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Interpreting resting heart rate variability in complex populations: the role of autonomic reflexes and comorbidities

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Abstract

Purpose—Resting heart rate variability (HRV) is an important biomarker linking mental health to cardiovascular outcomes. However, resting HRV is also impaired in autonomic neuropathy, a common and underdiagnosed complication of common medical conditions which is detected by testing autonomic reflexes. We sought to describe the relationship between autonomic reflex abnormalities and resting HRV, taking into consideration medical comorbidities and demographic variables.

Methods—Participants (n = 209) underwent a standardized autonomic reflex screen which was summarized as the Composite Autonomic Severity Score (CASS) and included measures of reflexive HRV, e.g., heart rate with deep breathing (HRDB). Resting HRV measures were: pNN50 (percentage of NN intervals that differ by > 50 ms) and cvRMSSD (adjusted root mean square of successive differences).

Results—In univariate analyses, lower resting HRV was associated with: older age, higher CASS, neuropathy on examination, hypertension, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, and psychiatric disease. Adaptive regression spline analysis revealed that HRDB explained 27% of the variability in resting HRV for participants with values of HRDB in the normal range. Outside this range, there was no linear relationship because: (1) when HRDB was low (indicating autonomic neuropathy), resting HRV was also low with low variance; and (2)

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All human and studies have been approved by the appropriate ethics committee and therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

when HRDB was high, the variance in resting HRV was high. In multivariate models, only HRDB was significantly independently associated with cvRMSSD and pNN50.

Conclusion—Subclinical autonomic neuropathy, as evidenced by low HRDB and other autonomic reflexes, should be considered as a potential confounder of resting HRV in research involving medically and demographically diverse populations.

Keywords

Heart rate variability; Autonomic function; Composite autonomic severity score; CASS; Neuropathy; Neurovisceral integration

Introduction

Heart rate variability (HRV) is the variation in time between sequential heart beats, measured as the R-R interval [1]. It is a reflection of the complex interaction of the heart, brain, and autonomic nervous system, and low resting HRV has been associated with poor cardiovascular outcomes[2-6], vascular disease[7, 8], and psychiatric disorders such as schizophrenia, depression, anxiety, post-traumatic stress disorder, and obsessive–compulsive disorder [9-15]. Within a given individual, resting HRV is also state-dependent, for example, worsening during panic attacks [9], and with increased severity of depression [16]. A model of neurovisceral integration has been developed to explain these relationships, whereby dysregulation of parasympathetic efferent pathways originating from the pre-frontal cortex results in a reduced ability to adapt to environmental, physiological, behavioral, and emotional challenges [11, 17].

Extensive experimental evidence supports the validity of the neurovisceral integration model [11, 17, 18]. However, it is currently unknown how dysfunction in autonomic pathways from other non-psychiatric causes, for example, subclinical autonomic neuropathy due to common systemic diseases, such as diabetes mellitus or HIV [19, 20] [21], might confound the relationship between resting HRV and psychiatric disorders and symptoms. If undiagnosed autonomic neuropathy explains a significant amount of the variance in resting HRV in medically complex populations, then this would reduce the utility of resting HRV as a state-sensitive biomarker, unless such confounders are properly accounted for. In both clinical and research settings, autonomic neuropathy is typically quantified by an autonomic reflex screen, which includes measures of reflexive HRV and sympathetically-mediated reflexes quantified by changes in blood pressure and sweat output in response to standardized stimuli [22]. Such testing is necessary to convincingly confirm or refute a diagnosis of autonomic neuropathy, given that autonomic neuropathy is commonly asymptomatic, and that symptoms, when present, are often non-specific. However, autonomic reflexes are rarely assessed in studies utilizing resting HRV as a biomarker.

Comprehensive autonomic reflex screens and markers of resting HRV have been employed together infrequently in the psychiatric literature. For example, in schizophrenia, a condition in which autonomic dysfunction has been a topic of significant focus [23], to our knowledge other than our own work [24], only two studies by Liu and colleagues have included measurement of an autonomic reflex (heart rate response to deep breathing)

[14, 25], and none have included a comprehensive autonomic reflex screen. To our knowledge, comprehensive autonomic screens and markers of resting HRV have been explicitly compared only in healthy controls and people with diabetes [22, 26-28], excluding those with known neurologic disease, or other common medical co-morbidities [29, 30]. Moreover, these relationships have not been examined in racially and ethnically diverse populations, which is likely important given prior literature indicating disparities in resting HRV [31, 32].

We undertook the present study to understand the importance of autonomic reflex abnormalities and demographic, medical, and neurologic factors as potential confounds in the interpretation of resting HRV as a biomarker. We hypothesized that markers of reflexive HRV would be associated with markers of resting HRV, but that the relationship might vary depending on the amount of reflexive HRV. We further hypothesized that age, medical comorbidities, evidence of peripheral nervous system (PNS), or central nervous system (CNS) dysfunction on neurologic examination, and dysfunction of sympathetic autonomic reflexes might contribute significantly to variance in resting HRV.

Methods

Participants

Data for this analysis were pooled from two studies with a total of 209 adult participants. All procedures to collect these data were performed under protocols approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai, and all participants provided written informed consent. A total of 114 participants were people living with HIV who were enrolled in a study examining the prevalence of autonomic dysfunction in this patient population, and 95 participants were enrolled from a general neurology clinic for a study examining the relationship between autonomic symptoms, medical comorbidities, and autonomic function testing [33-35]. Both studies were conducted contemporaneously using identical recruitment techniques, enrolling sequential willing and eligible participants from clinic waiting rooms in the same building at an urban academic center. Both clinics serve the same communities; however one clinic specializes in primary care for people living with HIV and the other in general neurology. The inclusion criteria for both studies were age greater than 18 years old, English speaking, and able to tolerate the autonomic testing; the only difference was that,, for the HIV-clinic-based study, participants had to have documented evidence of HIV. The exclusion criteria for both studies were identical, and pertained to the safety of performing the autonomic function testing and the ability to interpret the results. They included history of uncontrolled glaucoma, aortic stenosis, myocardial infarction within 6 months, retinopathy, unclipped cerebral aneurysm, cardiac arrhythmias, or pacemaker implantation.

Autonomic testing procedures

A standardized autonomic reflex screen (WR Medical Electronics, Maplewood, MN, USA) was performed, including: quantitative sweat testing (Q-Sweat), heart rate response to deep breathing (HRDB), heart rate (HR), and blood pressure (BP) response to the Valsalva maneuver (VM), and HR and BP response to tilt table testing [27, 36, 37]. For Q-Sweat,

sweat output is measured in four standardized locations, in response to iontophoresis of acetylcholine into the skin. For HRDB, VM, and tilt table testing, BP (Nexfin system; www.bmeye.com) and a 3-lead surface electrocardiogram were monitored continuously during: VM (participant directed to exhale to a pressure of 40 mmHg for 15 s); a standardized deep breathing exercise consisting of six rhythmic breaths paced by an electronic metronome; and a tilt table test for which the participant rested in the supine position for 5 min before being brought to an upright position for 10 min (as tolerated).

Calculation of autonomic indices

Two markers of reflexive HRV were calculated, HRDB and Valsalva ratio (VR), where HRDB is the difference between the highest and lowest HR in each breath cycle averaged over six consecutive breaths, and VR is the ratio of the highest to lowest HR measured during and immediately after release of VM. The validated Composite Autonomic Severity Score (CASS) was used as an overall measure of autonomic reflexive function. The CASS is comprised of three subscores (cardiovagal, adrenergic, and sudomotor) [27, 36, 37]. The cardiovagal subscore is based on the HRDB and VR; the adrenergic subscore is based on BP changes during VM and tilt table testing; and the sudomotor subscore is based on the Q-Sweat.

Measures of resting HRV were calculated using the resting heart rate data from the first 5 min of the tilt table test recording, where the participant was supine and resting quietly. Given that the tilt table is the last test performed in this autonomic battery, the participant has been supine for at least 40 min at this time. Using the RHRV package in R, the data was filtered in two stages, using the package's standard parameters, which are as follows [38-42]. First, all heart rates clearly outside of the physiologic resting range for adults are removed (25–180 beats per minute) [39]. Next, non-physiologic changes in heart rate are removed, defined as any rate that was greater than 50% above the mean of the 10 preceding rates. In addition to these standard procedures, a Hampel filter [43, 44] was used to remove beats that were 3 median absolute deviations away from the median value of a 5-beat window, because visual inspection revealed remaining artifactual heart rates following the first two steps. Following this final automated filtering step, the data were visually reinspected for any additional artifactual heart rates. Data were then interpolated to replace removed values using the method of locally estimated scatterplot smoothing. We calculated two summary measures of these data: the heart rate adjusted root mean square of successive differences between normal heartbeats (cvRMSSD), which is defined as 100 × (RMSSD/median RR interval), and the percentage of NN intervals that are different by more than 50 ms (pNN50) [45]. There are numerous methods of quantifying resting HRV [6], and analysis using frequency domains was initially considered. However, pNN50 and cvRMSSD were ultimately chosen as our resting HRV variables, because they do not require specialized or proprietary software to compute, and are therefore more generally accessible [10].

Additional measures

All participants underwent a comprehensive neurologic examination, including the motor portion (part 3) of the United Parkinson's Disease Rating Scale (UPDRS), which was used

as a marker for CNS dysfunction [46]. Additionally, distal sensory polyneuropathy (DSP) was diagnosed using clinical criteria of two of the following three signs on neurologic exam: (1) ankle reflexes absent or reduced as compared to the knee; (2) reduced distal sharp sensation; and (3) reduced distal vibration sensation [47]. The presence of relevant medical comorbidities was established by review of the electronic health record using a standardized case report form across both studies.

Statistical analysis

Spearman's rank correlation was performed for the resting HRV measures (cvRMSSD and pNN50) and (1) age, (2) the reflexive HRV measures (HRDB and VR), (3) the UPDRS, and (4) the CASS. Wilcoxon rank sum tests were used to assess the association of cvRMSSD and pNN50 with (1) DSP on neurologic examination, (2) comorbidities, and (3) the presence of abnormal CASS adrenergic and sudomotor subscores (the cardiovagal subscore was omitted as redundant because it is comprised of HRDB and VR). The test reports the median difference between the groups and 95% confidence intervals for significance.

For subsequent analyses, we focused on HRDB as the measure of reflexive HRV. Adaptive regression splines were used to analyze the relationship between HRDB and markers of resting HRV. This method was chosen because of its ability to model relationships which vary based on the value of the independent variable (i.e., HRDB). The method identifies threshold values of the independent variables (i.e., knots) which define regions, and then fits individual linear regressions (i.e., splines) to each region. This is a recursive process which uses cross-validation to optimize the number of knots.

Multivariate models were used to assess whether associations of variables with resting HRV found in univariate analyses were independent of one another. Given skewness in the data, cvRMSSD was log-transformed prior to use in a linear regression model. Ordinal logistic regression was used for pNN50 divided into three groups: zero, and below and above the median value. The Brant test ($p > 0.05$) was used to test the proportional odds assumption. Bivariate assessment was conducted using Chi-square, and Fisher's exact tests where necessary before fitting the regression models. Additionally, model diagnostics were used to assess overfitting and variance inflation factor for multi-collinearity. The sample size was based on the available data. However 209 participants provided 99% power to detect a correlation of 0.45 at a 0.05 significance level.

Results

Participant characteristics

A total of 105 (50.24%) female and 104 (49.76%) male participants were included in this study (see Table 1). The mean age was 50 (IQR 41, 57) years. Participants (n = 209) were predominantly Black/African-American (49.76%, $n = 104$) and Hispanic/Latinx (39.23%, $n = 82$). Medical comorbidities were common (see Table 1), especially hypertension (45.85%), chronic liver disease (including hepatitis B or C infection, other chronic hepatitis, and cirrhosis) (29.19%), and diabetes (19.14%). There was a high prevalence of psychiatric disease (45.5%), including anxiety, depression, and trauma-related, bipolar, and psychotic

disorders. Given the recruitment sites, both HIV and neurologic disorders were also highly prevalent. On neurologic examination, DSP was found in 38.76%. Of the participants, 43% had a UPDRS of zero (i.e., completely normal), and 97% scored < 15 on the UPDRS, which correlates with complete independence of activities of daily living [46].

Effects of filtering and correction procedures on indices of resting HRV

The filtering and correction procedures applied to the raw ECG data prior to calculating the measures of resting HRV overall resulted in modest changes. For pNN50, the mean difference between original and filtered values was 1.11 (SE = 0.28) which represents a median percent change of zero (IQR = – 1.81, 0.30%). Similarly for cvRMSSD, the mean difference between original and filtered values was 2.78 (SE = 0.70) which represents a median percent change of – 0.05% (IQR = – 4.74, 0.11%). Visual inspection of the distribution of cvRMSSD and PNN50 data before and after correction revealed two participants who had a particularly large change in cvRMSSD and no such outliers for PNN50. Examination of the raw ECG data for these two participants revealed that the filtering procedure had correctly removed data that was consistent with motion artifact. Thus, these individuals were included in the analyses.

Univariate analyses

Univariate analyses are shown in Table 2 for continuous measures and in Table 3 for non-continuous measures. As expected, age was negatively correlated with cvRMSSD and pNN50. There was no difference in cvRMSSD or pNN50 between sexes. Black/African-American participants had numerically higher markers of resting HRV, e.g., a pNN50 of 7.66 versus 3.17 and 2.63, respectively, in the Hispanic/Latinx and White/Asian/Other groups; however, this was not statistically significant. With regard to neurologic examination findings, cvRMSSD and pNN50 were significantly lower in participants with DSP, and there was a trend for lower cvRMSSD and pNN50 among participants with higher (i.e., more abnormal) UPDRS scores. However, a chart-derived diagnosis of a neurologic disease (CNS or PNS) was not associated with cvRMSSD or pNN50. We also observed significantly lower markers of resting HRV in association with most of the medical comorbidities (see Table 3), including a marginal association for the presence of psychiatric disease.

Several aspects of the autonomic reflex screen were associated with measures of resting HRV (Tables 2, 3); unsurprisingly, the strongest associations were with measures of reflexive HRV. In the overall study population, both cvRMSSD and pNN50 had moderate correlation with HRDB, in the expected direction (rho = 0.50, $p < 0.0001$, rho = 0.53, $p < 0.0001$, respectively), and also moderate correlation with VR in the expected direction. Additionally, lower RMSSD and pNN50 were associated with the total CASS score. An abnormal adrenergic subscore was significantly associated with lower pNN50 and a similar non-significant trend was seen for cvRMSSD. The sudomotor subscore was not associated with cvRMSSD or pNN50.

Adaptive regression spline model

Adaptive regressive spline models for cvRMSSD (Fig. 1) and pNN50 as functions of HRDB produced knots which approximated the range of expected normal HRDB values for the age

group in this study, with knots at 11.6 and 32.2 for cvRMSSD and at 12.3 and 33.5 for pNN50. Within these ranges, cvRMSSD and pNN50 both increased linearly with HRDB, with a slope of 1.16 and 1.26, respectively (i.e., estimated increase in pNN50 or cvRMSSD for each unit increase in HRDB), with HRDB explaining 27% of the variability for both cvRMSSD and pNN50 (i.e., $R^2 = 0.27$). At values of HRDB below this range, the model showed no relationship between HRDB and cvRMSSD or pNN50. At values of HRDB above this range, the models actually predicted an inverse relationship between HRDB and cvRMSSD/pNN50 (slopes of – 4.21 and – 4.53, respectively). However, this should be interpreted with caution, given the small number of observations in this range and the presence of three outliers with high HRDB and low cvRMSSD/pNN50. Moreover, at higher values of HRDB, there was greater variability in the markers of resting HRV. For example, the standard deviation of pNN50 increased by 0.51 (± 0.08) as HRDB increased.

Multivariate models

HRDB and the covariates identified as significant in univariate analyses (see Table 3) were entered into a multivariate linear regression model with log cvRMSSD as the outcome variable, and into an ordinal regression model with pNN50 as the outcome variable. Only HRDB remained significant in both models (see Table 4). In the linear regression model every unit increase in HRDB resulted in a 0.033 increase in log cvRMSSD explaining – 20% of the variance. The ordinal regression model predicted that as HRDB increases by one unit the likelihood of a pNN50 score greater than 4.9 increased by 1.12 (1.08, 1.16).

Discussion

A significant literature supports the role of resting HRV as an index of self-regulatory ability in the service of goal-directed behavior [17, 32, 48]. However, this interpretation depends upon the structural integrity of the underlying autonomic pathways. This is a very reasonable assumption in younger, medically healthy people. However, it bears closer examination in diverse populations including older patients and those who are medically and/or neurologically complex. In such populations, degeneration of structures of the central autonomic network is still expected to be rare enough so as not to warrant specific attention; however, subclinical dysfunction of peripheral autonomic structures, i.e., autonomic neuropathy, is fairly common. Both resting HRV (i.e., pNN50, cvRMSSD) and reflexive HRV (i.e., HRDB) are essentially measures of responsiveness of the sinus node to neural outflow, either at rest or during a specific stimulus, respectively. However, there are subtle but important differences. In contrast to resting HRV, autonomic reflexes, which are used to quantify autonomic neuropathy, are not strongly influenced by cortical inputs given (1) the neuroanatomy involving primarily peripheral nerve and brainstem structures, and (2) the use of standardized physical maneuvers to evoke the reflex which would be expected to overwhelm more subtle cortical inputs.

In the current study, we sought to understand how resting HRV might be influenced by demographic, neurologic,and medical factors, focusing on autonomic neuropathy as quantified by autonomic reflexes. In univariate analyses, we found that lower resting HRV was associated with markers of autonomic neuropathy, especially decreased reflexive HRV,

but also the total CASS score and adrenergic CASS subscore. In addition, consistent with prior literature, many of the other factors we studied were associated with one or more of the resting HRV indices in univariate analyses, including age, DSP on neurological examination, the presence of psychiatric disease, hypertension, DSP, diabetes, COPD, and CKD [26, 29, 49-51].

Some of the results of this study were to be expected; however, there are relatively few prior studies examining associations between autonomic reflexes and resting HRV. Perhaps the largest group of such studies was published from 1988 to 2003, and took the perspective of validating the then more newly developed spectral analyses of resting HRV against autonomic reflex screens [22, 27, 28, 30, 50, 52]. Autonomic reflexes have also occasionally been measured in studies of HRV in psychiatric conditions. One study found that HRDB was reduced in patients with schizophrenia and their first degree relatives as compared to healthy controls [25]. Relationships between measures of resting HRV and demographic factors (without measurement of autonomic reflexes) have been more commonly described [26, 50, 51, 54]. For example, resting HRV decreases as age increases, which may be due to a decline in both parasympathetic activity and sympathetic activity [51, 54].

Subsequent analyses provided additional context as to the importance of HRDB in the interpretation of resting HRV. The adaptive regression models revealed that, for values of HRDB below approximately 12, which approximates the lower limit of normal for HRDB in the age range under study, resting HRV was also generally low. Thus, for participants in this range, resting HRV is unlikely to be a useful behavioral biomarker, because dysfunction of the more distal vagal pathway limits the responsiveness of heart rate to cortical influences [17, 18]. At HRDB values over 12, a fairly linear relationship between HRDB and resting HRV was observed, with HRDB explaining a moderate portion of the variance in the measures of resting HRV, indicating that, in this range, a significant portion of the variance in resting HRV is due to other unmeasured factors (e.g., cortical inputs) [17, 18]. Moreover, at the highest levels of HRDB (indicating unequivocally normal subcortical and peripheral vagal function), we observed significantly more variance in the resting HRV measures, indicating that, for these participants, HRDB has little relationship to resting HRV. Multivariate models indicated that demographic, psychiatric, and medical factors are not associated with resting HRV independent of HRDB. This is likely because many of these factors are associated with autonomic neuropathy (represented in the multivariate model by HRDB) and do not have additional independent effects on resting HRV. The exception to this is psychiatric disease, which would not be expected to be associated with autonomic neuropathy. In the univariate analysis, the presence of psychiatric disease was associated with lower pNN50 and a trend towards lower cvRMSSD, associations which did not persist in the multivariate model. These findings are in keeping with the body of literature which demonstrates lower resting HRV in psychiatric disease, and also with our hypothesis that these more subtle cortical inputs can be readily overshadowed by autonomic reflexes evoked by physical maneuvers.

This study has limitations. First, there were multiple limitations related to this being secondary analysis. Brown et al. previously showed that differences in breathing frequency while recording resting HRV may be an important confounder [55]. We did not control

for the variation in respiratory rate in this study, although all participants were resting quietly. Next, a lack of detailed psychiatric information, including symptoms at the time of the autonomic testing, limited our ability to address the important question of how much of the remaining variance in measures of resting HRV (i.e., not explained by HRDB) is attributable to psychiatric or psychological factors. Also, these are pooled data from two studies, and, although both samples are drawn from the same general population, by definition one group were people living with HIV while the other had a neurologic disorder or symptoms. Additionally, these two groups are comparable with respect to our main predictor and outcomes; however, significant differences are observed for race, ethnicity, and a few comorbidities. Finally, a control group consisting of healthy participants from the community could have provided additional information about the relationship between resting and reflexive HRV. Future studies would benefit from adding these data.

Our study population is likely enriched for autonomic neuropathy. This was advantageous, because it allowed for better characterization of how resting HRV behaves when HRDB is low, which may not have been possible in a community-based sample; however, it limits generalizability. Next, HRV may have additional input from other reflexes that exist outside the sinus node, such as the baroreflex, and this should be considered in future studies [56]. Finally, there are participants who had low HRDB and higher markers of resting HRV. This likely represents poor effort with the HRDB task, highlighting a limitation in reflexive measures, i.e., that they require cooperation.

Conclusions

This study demonstrates that, in diverse medically and neurologically complex populations, knowledge of the function of peripheral autonomic pathways is necessary to properly interpret the significance of resting HRV as a behavioral biomarker. Thus, ideally, measurement of resting HRV should be accompanied by an autonomic reflex screen in these populations, and interpreted as a behavioral biomarker only after autonomic neuropathy has been convincingly excluded. If resources to assess autonomic reflexes are not available, at a minimum a careful medical history should be obtained, and relevant comorbidities (e.g., DSP, HTN, DM, COPD, CKD, liver disease) included as covariates. Future studies using combined measures of resting and reflexive HRV might be able to better localize dysfunction along the vagal pathways, enhancing understanding of their role in health and disease.

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References

1. McCraty R, Shaffer F (2015) Heart rate variability: new perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. Glob Adv Health Med 4(1):46–61
2. Kleiger RE et al. (1987) Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59(4):256–262 [PubMed: 3812275]

3. Fang SC, Wu YL, Tsai PS (2020) Heart rate variability and risk of all-cause death and cardiovascular events in patients with cardiovascular disease: a meta-analysis of cohort studies. Biol Res Nurs 22(1):45–56 [PubMed: 31558032]
4. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task force of the European society of cardiology and the North American society of pacing and electrophysiology. Circulation (1996) 93(5): 1043–65 [PubMed: 8598068]
5. Steger A et al. (2019) Polyscore of Non-invasive Cardiac Risk Factors. Front Physiol 10:49 [PubMed: 30778303]
6. Sassi R et al. (2015) Advances in heart rate variability signal analysis: joint position statement by the e-cardiology ESC working group and the european heart rhythm association co-endorsed by the Asia Pacific heart rhythm society. Europace 17(9):1341–1353 [PubMed: 26177817]
7. Carthy ER (2014) Autonomic dysfunction in essential hypertension: a systematic review. Ann Med Surg (Lond) 3(1):2–7 [PubMed: 25568776]
8. Palatini P, Julius S (2009) The role of cardiac autonomic function in hypertension and cardiovascular disease. Curr Hypertens Rep 11(3):199–205 [PubMed: 19442329]
9. Chalmers JA et al. (2014) Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. Front Psychiatry 5:80 [PubMed: 25071612]
10. Shaffer F, Ginsberg JP (2017) An overview of heart rate variability metrics and norms. Front Public Health 5:258 [PubMed: 29034226]
11. Thayer JF, Yamamoto SS, Brosschot JF (2010) The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 141(2):122–131 [PubMed: 19910061]
12. Lampert R et al. (2008) Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. Am Heart J 156(4):759.e1–7
13. Clamor A et al. (2016) Resting vagal activity in schizophrenia: meta-analysis of heart rate variability as a potential endophenotype. Br J Psychiatry 208(1):9–16 [PubMed: 26729841]
14. Liu Y et al. (2021) Altered heart rate variability in patients with schizophrenia during an autonomic nervous test. Front Psychiatry 12:626991 [PubMed: 33912081]
15. Benjamin BR et al. (2021) Heart rate variability is associated with disease severity in psychosis spectrum disorders. Prog Neuropsychopharmacol Biol Psychiatry 111:110108 [PubMed: 32946948]
16. Agelink MW et al. (2002) Relationship between major depression and heart rate variability clinical consequences and implications for antidepressive treatment. Psychiatry Res 113(1–2):139–49 [PubMed: 12467953]
17. Thayer JF, Lane RD (2000) A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord 61(3):201–216 [PubMed: 11163422]
18. Smith R et al. (2017) The hierarchical basis of neurovisceral integration. Neurosci Biobehav Rev 75:274–296 [PubMed: 28188890]
19. Askgaard G et al. (2011) Decreased heart rate variability in HIV positive patients receiving antiretroviral therapy: importance of blood glucose and cholesterol. PLoS ONE 6(5):e20196 [PubMed: 21655281]
20. Benseñor IM et al. (2011) Heart rate variability in HIV patients, diabetics, and controls: the AGATAA study. ISRN Vasc Med 2011:876864
21. Lebech AM et al. (2007) Autonomic dysfunction in HIV patients on antiretroviral therapy: studies of heart rate variability. Clin Physiol Funct Imaging 27(6):363–367 [PubMed: 17944658]
22. Pagani M et al. (1988) Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. J Auton Nerv Syst 23(2):143–153 [PubMed: 3049759]
23. Stogios N et al. (2021) Autonomic nervous system dysfunction in schizophrenia: impact on cognitive and metabolic health. npj Schizophrenia 7(1):22 [PubMed: 33903594]
24. Joe PCJ, Piras E, Wallach DS, Robinson-Papp J, Boka E, Brooke Remsen B, Bonner M, Goetz D, Hoffman K, Lee J, Fendrich S, Gonen O, Malaspina D (2021) An integrative study of the microbiome gut-brain-axis and hippocampal inflammation in psychosis: persistent effects from mode of birth. Schizophrenia Res. 10.1016/j.schres.2021.09.019

25. Liu YW et al. (2016) Reduced cardiac autonomic response to deep breathing: a heritable vulnerability trait in patients with schizophrenia and their healthy first-degree relatives. Psychiatry Res 243:335–341 [PubMed: 27442977]
26. Agelink MW et al. (2001) Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. Clin Auton Res 11(2):99–108 [PubMed: 11570610]
27. Freeman R et al. (1991) Spectral analysis of heart rate in diabetic autonomic neuropathy a comparison with standard tests of autonomic function. Arch Neurol 48(2):185–90 [PubMed: 1993010]
28. Sega S, Jager F, Kiauta T (1993) A comparison of cardiovascular reflex tests and spectral analysis of heart rate variability in healthy subjects. Clin Auton Res 3(3):175–182 [PubMed: 8400817]
29. Gerritsen J et al. (2003) Measures of cardiovascular autonomic nervous function: agreement, reproducibility, and reference values in middle age and elderly subjects. Diabetologia 46(3):330–338 [PubMed: 12687330]
30. Ewing DJ et al. (1991) Twenty four hour heart rate variability: effects of posture, sleep, and time of day in healthy controls and comparison with bedside tests of autonomic function in diabetic patients. Br Heart J 65(5):239–244 [PubMed: 2039667]
31. Sharpee TO et al. (2016) 25th Annual Computational Neuroscience Meeting: CNS-2016. BMC Neurosci 17(Suppl 1):54 [PubMed: 27534393]
32. Neblett EW Jr, Roberts SO (2013) Racial identity and autonomic responses to racial discrimination. Psychophysiology 50(10):943–53 [PubMed: 23889076]
33. Robinson-Papp J et al. (2013) Autonomic dysfunction is common in HIV and associated with distal symmetric polyneuropathy. J Neurovirol 19(2):172–180 [PubMed: 23580249]
34. Robinson-Papp J, Sharma SK (2013) Autonomic neuropathy in HIV is unrecognized and associated with medical morbidity. AIDS Patient Care STDS 27(10):539–543 [PubMed: 24032624]
35. Robinson-Papp J et al. (2017) Assessment of autonomic symptoms in a medically complex, urban patient population. Clin Auton Res 27(1):25–29
36. Low PA (1993) Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc 68(8):748–752 [PubMed: 8392653]
37. Spiers JP et al. (1993) Time and frequency domain assessment of heart rate variability: a theoretical and clinical appreciation. Clin Auton Res 3(2):145–158 [PubMed: 8324377]
38. Niskanen J-P et al. (2004) Software for advanced HRV analysis. Comput Methods Programs Biomed 76(1):73–81 [PubMed: 15313543]
39. Rodríguez-Liñares L, Vila XA, Méndez AJ, Lado MJ, Olivieri D (2008) R-HRV: An R-based software package for heart rate variability analysis of ECG recordings. In 3rd iberian conference in systems and information technologies (CISTI 2008). Ourense, Spain, p 565–574
40. Tarvainen MP, Ranta-aho PO, Karjalainen PA (2002) An advanced detrending method with application to HRV analysis. IEEE Trans Biomed Eng 49(2):172–175 [PubMed: 12066885]
41. Mateo J, Laguna P (2003) Analysis of heart rate variability in the presence of ectopic beats using the heart timing signal. IEEE Trans Biomed Eng 50(3):334–343 [PubMed: 12669990]
42. Osman HA, Eid M, Saddik AE (2015) A pattern-based windowed impulse rejection filter for nonpathological HRV artifacts correction. IEEE Trans Instrum Meas 64(7):1944–1957
43. Pearson RK et al. (2016) Generalized hampel filters. EURASIP J Adv Signal Process 2016(1):87
44. Ghaleb FA et al. (2018) Two-stage motion artefact reduction algorithm for electrocardiogram using weighted adaptive noise cancelling and recursive hampel filter. PLoS ONE 13(11):e0207176 [PubMed: 30457996]
45. de Geus EJC et al. (2019) Should heart rate variability be “corrected” for heart rate? biological, quantitative, and interpretive considerations. Psychophysiology 56(2):e13287 [PubMed: 30357862]
46. Fahn S, Elton RL (1987) UPDRS program members. Unified Parkinsons Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Caine DB (eds) Recent developments in Parkinson’s disease, vol 2. Macmillan Healthcare Information, Florham Park, pp 153–163

47. Cornblath DR et al. (1999) Total neuropathy score: validation and reliability study. Neurology 53(8):1660–1664 [PubMed: 10563609]
48. Rajendra Acharya U et al. (2006) Heart rate variability: a review. Med Biol Eng Comput 44(12):1031–1051 [PubMed: 17111118]
49. Sinnreich R et al. (1998) Five minute recordings of heart rate variability for population studies: repeatability and age-sex characteristics. Heart 80(2):156–162 [PubMed: 9813562]
50. Umetani K et al. (1998) Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol 31(3):593–601 [PubMed: 9502641]
51. Voss A et al. (2015) Short-term heart rate variability–influence of gender and age in healthy subjects. PLoS ONE 10(3):e0118308 [PubMed: 25822720]
52. Ewing DJ (1991) Heart rate variability: an important new risk factor in patients following myocardial infarction. Clin Cardiol 14(8):683–685 [PubMed: 1914273]
53. Masaoka S et al. (1985) Heart rate variability in diabetes: relationship to age and duration of the disease. Diabetes Care 8(1):64–68 [PubMed: 3971850]
54. O'Brien IA, O'Hare P, Corrall RJ (1986) Heart rate variability in healthy subjects: effect of age and the derivation of normal ranges for tests of autonomic function. Br Heart J 55(4):348–354 [PubMed: 3964501]
55. Brown TE et al. (1993) Important influence of respiration on human R-R interval power spectra is largely ignored. J Appl Physiol (1985) 75(5):2310–7 [PubMed: 8307890]
56. de Moura-Tonello SC et al. (2016) Cardiovascular variability analysis and baroreflex estimation in patients with type 2 diabetes in absence of any manifest neuropathy. PLoS ONE 11(3):e0148903 [PubMed: 26987126]

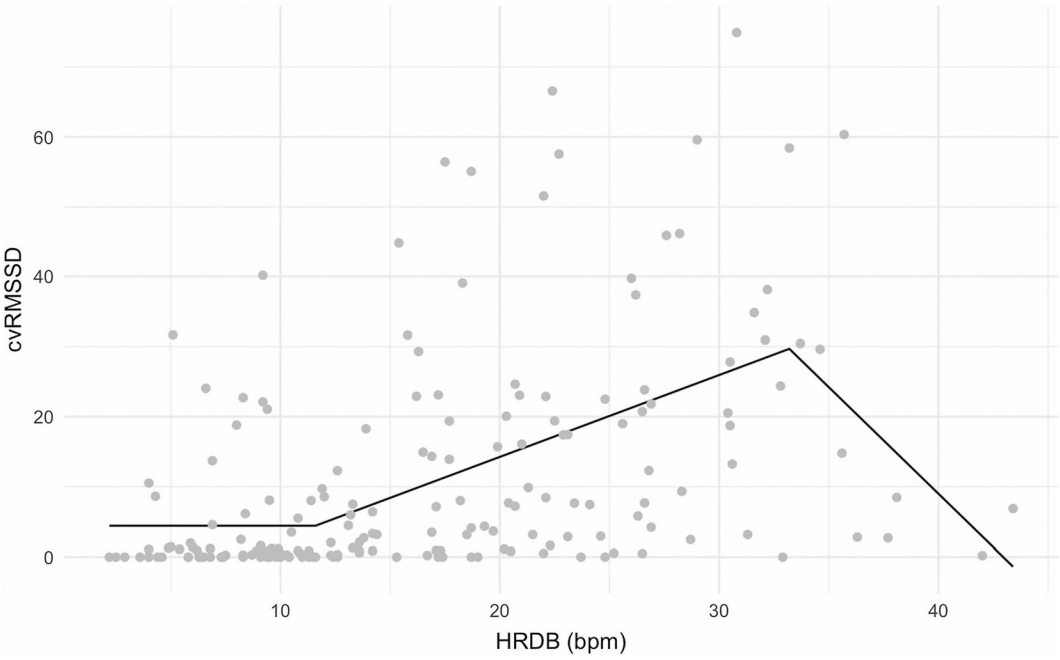

Fig. 1.

Relationship between HRDB [a measure of reflexive HRV in beats per minute (bpm)) and cvRMSSD (a measure of resting HRV). The *solid line* represents the prediction of the adaptive regression spline model. *cvRMSSD* the heart rate adjusted root mean square of successive differences between normal heartbeats, *HRDB* heart rate with deep breathing (in bpm)

Table 1

Participant characteristics (n = 209)[a]

Age, years	50 (41.00, 57.00)
Sex	
Female	105 (50.24%)
Male	104 (49.76%)
Race/ethnicity	
Black	104 (49.76%)
Hispanic	82 (39.23%)
Non-Hispanic white	18 (8.61%)
Asian	2 (0.96%)
Other	3 (1.44%)
Comorbidities	
Hypertension	94 (45.85%)
Diabetes	40 (19.14%)
Cardiovascular disease[b]	22 (10.53%)
Hyperlipidemia	58 (28.28%)
Obesity	31 (15.12%)
COPD	21 (10.05%)
HIV	114 (54.55%)
Chronic kidney disease	20 (9.57%)
Chronic liver disease[c]	61 (29.19%)
Rheumatologic disorders	36 (17.22%)
Neurologic disorders	149 (71.3%)
CNS[d]	96 (45.9%)
PNS[e]	81 (38.8%)
Psychiatric disorders	95 (45.5%)
Neurologic examination	
Distal sensory polyneuropathy	81 (38.76%)
UPDRS normal	90 (43%)

UPDRS United Parkinson's Disease Rating Scale, an indicator of abnormal neurologic examination finding referable to the central nervous system, *COPD* chronic obstructive pulmonary disease, *CNS* central nervous system, *PNS* peripheral nervous system

[a] Values are median (interquartile range) or frequency (percentage)

[b] Includes coronary artery disease, congestive heart failure, myocardial infarction, peripheral vascular disease, and arrhythmia

[c] Includes hepatitis B, hepatitis C, other chronic hepatitis and cirrhosis

[d] Includes epilepsy, headache, memory disorders, movement disorders, multiple sclerosis, stroke, traumatic brain injury, vertigo

[e] Includes myopathy, neuromuscular junction disorders, peripheral neuropathies, radiculopathy

Table 2

Univariate correlation coefficients (Spearman's rho) for cvRMSSD and pNN50 and with participant factors (continuous variables)

Variable	cvRMSSD	pNN50
Age	− 0.2160077 ($p = 0.001682$)	− 0.2547 ($p = 0.0002$)
HRDB	0.4978859 ($p < 0.001$)	0.5266 ($p < 0.0001$)
VR	0.4599434 ($p < 0.001$)	0.4450 ($p < 0.0001$)
CASS	− 0.2838831 ($p < 0.001$)	− 0.3063 ($p < 0.0001$)
UPDRS	− 0.1259396 ($p = 0.06922$)	− 0.1252 ($p = 0.0708$)

HRDB heart rate response to deep breathing, *VR* valsalva ratio, *CASS* Composite Autonomic Severity Score, *UPDRS* United Parkinson's Disease Rating Scale

Table 3

Association of RMSSD and pNN50 with participant factors (categorical variables)

	Median cvRMSSD (IQR)	cvRMSSD *p* value	Median pNN50 (IQR)	pNN50 *p* value
Sex		$p = 0.230$		$p = 0.630$
Male	2.99 (2.02, 4.84)		4.42 (0.54, 19.04)	
Female	3.22 (2.40, 5.36)		6.10 (0.61, 22.12)	
Race/ethnicity		$p = 0.487$		$p = 0.450$
Black/African-American	3.81 (2.46, 5.47)		7.66 (0.87, 22.21)	
Hispanic/latinx	2.88 (1.99, 4.26)		3.17 (0.38, 14.48)	
White/Asian/other	2.85 (1.82, 4.01)		2.63 (0.29, 18.71)	
DSP		$p = 0.002$		$p = 0.001$
Absent	3.52 (2.44, 5.42)		7.66 (0.90, 22.80)	
Present	2.78 (1.62, 4.25)		2.03 (0, 13.78)	
Adrenergic subscore[a]		$p = 0.101$		$p = 0.010$
Normal	3.69 (2.53, 5.20)		8.49 (2.22, 27.09)	
Abnormal	3.05 (1.95, 5.17)		4.22 (0.35, 17.39)	
Sudomotor subscore[a]		$p = 0.959$		$p = 0.647$
Normal	3.22 (1.86, 5.09)		5.90 (0, 21.59)	
Abnormal	3.14 (2.14, 5.17)		4.64 (0.80, 19.15)	
Hypertension		$p = 0.029$		$p = 0.003$
Absent	3.51 (2.20, 5.40)		7.67 (0.82, 23.36)	
Present	2.97 (1.81, 4.61)		2.35 (0.25, 13.23)	
Diabetes		$p = 0.069$		$p = 0.016$
Absent	3.39 (2.25, 5.17)		6.87 (0.82, 20.73)	
Present	2.94 (1.53, 4.48)		1.37 (0, 13.12)	
COPD		$p = 0.049$		$p = 0.019$
Absent	3.38 (2.12, 5.23)		6.12 (0.62, 20.63)	
Present	2.51 (1.61, 3.21)		0.87 (0, 7.65)	
CKD		$p = 0.026$		$p = 0.040$
Absent	3.35 (2.15, 5.18)		6.10 (0.63, 20.06)	
Present	2.08 (1.12, 4.47)		1.08 (0, 8.06)	

	Median cvRMSSD (IQR)	cvRMSSD *p* value	Median pNN50 (IQR)	pNN50 *p* value
CVD		$p = 0.200$		$p = 0.510$
Absent	3.21 (2.08, 5.24)		5.49 (0.51, 20.53)	
Present	2.93 (1.87, 3.63)		2.42 (0.26, 9.34)	
Chronic liver disease		$p = 0.861$		$p = 0.080$
Absent	3.25 (2.13, 5.00)		4.74 (0.57, 20.63)	
Present	3.06 (2.04, 5.27)		5.49 (0.55, 17.43)	
CNS neurologic disease		$p = 0.156$		$p = 0.268$
Absent	2.96 (2.02, 5.11)		4.11 (0.51, 18.80)	
Present	3.37 (2.42, 5.39)		6.28 (0.85, 23.06)	
PNS neurologic disease		$p = 0.273$		$p = 0.089$
Absent	3.44 (2.06, 5.37)		6.78 (0.51, 23.06)	
Present	2.98 (2.14, 4.28)		4.11 (0.78, 13.78)	
Psychiatric disorders		$p = 0.071$		$p = 0.049$
Absent	3.42 (2.09, 5.44)		7.33 (0.86, 22.04)	
Present	2.89 (2.03, 4.28)		3.50 (0.30, 13.9)	

DSP distal sensory polyneuropathy, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *CNS* central nervous system, *PNS* peripheral nervous system

[a]Derived from Composite Autonomic Severity Score (CASS)

Table 4

Multivariate models including ordinal regression (outcome is pNN50) and linear regression (outcome is log cvRMSSD)

Variable	pNN50 (IQR)	*p* value	Log cvRMSSD (IQR)	*p* value
HRDB	1.11 (1.07, 1.16)	< 0.001	1.03 (1.02, 1.04)	< 0.001
Age	1.01 (0.98, 1.04)	0.245	1.00 (0.99, 1.01)	0.938
Sudomotor subscore	NA		0.93 (0.86, 1.01)	0.080
DSP	0.60 (0.33, 1.08)	0.956	0.90 (0.74, 1.10)	0.292
Hypertension	1.10 (0.59, 2.06)	0.382	1.00 (0.82, 1.21)	0.957
CVD	NA		0.99 (0.72, 1.34)	0.920
Psych	NA		0.94 (0.79, 1.13)	0.521
Diabetes	0.49 (0.24, 1.01)	0.974	NA	

HRDB heart rate with deep breathing, *DSP* distal sensory polyneuropathy, *CVD* cardiovascular disease, *Psych* history of psychiatric disease