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Cortical thickness and resting-state cardiac function across the lifespan: A cross-sectional pooled mega-analysis

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Abstract

Understanding the association between autonomic nervous system [ANS] function and brain morphology across the lifespan provides important insights into neurovisceral mechanisms underlying health and disease. Resting-state ANS activity, indexed by measures of heart rate [HR] and its variability [HRV] has been associated with brain morphology, particularly cortical thickness [CT]. While findings have been mixed regarding the anatomical distribution and direction of the associations, these inconsistencies may be due to sex and age differences in HR/HRV and CT. Previous studies have been limited by small sample sizes, which impede the assessment of sex differences and aging effects on the association between ANS function and CT. To overcome these limitations, 20 groups worldwide contributed data collected under similar protocols of CT assessment and HR/HRV recording to be pooled in a mega-analysis ($N = 1,218$ (50.5% female), mean age 36.7 years (range: 12–87)). Findings suggest a decline in HRV as well as CT with increasing age. CT, particularly in the orbitofrontal cortex, explained additional variance in HRV, beyond the effects of aging. This pattern of results may suggest that the decline in HRV with increasing age is related to a decline in orbitofrontal CT. These effects were independent of sex and specific to HRV; with no significant association between CT and HR. Greater CT across the adult lifespan may be vital for the maintenance of healthy cardiac regulation via the ANS—or greater cardiac vagal activity as indirectly reflected in HRV may slow brain atrophy. Findings reveal an important association between CT and cardiac parasympathetic activity with implications for healthy aging and longevity that should be studied further in longitudinal research.

KEYWORDS

aging, autonomic nervous system, cortical thickness, heart rate, heart rate variability, sex

1 | INTRODUCTION

Measures of heart rate [HR] and its variability [HRV] index the activity of the autonomic nervous system [ANS], and hence are related to physiological function, general health, and well-being. HRV refers to the variation in time between successive heartbeats and provides a reliable estimate of cardiac parasympathetic (vagal) regulation of HR (Camm, 1996). Neural control of the heart is achieved via feedforward and feedback mechanisms (efferent and afferent pathways) along the neuraxis (Dampney, 2016; Palma & Benarroch, 2014), involving forebrain areas such as the insular cortex, the anterior cingulate cortex [ACC], and the central nucleus of the amygdala. Only recently has research aimed to understand individual differences in the association between brain morphology and ANS function, potentially reflecting integrated brain-body health.

Several studies have recently shown that resting-state HRV is associated with the morphology of the brain across regions of interest [ROI], indexed by cerebral cortical thickness [CT] (Carnevali et al., 2019; Koenig et al., 2018; Lin et al., 2017; Wei, Chen, & Wu, 2018a, 2018b; Winkelmann et al., 2016; Wood, Badrov, Speechley, & Shoemaker, 2017; Woodward, Kaloupek, Schaer, Martinez, & Eliez, 2008; Yoo et al., 2017). CT is considered to reflect cellular aspects

of the cortical organization (Lerch, 2001). It has been suggested that—in contrast to measures of brain volume—CT may present a more sensitive measure to index normative and pathological changes in the brain structure (e.g., Thambisetty et al., 2010). The first study addressing associations between HRV and brain structure reported an association between resting-state respiratory sinus arrhythmia and the volume of the right but not left ACC (manually traced) in 77, predominantly male, U.S. combat veterans, suggesting that smaller ACC volume was associated with less parasympathetic regulation of HR (lower HRV) (Woodward et al., 2008). Since then, several studies (Carnevali et al., 2019; Koenig et al., 2018; Lin et al., 2017; Wei, Chen, & Wu, 2018b; Wei, Chen, & Wu, 2018a; Winkelmann et al., 2016; Wood et al., 2017; Yoo et al., 2017) with varying sample sizes ($n = 20$ to 185) have examined the association between HRV and brain morphology, predominantly focusing on CT (*for a comprehensive review see* Carnevali, Koenig, Sgoifo, & Ottaviani, 2018). The majority of studies in adults have reported positive correlations between CT and HRV (Carnevali et al., 2019; Winkelmann et al., 2016; Wood et al., 2017; Woodward et al., 2008; Yoo et al., 2017). However, sex and age differences in ANS function and brain morphology exist, but have not previously been jointly considered in studies examining the association between CT and HR/HRV, due to small sample sizes.

1.1 | Sex differences

Sex differences in resting-state HR and HRV have been reported. In adults, females show greater cardiac vagal activity, indexed by greater HRV, despite higher HR (Koenig & Thayer, 2016). In children and adolescents, females show lower HRV and higher HR (Koenig, Rash, Campbell, Thayer, & Kaess, 2017). Neuroimaging meta-analyses examining sex differences in brain morphology have shown that, compared to females, males have larger total brain volumes (Ruigrok et al., 2014). Sex differences in volume and tissue density have been shown for specific brain regions including the amygdala, hippocampus, and insula (Ruigrok et al., 2014). Regarding CT, studies suggest greater thickness of temporal and parietal cortices in females that are maintained across aging (Sowell et al., 2007). More recently, the largest single-sample study drawing on data from the UK Biobank ($n = 5,216$) showed that although adult males have larger cortical and subcortical volumes—except the right insula—adult females showed greater CT in 47 out of 68 ROI investigated (Ritchie et al., 2018). Given the positive association between CT and HRV in adults (Carnevali et al., 2019; Winkelmann et al., 2016; Wood et al., 2017; Woodward et al., 2008; Yoo et al., 2017), greater CT in females may be associated with sex differences in cardiac vagal activity (Koenig &

Thayer, 2016). However, previous work has not been sufficiently powered to realistically address this hypothesis. Further, the direction of association remains speculative.

1.2 | Age differences

Cardiac ANS function changes across the lifespan. Healthy aging is associated with a steady decrease in HRV (Antelmi et al., 2004; Jandackova, Scholes, Britton, & Steptoe, 2016; Voss, Schroeder, Heitmann, Peters, & Perz, 2015; Zhang, 2007). Potential mechanisms underlying this decrease include changes in baroreceptor sensitivity, structural, and functional changes in the sinoatrial node, as well as changes in vascular wall receptor sensitivity and adrenergic activity in general (Seals & Esler, 2000). Similarly, CT declines with increasing age (Storsve et al., 2014; Thambisetty et al., 2010). Studies examining the association between HRV and CT have shown that the correlation between vagally mediated HRV and CT changes as a function of age (Wood et al., 2017; Yoo et al., 2017), even after adjusting for cardiorespiratory fitness (Wood et al., 2017). Studies illustrating weaker correlations between brain morphology and ANS function in older age suggest that reduced CT (in particular of the ACC (Carnevali et al., 2018; Yoo et al., 2017) and medial prefrontal cortex (mPFC) (Wood et al., 2017). in aging may contribute to the reduction in cardiac vagal activity with advancing age (alongside peripheral factors). However, CT of other ROI, such as the left lateral orbitofrontal cortex (OFC) (Wood et al., 2017), show age-invariant associations with vagally mediated HRV. Most interestingly, the association between CT and ANS function seems to change in direction from adolescence to adulthood (Koenig et al., 2018). That is, unlike in adults where studies repeatedly have shown a positive association between HRV and CT (Carnevali et al., 2019; Winkelmann et al., 2016; Wood et al., 2017; Woodward et al., 2008; Yoo et al., 2017), this pattern is inverted in adolescents (Koenig et al., 2018). However, no single study has previously examined the relationship between HRV and CT across a continuum from adolescence to older age. Moreover, no study has been sufficiently powered to examine the association between HRV and CT across the lifespan, while also robustly investigating potential interactions with sex.

1.3 | Study aims and hypotheses

The aim of the present study was to pool existing data on CT and autonomic function, indexed by HR and HRV, to identify differences in the association between brain morphology and resting-state ANS activity (a) across aging and (b) as a function of sex in healthy subjects. We focused on HRV as the primary outcome of ANS function and aimed to conduct all analyses on HR and HRV, addressing HRV (in contrast to HR) as an indirect

correlate of cardiac vagal activity. We focused on CT in seven ROI per hemisphere, that have previously been shown to be associated with HRV (Carnevali et al., 2019; Koenig et al., 2018; Lin et al., 2017; Wei et al., 2018a; Wei et al., 2018b; Winkelmann et al., 2016; Wood et al., 2017; Woodward et al., 2008; Yoo et al., 2017). However, assuming that the association between HRV and CT would vary by region we further assessed whole-brain morphology, quantifying CT for a total of 68 ROI (34 for each hemisphere) according to the Desikan-Killiany atlas (Desikan et al., 2006). We hypothesized that higher HRV and lower HR are associated with greater CT and those correlations between HRV and CT are stronger than correlations between HR and CT. Based on prior findings, we expected that HRV and CT decrease with increasing age (continuous correlation). Given that different regions of the brain change differentially over time, we aimed to identify specific brain regions associated with the decline in HRV.

Regarding sex differences, we expected that females would show higher HR, higher HRV, and greater CT compared to males (group comparisons). Addressing the interaction between age and sex, we hypothesized that the decrease in HRV and CT with increasing age is smaller in females compared to males (relative change in HRV/CT per life-year). We also addressed potential sex differences in the association between CT and HR/HRV independent of age, with no a priori directed hypotheses. Finally, addressing if CT predicts HR/HRV as a function of age and sex, we hypothesized that slower decline of CT in females is associated with slower decline in HRV across aging.

2 | METHOD

Authors of previous studies and those with potential access to data on the association between HRV and CT were contacted and invited to participate in the project. A preprint detailing the hypotheses, strategies for pooling of data, and analyses of the project was posted on the Open Science Framework (https://osf.io/btjpw/) on April 1, 2018 to attract additional potential collaborators. To pool data across participants from each research group, the variables listed in Table 1 were provided by all contributing authors.

2.1 | Heart rate and heart rate variability

Recordings of HR/HRV based on electrocardiography (ECG) and photoplethysmography (PPG) were eligible for inclusion. There were no restrictions with respect to other features of the recording of HR and HRV (e.g., sampling frequency, body position). Contributing authors were requested to provide details on procedures and methodological features of HR/HRV recordings according to standard reporting items following the GRAPH recommendations (Quintana, Alvares, & Heathers, 2016), which are available for each research group as Supporting Information (see online Appendix A). RMSSD is a time-domain measure of HRV, reflecting cardiac vagal control. Time-domain measures of vagally mediated HRV, such as RMSSD, and HRV indices derived from frequency domain analysis, such as spectrally derived high-frequency (HF) HRV, provide information of different qualities and details (Hill, Siebenbrock, Sollers, & Thayer, 2009; Penttilä et al., 2001; Sinnreich, Kark, Friedlander, Sapoznikov, & Luria, 1998). Although RMSSD and HF-HRV are highly correlated (Goedhart, van der Sluis, Houtveen, Willemsen, & de Geus, 2007), time domain parameters may be estimated with less bias and considerably smaller error compared with frequency-domain parameters (Kuss, Schumann, Kluttig, Greiser, & Haerting, 2008). Further, frequency-domain measures such as HF-HRV are more likely to be affected by respiration (Hill et al., 2009; Penttilä et al., 2001), which varies by age (Fleming et al., 2011). Misspecifying frequency-bands or applying

TABLE 1 Variables for pooling data

Variable	Description
Id	A random number (no original study ID) that was re-coded after pooling of data
Sex	Participants' sex, coded as female (no [0]/ yes [1])
Age	Participants' age in years
Height	Participants' height in centimeters [cm]; if data were provided in units other than cm, data were transformed according to established conversion factors
Weight	Participants' weight in kilograms [kg]; if data were provided in units other than kg, data were transformed according to established conversion factors
RMSSD	The root mean square of successive differences between adjacent R-R intervals in milliseconds [ms], as a measure of vagally mediated HRV
HR	Mean HR in beats per minute [bpm]
Thick_*	CT of ROI in millimeters [mm]; 68 (34 for each hemisphere) ROI defined according to the Desikan-Killiany atlas (Desikan et al., 2006)

identical frequency-bands across aging might, therefore, lead to erroneous data (Shader et al., 2018). Further, the estimation of RMSSD is more robust at lower sample rates compared to frequency-domain measures (Ellis, Zhu, Koenig, Thayer, & Wang, 2015). In sum, RMSSD is robust across sampling methods (including relatively short recordings (Munoz et al., 2015), making it a useful measure of HRV when pooling data from multiple cohorts with varying recording and experimental protocols.[1] Further, in line with recent recommendations (Geus, Gianaros, Brindle, Jennings, & Berntson, 2019), we repeated the HRV analysis using the coefficient of variation (CV) of HRV to account for chronotropic state in sensitivity analyses $(CV = 100 \times (RMSSD/HR)$.[2]

2.2 | Cortical thickness

Contributing authors were required to report the procedures and methodological features of brain morphology measurement according to recent suggestions (Vijayakumar, Mills, Alexander-Bloch, Tamnes, & Whittle, 2017). Reporting items were collected using a pre-formatted method sheet, provided for each research group within the Supporting Information (see online Appendix A). Based on the existing literature (Carnevali et al., 2019; Koenig et al., 2018; Lin et al., 2017; Wei et al., 2018a, 2018b; Winkelmann et al., 2016; Wood et al., 2017; Woodward et al., 2008; Yoo et al., 2017) reporting on the association between CT and HR/HRV, seven ROI (caudal anterior cingulate cortex [caudal ACC]; rostral anterior cingulate cortex [rostral ACC]; insula; medial orbitofrontal cortex [medial OFC]; lateral orbitofrontal cortex [lateral OFC]; rostral middle frontal gyrus [rostral MFG]; superior frontal gyrus [SFG]), each for the left and right hemisphere (i.e., total of 14 ROI), were pre-selected for full reporting of statistics and graphical display in the manuscript. Full reporting of findings on all 68 ROI and additional data for meta-analytical research are available in the Supporting Information (see online Appendix B). All data were provided as CSV files that were pooled by the corresponding author using scripts in STATA (Version 15; StataCorp LP, College Station, TX, USA), ensuring the reproducibility of pooling procedures.

2.3 | Statistical analyses

In the initial study protocol, we did not consider the exclusion of outliers after pooling of data. Thus, in a deviation

from the original plan, multivariate outliers (including RMSSD and CT in 14 pre-selected ROI) were detected and removed for each research group's data set (rather than the sample as a whole) using the "mvoutlier" package in R (Filzmoser, Maronna, & Werner, 2008). RMSSD values that were physiologically unlikely (>150 ms) and body mass index [BMI] values indicative of morbid obesity (>45 kg/m^2) were also excluded from the data set. Summary statistics for the pooled sample were calculated for the following variables: age (in years); HR (in bpm); HRV (in ms) and BMI (in kg/m^2). Welch's t tests were used to compare HRV and HR between sexes, and Pearson correlations were computed for the relationship between HRV and HR, as well as age and BMI.

A series of regression models were used to predict HR or HRV by the research group (data set), age, sex, sex × age, and CT for each of the 68 ROI, with all variables added at once to each model. To address issues of multiple testing within a frequentist framework, we used the false discovery rate (FDR) method. P values lower than .05 were considered statistically significant. The t-statistics, p values, and FDR corrected p values for the brain region coefficients were of specific interest as these assess the relationship between CT and HR or HRV after adjusting for the research group (data set), age, sex, and sex × age. The p values and FDR corrected p values were computed for each ROI.

A series of Bayesian regression models were also used to assess the relative evidence of two models predicting the cardiac measures: A full model (CT for a given ROI, research group, BMI, age, sex, sex × age) and a covariate model (research group, BMI, age, sex, sex × age). Greater relative evidence for the full model, relative to the covariate model, would suggest that CT is related to HRV over and above the effects of research group, BMI, age, sex, and sex × age. Full models were constructed for all 68 ROI. A conservative default prior distribution with an r scale of 0.354, which is often referred to as a "medium" r scale, were used. This prior width reflects a belief that there is a 50% chance that the *true* effect size is within a −0.354 to +0.354 interval, which is consistent with a small effect size. Bayes factors (*BF*) greater than 3 and 10 were considered moderate and strong evidence, respectively, for one model relative to the other (Jeffreys, 1998; Quintana & Williams, 2018). All analyses and figures were prepared using the R statistical environment (version 3.3.2).

3 | RESULTS

3.1 | Sample characteristics

After removal of multivariate outliers, the final sample comprised 1,218 participants (50.5% female). The mean age was

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[1]As explained in Appendix A of the Supporting Information, one group provided absolute MSD, a mathematical approximate of RMSSD (Allen et al. 2007).

[2]Note that the original paper suggests to use IBI, that was not available for all studies in this pooled analysis. Therefore, we used mean HR.

36.7 [standard deviation [SD] =14.9 [range: 12–87]) years. Participants' mean height was 172.7 (9.9 [130–210.8]) cm, and mean weight was 74.8 (15.7 [36.1–132.4]) kg. The mean BMI was 25 (4.6 [16–44.3]) kg/m^2. Mean HR was 68.6 (10.7 [38–115.9]) bpm. Mean HRV (RMSSD) was 39.9 (25 [2–148.8]) ms. There were significant differences in the male:female ratio by the research group [$\chi^2(19) = 121.1$, $p < .001$]. Sample characteristics by the research group are provided in the Supporting Information (online Appendix B, Table S1–S4).

3.2 | Differences in heart rate and heart rate variability by age and sex

There were no sex differences in HRV ($p = .39$; $BF = 0.18$; $d = 0.05$; Figure 1a), but females had higher HR than males ($p < .001$; $BF > 1,000$; $d = 0.28$; Figure 1b). On average, males had higher BMI than females ($p = .045$; $BF = 0.85$;

$d = 0.11$). There was a negative correlation between HRV and age [$r = −0.44$, 95% CI ($−0.49$, $−0.4$), $p < .001$, $n = 1,218$; Figure 1c), but no correlation between HR and age [$r = 0.04$, 95% CI ($−0.02$, 0.1), $p = .16$, $n = 1,218$; Figure 1d). Accounting for the research group, there was no sex × age interaction for HRV ($t = 0.89$, $p = .37$) or HR ($t = −1.16$, $p = .25$).

3.3 | Associations between cortical thickness and age

There was no sex difference in mean CT across ROI ($p = .08$; $BF = 0.57$; $d = 0.1$). There was a negative correlation between age and mean CT across ROI [$r = −0.49$; 95% CI ($−0.53$, $−0.44$); $p < .001$], and between age and CT for each ROI. CT in the preselected 14/68 ROI was negatively associated with age, accounting for the research group (all FDR corrected p values < 0.001; online Appendix B,
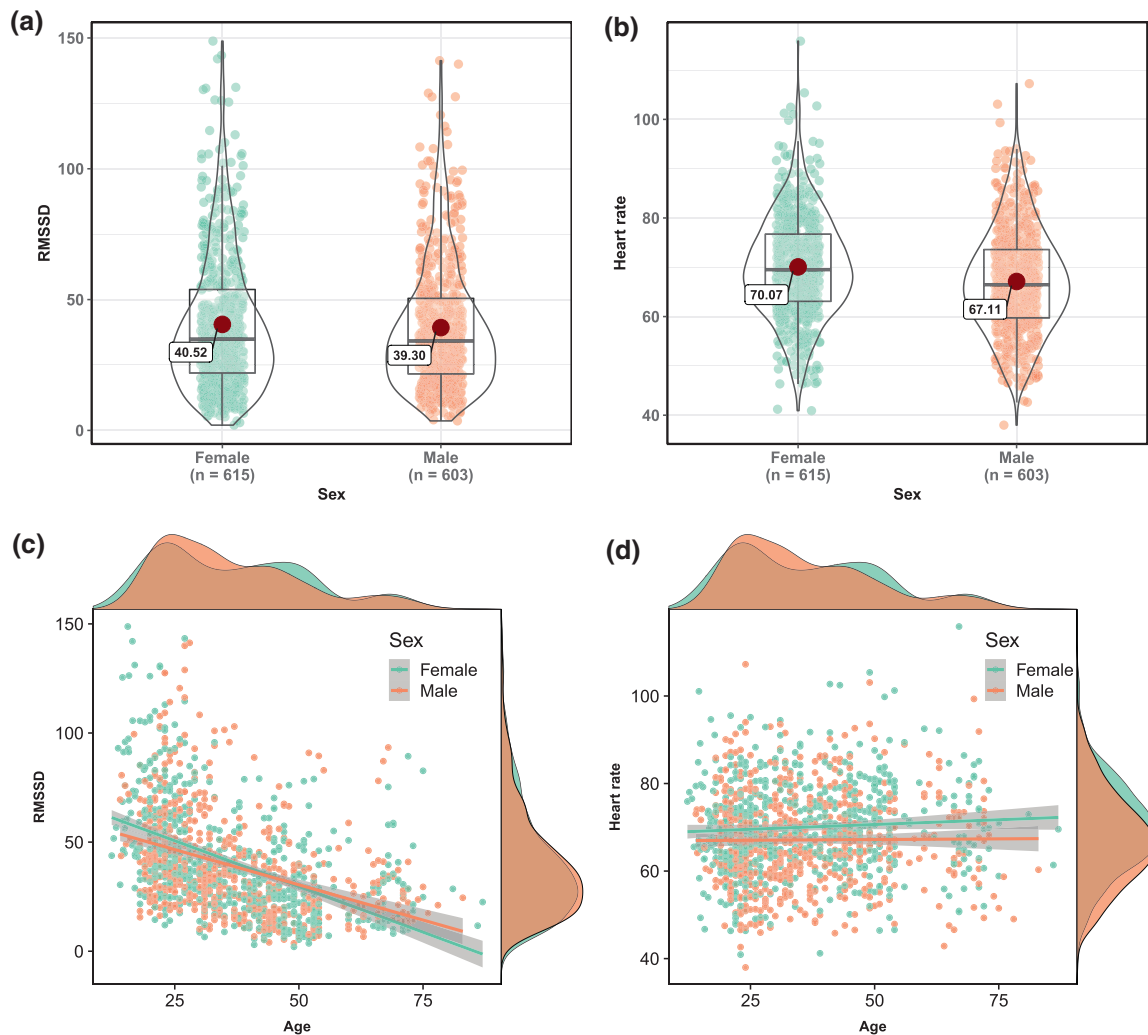
FIGURE 1 Resting heart rate (HR) and heart rate variability by sex and age. Box and violin plots illustrate HRV (indexed by RMSSD) (a) and HR (b) in males and females, with red dots reflecting mean values. Scatterplots with marginal distributions illustrate the relationship between HRV (indexed by RMSSD) (c) and HR (d) with age. A line of best fit for both males and females (95% confidence region in grey) was overlaid in each scatterplot

Figure S1 and Table S2). Accounting for the research group, there was a significant effect of age ($t = -16.2$, $p < .001$), but no effect of sex ($t = 0.82$, $p = .41$) or sex × age interaction ($t = 0.29$, $p = .78$) on mean CT. Regarding our pre-selected 14/68 ROI, there were significant sex differences in the CT of the left and right caudal ACC (thinner in females), left and right insula (thicker in females), left lateral OFC (thicker in females), and left medial OFC (thicker in females) ($p < .05$ after applying a FDR correction for 14 tests; online Appendix B, Table S3).
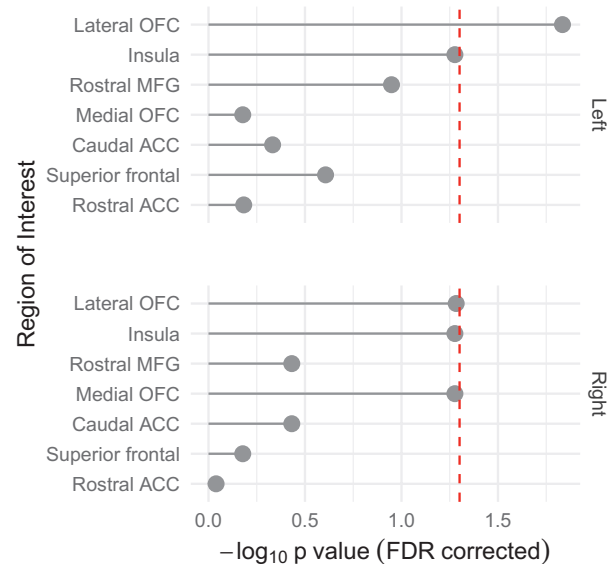
3.4 | Associations between cortical thickness, heart rate, and heart rate variability

Overall, there was a correlation between HRV and mean CT ($r = .23$, $p < .0001$), but no significant relationship between HR and mean CT ($r = -.02$, $p = .4$). Zero-order correlations between HR/HRV and CT by sex are provided in the Supporting Information (online Appendix B, Tables S4–S9).

Regression models for each of the 14 pre-selected ROI predicting HRV by CT, age, and research group revealed that CT was associated with HRV when accounting for age and research group for the left ($t = 3.26$, $p = .001$; FDR corrected $p = .016$) and right ($t = 2.82$, $p = .005$, FDR corrected $p = .034$) lateral OFC (online Appendix B, Figure S2; Table S10). Age was associated with HRV when accounting for CT and research group for all 14 pre-specified ROI (all FDR corrected p values < 0.001; online Appendix B, Table S11). There were no main effects of sex or age or sex × age interactions for the prediction of HRV for any of the pre-selected ROI, accounting for the research group (online Appendix B, Table S12). Regression models for each pre-selected ROI predicting HR by CT, age, sex, sex × age interaction, and research group revealed no main effects or interactions after FDR corrections (online Appendix B, Table S13).

3.5 | Primary analyses

Frequentist analyses on the relationship between pre-specified ROI and HRV revealed a significant relationship between CT of the left lateral OFC and HRV ($t = 3.29$, $p = .001$; FDR corrected $p = .015$) accounting for all potential confounds including research group, BMI, age, sex, and sex × age (Figures 2 and 3). There was an association between HRV and CT of the right lateral OFC ($t = 2.68$, $p = .007$), right medial OFC ($t = 2.39$, $p = .017$), right insula ($t = 2.47$, $p = .014$), and left insula ($t = 2.35$, $p = .019$), but these effects did not remain significant after FDR correction (online Appendix B, Table S14). Analysis also revealed an
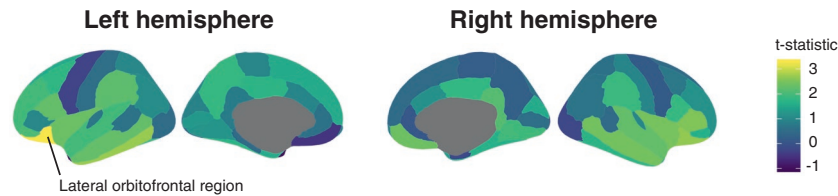

FIGURE 2 Association between heart rate variability and cortical thickness in pre-specified ROI accounting for research group, BMI, age, sex, and sex × age. Grey dots represent the FDR corrected p values of pre-specified ROI coefficients. A $-\log_{10}$ transformed p value was used for the purposes of visualization. The vertical dashed red line represents an FDR corrected p value threshold of .05 ($-\log_{10}$ transformed)

association between age and HRV accounting for sex, research group, BMI, and CT for the 14 pre-specified ROI (all FDR corrected p values < 0.001), suggesting that HRV decreases with age (Table S14). However, there was no effect of sex or sex × age on HRV, accounting for research group, age, BMI, and CT of the 14 pre-specified ROI (all FDR corrected p values > .05).

Frequentist analyses revealed no relationship between CT of any of the 14 pre-specified ROI and HR (Table S9) accounting for research group, BMI, age, sex, and sex × age. There was no significant effect of age or sex × age on HR accounting for sex, research group, BMI, and CT of the 14 pre-specified ROI (online Appendix B, Table S15).

When adjusting HRV for HR, there was also a statistically significant relationship between CV and CT of the left lateral OFC ($t = 2.74$, $p = .006$), left insula ($t = 2.45$, $p = .01$), right lateral OFC ($t = 2.49$, $p = .01$), right medial OFC ($t = 2.48$, $p = .01$), and right insula ($t = 2.3$, $p = .02$) accounting for potential confounds. However, after FDR correction these relationships were only on the border of traditional statistical significance in frequentist analyses (all $p's < .06$). Analysis also revealed significant FDR corrected relationships between age and HRV, accounting for sex, research group, BMI, and CT for all 14 pre-specified ROI, suggesting that HRV adjusted for HR decreases with age. However, there were no statistically significant age × sex interactions for any pre-specified ROI.

FIGURE 3 The relationship between heart rate variability and cortical thickness across 68 brain regions, accounting for BMI, age, sex, sex × age, and research group. For the pre-specified ROI analysis, the cortical thickness of the lateral orbitofrontal region was significantly related to HRV ($p = .015$, FDR corrected), accounting for covariates. Color scale reflecting t-statistics

Exploratory analysis of all 34 ROI in the right hemisphere revealed significant associations between RMSSD and CT of the isthmus cingulate ($t = 2.15$, $p = .03$), lateral OFC ($t = 2.68$, $p = .007$), lingual ($t = 1.96$, $p = .049$), medial OFC ($t = 2.39$, $p = .02$), middle temporal ($t = 2.45$, $p = .01$), pars triangularis ($t = 2.55$, $p = .01$), insula ($t = 2.47$, $p = .012$), and superior temporal regions ($t = 2.26$, $p = .02$; Figure 3; online Appendix B, Table S16), accounting for research group, BMI, age, sex, and sex × age. However, none of these effects remained significant after FDR correction. There were no FDR corrected significant associations between HR and CT for any region after accounting for research group, BMI, age, sex, and sex × age (online Appendix B, Table S17).

Exploratory analysis of all 34 regions in the left hemisphere revealed associations between HRV and CT of the inferior temporal gyrus ($t = 2.73$, $p = .006$; FDR corrected $p = .11$), lateral OFC ($t = 3.29$, $p = .001$; FDR corrected $p = .04$) middle temporal ($t = 2.28$, $p = .02$; FDR corrected $p = .16$), pars opercularis ($t = 2.27$, $p = .02$; FDR corrected $p = .16$), pars orbitalis ($t = 2.05$, $p = .04$; FDR corrected $p = .18$), rostral MFG ($t = 1.98$, $p = .048$; FDR corrected $p = .18$) superior temporal ($t = 1.99$, $p = .047$; FDR corrected $p = .18$), supra marginal ($t = 2.21$, $p = .03$; FDR corrected $p = .16$), and insula regions ($t = 2.35$, $p = .02$; FDR corrected $p = .16$; Figure 3; online Appendix B, Table S16), accounting for research group, BMI, age, sex, and sex × age. There was no association between CT of any pre-specified ROI or any right or left hemisphere region and HR accounting for research group, BMI, age, sex, and sex × age after FDR correction (online Appendix B, Table S17).

Exploratory analysis of all 34 ROI in the right hemisphere revealed significant associations between HRV adjusted for HR (CV and CT of the lateral OFC ($t = 2.49$, $p = .01$), medial OFC ($t = 2.48$, $p = .01$), middle temporal ($t = 2.3$, $p = .02$), parahippocampal ($t = 2.26$, $p = .02$), pars triangularis ($t = 2.26$, $p = .02$), superior temporal ($t = 2.53$, $p = .01$), and insula ($t = 2.3$, $p = .02$). None of these statistically significant associations survived FDR correction for multiple tests. Exploratory analysis of all 34 ROI in the left hemisphere revealed significant associations between HRV adjusted for HR (CV) and CT of the entorhinal ($t = 2.19$, $p = .03$), inferior temporal ($t = 2.59$, $p = .01$), lateral OFC ($t = 2.74$, $p = .01$), middle temporal ($t = 2.21$, $p = .03$), pars opercularis ($t = 1.99$, $p = .047$), superior temporal

($t = 2.16$, $p = .03$), supramarginal ($t = 2.09$, $p = .04$), and insula ($t = 2.4$, $p = .01$). None of these statistically significant associations survived FDR correction for multiple tests in traditional frequentist analyses.

Bayesian analysis revealed moderate evidence for the full model (CT for a given ROI, research group, BMI, age, sex, sex × age) relative to the covariate model (research group, BMI, age, sex, sex × age) for the prediction of HRV for analyses including CT of the left lateral OFC ($BF = 5.22$) and left inferior temporal gyrus ($BF = 8.83$; Figure 4, online Appendix B, Table S18). This suggests that CT in these regions is related to HRV over and above the effects of research group, age, sex, and sex × age. In regards to the prediction of HR, there was moderate evidence for the full relative to the covariate model when including CT of the left ($BF = 7.51$) and right ($BF = 3.09$) parahippocampal regions, suggesting that CT in these regions is related to HR over and above the effects of research group, age, sex, and sex × age (online Appendix B, Table S19).

4 | DISCUSSION

4.1 | Summary of findings

Understanding the brain morphological correlates of autonomic function is important for basic research and clinical applications. To this end we pooled data from 20 research groups worldwide, comprising a total of $n = 1,218$ healthy participants. Our results illustrate, that some of the previously reported associations between CT and HRV are likely attributable to type 1 errors and, moreover, some likely existing associations have been missed due to type II error—considering a traditional frequentist framework relying on the interpretation of p values. In principle, we were able to confirm findings from prior studies, illustrating that HRV (measured in the time domain) and CT decline with increasing age. We found no evidence for a linear increase or decrease in HR across aging. We found that HRV was associated with both mean CT across all ROI and CT for the 14 selected ROI hypothesized to be most integral to changes in cardiac function (i.e., HR and HRV). No such associations were found for HR. Strongest evidence was found for an association between the
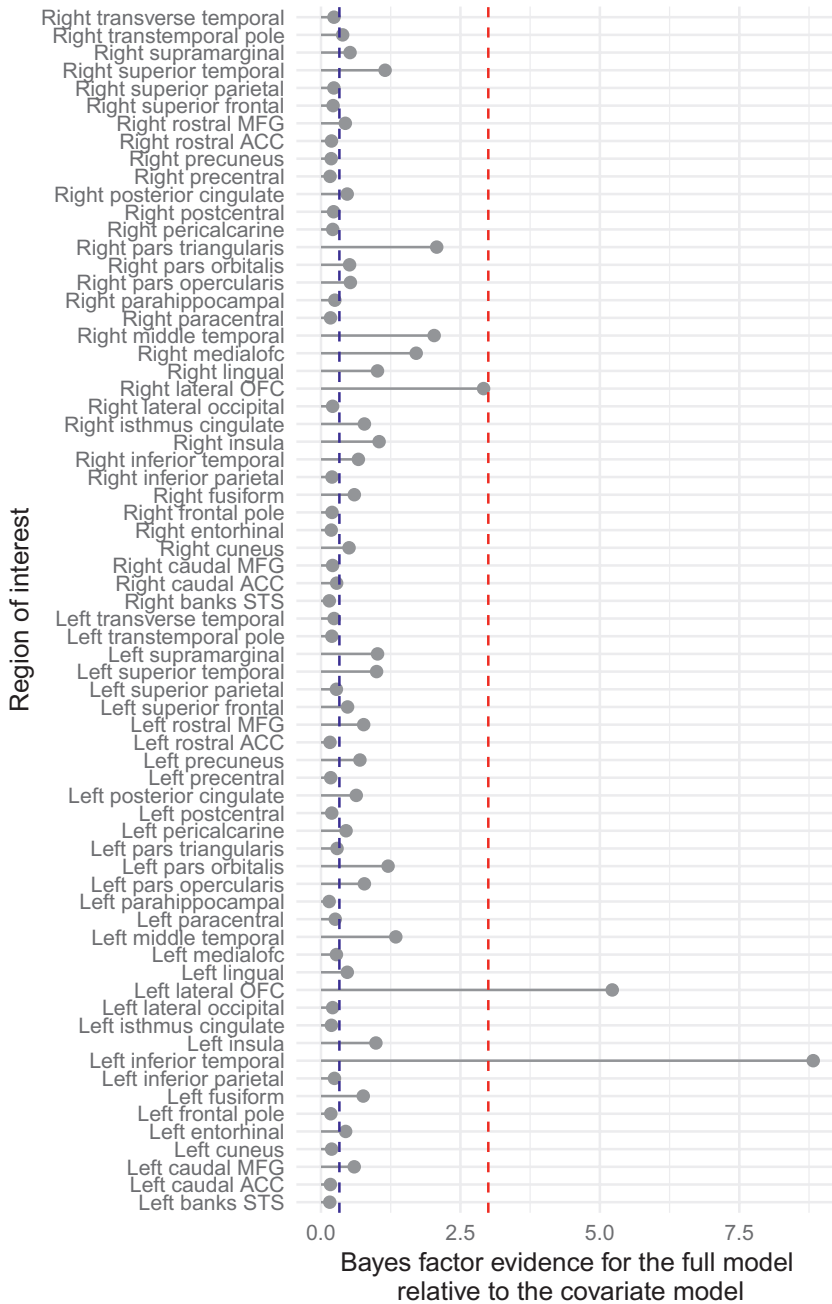
FIGURE 4 Association between heart rate variability and cortical thickness in all ROI, accounting for research group, BMI, age, sex, and sex × age. Grey dots represent the Bayes factors for the comparison of a covariate model and a model with covariates and cortical thickness (full model). The dashed vertical blue line represents a Bayes factor of 0.33 and the dashed vertical red line represents a Bayes factor of 3. Bayes factor values above three are considered moderate evidence for a model, relative to a competing model

decline in lateral OFC thickness and decline in HRV across aging. In contrast to our hypothesis, no correlations between HR and CT were found. Findings suggest that the associations between brain structure and cardiac function may be specific to cardiac vagal activity, indexed by HRV, as suggested in previous studies (Koenig et al., 2018; Yoo et al., 2017). In our statistical approach, we corrected for multiple testing, used Bayesian models with a conservative default prior distribution and further presented sensitivity analyses adjusting HRV for HR, to account for chronotropic states—the later not being necessarily required when investigating healthy cardiac function (Geus et al., 2019). Given this large set of analyses, we will focus the discussion on the general pattern of results that emerged.

Based on recent meta-analytic evidence (Koenig & Thayer, 2016), we expected sex differences in HR, HRV and CT. In line with our hypotheses, we found higher HR in females compared to males; however, there were no sex differences in HRV. Prior studies have shown that sex differences in HRV and HR vary across age groups. That is, in children and adolescents, HRV is decreased and HR increased in females, whereas in adults, HRV and HR are both increased in females (Koenig et al., 2017; Koenig & Thayer, 2016). Again, the present sample included children and adolescents as well as adults, potentially masking sex effects to some degree. Regarding brain morphology, we found no sex differences in mean CT (across all ROI), but there were differences for a subset of the 14 pre-selected ROI including the

left and right caudal ACC, left and right insula, and left lateral OFC. In line with findings from previous studies (Sowell et al., 2007)—with the exception of the left and right ACC (thinner in females)—females showed greater CT in each of these ROI. Differences in CT for these ROI could explain sex differences in cardiac function on a neural structural level. However, we only found significant sex differences for HR (but not for HRV), which did not show any direct association with CT.

Different from our hypotheses, we found no evidence for differences between males and females in the effects of aging on cardiac function or CT. The decline in CT and HRV with increasing age was observed even after adjusting for sex. Based on the present findings, it is suggested that the decline in HRV across aging is associated with a decline in mean CT across all ROI, independent of sex. Importantly, this association was specific for HRV and not found for HR. Frequentist analyses including FDR correction and complementary Bayesian analyses suggest that a decline of OFC CT in both hemispheres is most strongly associated with the decline in HRV.

A recent study illustrated the association between various vascular risk factors and atrophy in grey and white matter macro- and microstructure (Cox et al., 2019), supporting the notion that atherosclerosis (or vascular health more generally) may be the underlying mechanism that explains the present observations. However, unlike Cox et al. found additive effects of small effect size across various ROI and magnetic resonance imaging measures, in addition to findings on global CT, we found converging evidence for a specific association between HRV and OFC CT in aging. Thus, one may speculate that in addition to the bottom-up effects of cardiac activity on brain morphology, top-down mechanisms may contribute to the present observations. In this regard, greater CT of the OFC may be vital to regulate ANS activity (Thayer & Lane, 2000, also see Thayer et al., 2009), ultimately promoting the maintenance of healthy cardiac function across aging. The strong association between OFC CT and HRV potentially illustrates a hub through which important psychological functions (i.e., cognitive, affective, and behavioral) are connected with physiological longevity on a neural and peripheral level (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). In this regard, HRV may promote better functional connectivity among ROI, ultimately preserving greater CT in aging (Mather & Thayer, 2018). Longitudinal studies are warranted to further clarify these associations. Physical activity and fitness (Williams et al., 2017) may further explain variance in both outcomes of interest and partially explain the association between HRV and CT. While evidence on fitness interventions in the elderly, to increase CT and reduced associated cognitive impairment is mixed (Frederiksen et al., 2018; Reiter et al., 2015), physical fitness may show differential association with CT by age group (Williams et al., 2017) and reduce cortical atrophy (Cox et al., 2019).

While HRV showed stronger associations with CT compared to HR, an interesting finding emerged regarding CT of the parahippocampal regions in both hemispheres, suggesting that CT in these regions is related to HR. Just recently, a study found that the spontaneous firing rate of more than a third of neurons in the anterior parahippocampal gyrus is directly related to the cardiac-cycle duration in humans (Kim et al., 2019). While animal studies have shown that parahippocampal structures project to autonomic nuclei on a functional level, we can only speculate on the present finding concerning the association between resting HR and CT. Further, evidence from clinical studies shows that atrophy of the parahippocampal gyrus is present in patients with heart failure (Meguro, Meguro, & Kunieda, 2017). While hypoperfusion is discussed as a mechanism underlying this association, our findings illustrate a general association between HR and CT of parahippocampal gyrus, as higher HR seems associated with lower CT in this ROI.

4.2 | Strengths and limitations

The present study draws on the—to-date—largest sample to investigate the association between resting-state ANS function and CT. However, the present approach of pooling data in a joint effort of researchers worldwide has some limitations that need to be addressed. Potential sociodemographic confounders of ANS function and CT were not available in the present study, including *ethnicity* (Hill et al., 2015) and *socioeconomic status* (Piccolo, Merz, He, Sowell, & Noble, 2016). In particular, the inability to control for ethnic differences is notable, as there is striking evidence for an ethnic difference in cardiovascular risk as well as mortality (e.g., Meadows et al., 2011) and health disparities in association with aging (Ferraro, Kemp, & Williams, 2017). These effects were potentially masked by not controlling for ethnicity. We included weight, height, and BMI as important confounders of HRV (Koenig et al., 2015) and CT (Medic et al., 2016), which were measured in most data sets. Broader consensus on variables that should be assessed in studies of HRV would facilitate similar projects of pooling HRV data in the future. Further, we did not address the impact of health-related variables such as *smoking* (Barutcu et al., 2005; Karama et al., 2015), *alcohol consumption* (Momenan et al., 2012; Quintana, Guastella, McGregor, Hickie, & Kemp, 2013) or general measures of health status (Jarczok et al., 2015), including physical activity, as these data were not available across all studies that contributed data. However, we included data from healthy participants only, as specified by the initial study protocols of included studies (see online Appendix A for further information). Regarding the analyses examining

sex differences, we were not able to address the potential influence of menopausal status or menstrual cycle phase in females (Bai, Li, Zhou, & Li, 2009; Herting, Gautam, Spielberg, Dahl, & Sowell, 2015), or the role of sex hormones in general (Herting et al., 2015). Although pooling of data enabled the present analyses on a large sample, and methodological differences and sample heterogeneity across primary studies were controlled for in statistical analyses, differences in preprocessing of data may still have contributed to the results. This seems particularly relevant when pooling data across children, adolescents, and adults. It has previously been shown that associations between CT and HRV are inverse in adolescents compared to adults (Koenig et al., 2018). Thus, while controlling for age in all analyses, such opposite trends in age groups might have resulted in diminishing the total effect. Finally, the present analyses were based on a commonly used brain atlas (i.e., Desikan-Killiany), investigating CT, thus not covering other structural information from potential regions of interest in detail (e.g., hippocampal volume).

The present study contributes to a better understanding of the association between healthy cardiac function across aging and brain morphology. Findings suggest an association between the decline of CT and the decline of HRV across the lifespan. The present analyses emphasize the important role of the bilateral OFC in maintaining greater vagal control over cardiac activity and suggest a cardio-protective mechanism underlying health and disease from a neurovisceral perspective. Understanding which brain areas are associated with autonomic function has important clinical implications, potentially leading to better focused clinical interventions (e.g., brain stimulation).

the idea for the project, handled the pooling of data, and wrote the first draft of the manuscript. Daniel Quintana and Tobias Kaufmann developed the R-script for analysis based on consensus with all co-authors, performed the statistical analyses, and prepared all graphs for publication. All authors extensively revised the manuscript and approved the final version before submission for publication. The authors have no competing financial interests to declare.

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REFERENCES

Allen, J. J. B., Chambers, A. S., & Towers, D. N. (2007). The many metrics of cardiac chronotropy: A pragmatic primer and a brief comparison of metrics. *Biological Psychology*, *74*(2), 243–262. https://doi.org/10.1016/j.biopsycho.2006.08.005

Antelmi, I., de Paula, R. S., Shinzato, A. R., Peres, C. A., Mansur, A. J., & Grupi, C. J. (2004). Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *The American Journal of Cardiology*, *93*(3), 381–385. https://doi.org/10.1016/j.amjcard.2003.09.065

Bai, X., Li, J., Zhou, L., & Li, X. (2009). Influence of the menstrual cycle on nonlinear properties of heart rate variability in young women. *American Journal of Physiology. Heart and Circulatory Physiology*, *297*(2), H765–774. https://doi.org/10.1152/ajpheart.01283.2008

Barutcu, I., Esen, A. M., Kaya, D., Turkmen, M., Karakaya, O., Melek, M., … Basaran, Y. (2005). Cigarette smoking and heart rate variability: Dynamic influence of parasympathetic and sympathetic maneuvers. *Annals of Noninvasive Electrocardiology*, *10*(3), 324–329. https://doi.org/10.1111/j.1542-474X.2005.00636.x

Camm, A. J., Malik, M., Bigger, J. T., Breithardt, G., Cerutti, S., Cohen, R. J., … Lombardi, F. (1996). 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*, *93*(5), 1043–1065. https://doi.org/10.1161/01.CIR.93.5.1043

Carnevali, L., Koenig, J., Sgoifo, A., & Ottaviani, C. (2018). Autonomic and brain morphological predictors of stress resilience. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00228

Carnevali, L., Mancini, M., Koenig, J., Makovac, E., Watson, D. R., Meeten, F., … Ottaviani, C. (2019). Cortical morphometric predictors of autonomic dysfunction in generalized anxiety disorder. *Autonomic Neuroscience: Basic & Clinical*, *217*, 41–48. https://doi.org/10.1016/j.autneu.2019.01.001

Cox, S. R., Lyall, D. M., Ritchie, S. J., Bastin, M. E., Harris, M. A., Buchanan, C. R., … Deary, I. J. (2019). Associations between vascular risk factors and brain MRI indices in UK Biobank. *European Heart Journal*, *40*(28), 2290–2300. https://doi.org/10.1093/eurheartj/ehz100

Dampney, R. A. L. (2016). Central neural control of the cardiovascular system: Current perspectives. *Advances in Physiology Education*, *40*(3), 283–296. https://doi.org/10.1152/advan.00027.2016

de Geus, E. J. C., Gianaros, P. J., Brindle, R. C., Jennings, J. R., & Berntson, G. G. (2019). Should heart rate variability be "corrected" for heart rate? Biological, quantitative, and interpretive considerations. *Psychophysiology*, *56*(2), e13287. https://doi.org/10.1111/psyp.13287

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Ellis, R. J., Zhu, B., Koenig, J., Thayer, J. F., & Wang, Y. (2015). A careful look at ECG sampling frequency and R-peak interpolation on short-term measures of heart rate variability. *Physiological Measurement*, *36*(9), 1827–1852. https://doi.org/10.1088/0967-3334/36/9/1827

Ferraro, K. F., Kemp, B. R., & Williams, M. M. (2017). Diverse aging and health inequality by race and ethnicity. *Innovation in Aging*, *1*(1). https://doi.org/10.1093/geroni/igx002

Filzmoser, P., Maronna, R., & Werner, M. (2008). Outlier identification in high dimensions. *Computational Statistics & Data Analysis*, *52*(3), 1694–1711. https://doi.org/10.1016/j.csda.2007.05.018

Fleming, S., Thompson, M., Stevens, R., Heneghan, C., Plüddemann, A., Maconochie, I., … Mant, D. (2011). Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: A systematic review of observational studies. *Lancet (London, England)*, *377*(9770), 1011–1018. https://doi.org/10.1016/S0140-6736(10)62226-X

Frederiksen, K. S., Larsen, C. T., Hasselbalch, S. G., Christensen, A. N., Høgh, P., Wermuth, L., … Garde, E. (2018). A 16-week aerobic exercise intervention does not affect hippocampal volume and cortical thickness in mild to moderate Alzheimer's disease. *Frontiers in Aging Neuroscience*, *10*. https://doi.org/10.3389/fnagi.2018.00293

Goedhart, A. D., van der Sluis, S., Houtveen, J. H., Willemsen, G., & de Geus, E. J. C. (2007). Comparison of time and frequency domain measures of RSA in ambulatory recordings. *Psychophysiology*, *44*(2), 203–215. https://doi.org/10.1111/j.1469-8986.2006.00490.x

Herting, M. M., Gautam, P., Spielberg, J. M., Dahl, R. E., & Sowell, E. R. (2015). A longitudinal study: Changes in cortical thickness and surface area during pubertal maturation. *PLoS One*, *10*(3), e0119774. https://doi.org/10.1371/journal.pone.0119774

Hill, L. B. K., Hu, D. D., Koenig, J., Sollers, J. J., Kapuku, G., Wang, X., … Thayer, J. F. (2015). Ethnic differences in resting heart rate variability: A systematic review and meta-analysis. *Psychosomatic Medicine*, *77*(1), 16–25. https://doi.org/10.1097/PSY.0000000000000133

Hill, L. K., Siebenbrock, A., Sollers, J. J. III, & Thayer, J. F. (2009). Are all measures created equal? Heart rate variability and respiration—Biomed 2009. *Biomedical Sciences Instrumentation*, *45*, 71–76.

Jandackova, V. K., Scholes, S., Britton, A., & Steptoe, A. (2016). Are changes in heart rate variability in middle-aged and older people normative or caused by pathological conditions? Findings from a large population-based longitudinal cohort study. *Journal of the American Heart Association*, *5*(2), e002365. https://doi.org/10.1161/JAHA.115.002365

Jarczok, M. N., Kleber, M. E., Koenig, J., Loerbroks, A., Herr, R. M., Hoffmann, K., … Thayer, J. F. (2015). Investigating the associations of self-rated health: Heart rate variability is more strongly associated than inflammatory and other frequently used biomarkers in a cross sectional occupational sample. *PLoS One*, *10*(2), e0117196. https://doi.org/10.1371/journal.pone.0117196

Jeffreys, S. H. (1998). *The theory of probability* (3rd edn). New York, NY: Oxford University Press.

Karama, S., Ducharme, S., Corley, J., Chouinard-Decorte, F., Starr, J. M., Wardlaw, J. M., … Deary, I. J. (2015). Cigarette smoking and thinning of the brain's cortex. *Molecular Psychiatry*, *20*(6), 778–785. https://doi.org/10.1038/mp.2014.187

Kim, K., Ladenbauer, J., Babo-Rebelo, M., Buot, A., Lehongre, K., Adam, C., … Tallon-Baudry, C. (2019). Resting-state neural firing rate is linked to cardiac-cycle duration in the human cingulate and parahippocampal cortices. *Journal of Neuroscience*, *39*(19), 3676–3686. https://doi.org/10.1523/JNEUROSCI.2291-18.2019

Koenig, J., Parzer, P., Reichl, C., Ando, A., Thayer, J. F., Brunner, R., & Kaess, M. (2018). Cortical thickness, resting state heart rate, and heart rate variability in female adolescents. *Psychophysiology*, *55*(5), e13043. https://doi.org/10.1111/psyp.13043

Koenig, J., Rash, J. A., Campbell, T. S., Thayer, J. F., & Kaess, M. (2017). A meta-analysis on sex differences in resting-state vagal activity in children and adolescents. *Frontiers in Physiology*, *8*. https://doi.org/10.3389/fphys.2017.00582

Koenig, J., & Thayer, J. F. (2016). Sex differences in healthy human heart rate variability: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, *64*, 288–310. https://doi.org/10.1016/j.neubiorev.2016.03.007

Koenig, J., Windham, B. G., Ferrucci, L., Sonntag, D., Fischer, J. E., Thayer, J. F., & Jarczok, M. N. (2015). Association strength of three adiposity measures with autonomic nervous system function in apparently healthy employees. *The Journal of Nutrition, Health & Aging*, *19*(9), 879–882. https://doi.org/10.1007/s12603-015-0508-x

Kuss, O., Schumann, B., Kluttig, A., Greiser, K. H., & Haerting, J. (2008). Time domain parameters can be estimated with less statistical error than frequency domain parameters in the analysis of heart rate variability. *Journal of Electrocardiology*, *41*(4), 287–291. https://doi.org/10.1016/j.jelectrocard.2008.02.014

Lerch, J. (2001). *Measuring cortical thickness* (PhD thesis). Montreal, Canada: McGillUniversity Montreal.

Lin, F., Ren, P., Wang, X., Anthony, M., Tadin, D., & Heffner, K. L. (2017). Cortical thickness is associated with altered autonomic function in cognitively impaired and non-impaired older adults. *The Journal of Physiology*, *595*(22), 6969–6978. https://doi.org/10.1113/JP274714

Mather, M., & Thayer, J. F. (2018). How heart rate variability affects emotion regulation brain networks. *Current Opinion in Behavioral Sciences*, *19*, 98–104. https://doi.org/10.1016/j.cobeha.2017.12.017

Meadows, T. A., Bhatt, D. L., Cannon, C. P., Gersh, B. J., Röther, J., Goto, S., … Steg, P. G. (2011). Ethnic differences in cardiovascular risks and mortality in atherothrombotic disease: Insights from the reduction of atherothrombosis for continued health (REACH) registry. *Mayo Clinic Proceedings*, *86*(10), 960–967. https://doi.org/10.4065/mcp.2011.0010

Medic, N., Ziauddeen, H., Ersche, K. D., Farooqi, I. S., Bullmore, E. T., Nathan, P. J., … Fletcher, P. C. (2016). Increased body mass index is associated with specific regional alterations in brain structure. *International Journal of Obesity*, *40*(7), 1177–1182. https://doi.org/10.1038/ijo.2016.42

Meguro, T., Meguro, Y., & Kunieda, T. (2017). Atrophy of the parahippocampal gyrus is prominent in heart failure patients

without dementia. *ESC Heart Failure*, *4*(4), 632–640. https://doi.org/10.1002/ehf2.12192

Momenan, R., Steckler, L. E., Saad, Z. S., van Rafelghem, S., Kerich, M. J., & Hommer, D. W. (2012). Effects of alcohol dependence on cortical thickness as determined by magnetic resonance imaging. *Psychiatry Research*, *204*(2–3), 101–111. https://doi.org/10.1016/j.pscychresns.2012.05.003

Munoz, M. L., van Roon, A., Riese, H., Thio, C., Oostenbroek, E., Westrik, I., … Snieder, H. (2015). Validity of (Ultra-) short recordings for heart rate variability measurements. *PLoS One*, *10*(9), e0138921. https://doi.org/10.1371/journal.pone.0138921

Palma, J.-A., & Benarroch, E. E. (2014). Neural control of the heart: Recent concepts and clinical correlations. *Neurology*, *83*(3), 261–271. https://doi.org/10.1212/WNL.0000000000000605

Penttilä, J., Helminen, A., Jartti, T., Kuusela, T., Huikuri, H. V., Tulppo, M. P., … Scheinin, H. (2001). Time domain, geometrical and frequency domain analysis of cardiac vagal outflow: Effects of various respiratory patterns. *Clinical Physiology (Oxford, England)*, *21*(3), 365–376. https://doi.org/10.1046/j.1365-2281.2001.00337.x

Piccolo, L. R., Merz, E. C., He, X., Sowell, E. R., & Noble, K. G. (2016). Age-related differences in cortical thickness vary by socioeconomic status. *PLoS One*, *11*(9), e0162511. https://doi.org/10.1371/journal.pone.0162511

Quintana, D. S., Alvares, G. A., & Heathers, J. A. J. (2016). Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH): Recommendations to advance research communication. *Translational Psychiatry*, *6*, e803. https://doi.org/10.1038/tp.2016.73

Quintana, D. S., Guastella, A. J., McGregor, I. S., Hickie, I. B., & Kemp, A. H. (2013). Moderate alcohol intake is related to increased heart rate variability in young adults: Implications for health and well-being. *Psychophysiology*, *50*(12), 1202–1208. https://doi.org/10.1111/psyp.12134

Quintana, D. S., & Williams, D. R. (2018). Bayesian alternatives for common null-hypothesis significance tests in psychiatry: A non-technical guide using JASP. *BMC Psychiatry*, *18*(1), 178. https://doi.org/10.1186/s12888-018-1761-4

Reiter, K., Nielson, K. A., Smith, T. J., Weiss, L. R., Alfini, A. J., & Smith, J. C. (2015). Improved cardiorespiratory fitness is associated with increased cortical thickness in mild cognitive impairment. *Journal of the International Neuropsychological Society*, *21*(10), 757–767. https://doi.org/10.1017/S135561771500079X

Ritchie, S. J., Cox, S. R., Shen, X., Lombardo, M. V., Reus, L. M., Alloza, C., … Deary, I. J. (2018). Sex differences in the adult human brain: Evidence from 5216 UK biobank participants. *Cerebral Cortex*, *28*(8), 2959–2975. https://doi.org/10.1093/cercor/bhy109

Ruigrok, A. N. V., Salimi-Khorshidi, G., Lai, M.-C., Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure. *Neuroscience and Biobehavioral Reviews*, *39*(100), 34–50. https://doi.org/10.1016/j.neubiorev.2013.12.004

Seals, D. R., & Esler, M. D. (2000). Human ageing and the sympathoadrenal system. *The Journal of Physiology*, *528*(Pt 3), 407–417. https://doi.org/10.1111/j.1469-7793.2000.00407.x

Shader, T. M., Gatzke-Kopp, L. M., Crowell, S. E., Jamila Reid, M., Thayer, J. F., Vasey, M. W., … Beauchaine, T. P. (2018). Quantifying respiratory sinus arrhythmia: Effects of misspecifying breathing frequencies across development. *Development and Psychopathology*, *30*(1), 351–366. https://doi.org/10.1017/S0954579417000669

Sinnreich, R., Kark, J., Friedlander, Y., Sapoznikov, D., & Luria, M. (1998). Five minute recordings of heart rate variability for population studies: Repeatability and age-sex characteristics. *Heart*, *80*(2), 156–162. https://doi.org/10.1136/hrt.80.2.156

Sowell, E. R., Peterson, B. S., Kan, E., Woods, R. P., Yoshii, J., Bansal, R., … Toga, A. W. (2007). Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cerebral Cortex*, *17*(7), 1550–1560. https://doi.org/10.1093/cercor/bhl066

Storsve, A. B., Fjell, A. M., Tamnes, C. K., Westlye, L. T., Overbye, K., Aasland, H. W., & Walhovd, K. B. (2014). Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: Regions of accelerating and decelerating change. *Journal of Neuroscience*, *34*(25), 8488–8498. https://doi.org/10.1523/JNEUROSCI.0391-14.2014

Thambisetty, M., Wan, J., Carass, A., An, Y., Prince, J. L., & Resnick, S. M. (2010). Longitudinal changes in cortical thickness associated with normal aging. *NeuroImage*, *52*(4), 1215–1223. https://doi.org/10.1016/j.neuroimage.2010.04.258

Thayer, J. F., Ahs, F., Fredrikson, M., Sollers, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience and Biobehavioral Reviews*, *36*(2), 747–756. https://doi.org/10.1016/j.neubiorev.2011.11.009

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders*, *61*(3), 201–216. https://doi.org/10.1016/S0165-0327(00)00338-4

Thayer, J. F., Sollers, J. J., Labiner, D. M., Weinand, M., Herring, A. M., Lane, R. D., & Ahern, G. L. (2009). Age-related differences in prefrontal control of heart rate in humans: A pharmacological blockade study. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *72*(1), 81–88. https://doi.org/10.1016/j.ijpsycho.2008.04.007

Vijayakumar, N., Mills, K. L., Alexander-Bloch, A., Tamnes, C. K., & Whittle, S. (2017). Structural brain development: A review of methodological approaches and best practices. *Developmental Cognitive Neuroscience*, *33*, 129–148. https://doi.org/10.1016/j.dcn.2017.11.008

Voss, A., Schroeder, R., Heitmann, A., Peters, A., & Perz, S. (2015). Short-term heart rate variability—Influence of gender and age in healthy subjects. *PLoS One*, *10*(3), e0118308. https://doi.org/10.1371/journal.pone.0118308

Wei, L., Chen, H., & Wu, G.-R. (2018a). Heart rate variability associated with grey matter volumes in striatal and limbic structures of the central autonomic network. *Brain Research*, *1681*, 14–20. https://doi.org/10.1016/j.brainres.2017.12.024

Wei, L., Chen, H., & Wu, G.-R. (2018b). Structural covariance of the prefrontal-amygdala pathways associated with heart rate variability. *Frontiers in Human Neuroscience*, *12*. https://doi.org/10.3389/fnhum.2018.00002

Williams, V. J., Hayes, J. P., Forman, D. E., Salat, D. H., Sperling, R. A., Verfaellie, M., & Hayes, S. M. (2017). Cardiorespiratory fitness is differentially associated with cortical thickness in young and older adults. *NeuroImage*, *146*, 1084–1092. https://doi.org/10.1016/j.neuroimage.2016.10.033

Winkelmann, T., Thayer, J. F., Pohlack, S., Nees, F., Grimm, O., & Flor, H. (2016). Structural brain correlates of heart rate

variability in a healthy young adult population. *Brain Structure & Function*, *222*(2), 1061–1068. https://doi.org/10.1007/s00429-016-1185-1

Wood, K. N., Badrov, M. B., Speechley, M. R., & Shoemaker, J. K. (2017). Regional cerebral cortical thickness correlates with autonomic outflow. *Autonomic Neuroscience*, *207*, 28–36. https://doi.org/10.1016/j.autneu.2017.05.012

Woodward, S. H., Kaloupek, D. G., Schaer, M., Martinez, C., & Eliez, S. (2008). Right anterior cingulate cortical volume covaries with respiratory sinus arrhythmia magnitude in combat veterans. *Journal of Rehabilitation Research and Development*, *45*(3), 451–463. https://doi.org/10.1682/JRRD.2007.06.0082

Yoo, H. J., Thayer, J. F., Greening, S., Lee, T.-H., Ponzio, A., Min, J., … Koenig, J. (2017). Brain structural concomitants of resting state heart rate variability in the young and old: Evidence from two independent samples. *Brain Structure & Function*, *223*(2), 727–737. https://doi.org/10.1007/s00429-017-1519-7

Zhang, J. (2007). Effect of age and sex on heart rate variability in healthy subjects. *Journal of Manipulative and Physiological Therapeutics*, *30*(5), 374–379. https://doi.org/10.1016/j.jmpt.2007.04.001

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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