57)	–		0.49 (0.38–0.59)	–	–	0.47 (0.35–0.57)	–	–	–	0.50 (0.39–0.60)
E11	E22		E21	E33	E32	E31	E44	E43	E42	E41
0.53 (0.43–0.64)	0.16 (0.14–0.19)		0.35 (0.26–0.45)	0.15 (0.13–0.17)	0.05 (0.04–0.07)	0.33 (0.25–0.44)	0.13 (0.11–0.15)	0.03 (0.02–0.05)	0.04 (0.03–0.06)	0.30 (0.21–0.40)
CSI										
A11	A22		A21	A33	A32	A31	A44	A43	A42	A41
0.37 (0.25–0.48)	–		0.36 (0.25–0.47)	–	–	0.34 (0.23–0.45)	–	–	0.05 (<0.001–0.10)	0.43 (0.31–0.55)
E11	E22		E21	E33	E32	E31	E44	E43	E42	E41
0.63 (0.52–0.75)	0.40 (0.34–0.45)		0.24 (0.16–0.33)	0.35 (0.31–0.40)	0.10 (0.06–0.14)	0.21 (0.13–0.30)	0.24 (0.19–0.30)	0.05 (0.03–0.07)	0.05 (0.02–0.08)	0.18 (0.11–0.27)

Dash (–) indicates parameter was dropped from best-fitting model; parameters may not add to 1.0 due to rounding error; all lower confidence intervals > 0 but < 0.005 have been rounded to 0.01 to indicate that the parameter did not overlap with 0.

A = Additive genetic parameter estimates

E = Unique environmental parameter estimates

A 11/E11 = 1st interval; A22/E22 = 2nd interval; A33/E33 = 3rd interval; A44/E44 = 4th interval

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