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Reduced functional connectivity between ventromedial prefrontal cortex and insula relates to longer corrected QT interval in HIV+ and HIV– individuals

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Abstract

Objective—Prolongation of the QT interval, i.e., measure of the time between the start of the Q wave and the end of the T wave, is a precursor to fatal cardiac arrhythmias commonly observed in individuals infected with the Human Immunodeficiency Virus (HIV), and is related to dysregulation of the autonomic nervous system. We investigated the relationship between QT interval length and resting state functional connectivity (rsFC) of the ventromedial prefrontal cortex (VMPFC), a core region of the brain that is involved with cardio-autonomic regulation.

Method—Eighteen HIV+ men on antiretroviral therapy and with no history of heart disease were compared with 26 HIV-negative control subjects who had similar demographic and cardio-metabolic characteristics. A seed-based rsFC analysis of the right and left VMPFC was performed at the individual subject level, and 2nd-level analyses were conducted to identify the following: group differences in connectivity, brain regions correlating with corrected (QTc) interval length before and after controlling for those group differences, and regions where seed-based rsFC correlates with CD4 count and QTc interval within HIV+ individuals.

Results—HIV-negative adults showed greater rsFC between the VMPFC seed regions and several default mode network structures. Across groups greater rsFC with the left anterior insula was associated with shorter QTc intervals, whereas right posterior insula connectivity with the VMPFC correlated with greater QTc intervals. HIV patients with lower CD4 counts and higher QTc intervals showed greater rsFC between the right VMPFC and the right posterior insula and dorsal cingulate gyrus.

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Conflict of Interest

Roger C. McIntosh; Dominic C. Chow; Corey J. Lump; Melissa Hidalgo; Cecilia M. Shikuma; and Kalpana J. Kallianpur declare that there is no conflict of interest.

Conclusions—This study demonstrates that QTc interval lengths are associated with distinct patterns of VMPFC rsFC with posterior and anterior insula. In HIV patients, longer QTc interval and lower CD4 count corresponded to weaker VMPFC connectivity with the dorsal striatum.

Significance—A forebrain control mechanism may be implicated in the suppression of cardiovagal influence that confers risk for ventricular arrhythmias and sudden cardiac death in HIV+ individuals.

Keywords

HIV; Resting state functional connectivity; Ventromedial prefrontal cortex; Anterior insula; Central autonomic network; QTc prolongation

1. Introduction

Despite the widespread availability of antiretroviral therapy, mortality from cardiovascular disease (CVD) has increased for persons infected with human immunodeficiency virus (HIV) (Enakpene et al., 2015). A large proportion of this CVD comorbidity has been attributed to sudden cardiac death (Tseng et al., 2012). The QT interval reflects the latency between the initiation of the QRS-complex and end of the T-wave and is used as a general marker of ventricular repolarization (Drew et al., 2010). Clinical presentation of ventricular arrhythmias (i.e., torsade de pointes) is partially attributed to prolongation of the QT interval (Viskin, 1999). The corrected QT interval (QTc) length is used clinically for predicting the risk of fatal arrhythmias and CVD mortality (Schouten et al., 1991). Increased sympathetic nervous activity and decreased parasympathetic activity may be linked to the clinical presentation of QT interval prolongation. Decades of research show that adrenergic stimulation of the left and right stellate ganglion causes prolongation followed by transient shortening of the QT interval (Abildskov, 1976; Zipes, 1991). This adrenergic influence is arrhythmogenic and can result in QT lengthening by contributing to the abnormal repolarization currents commensurate with ventricular arrhythmias (Jackman et al., 1988; Zipes, 1991; Shen and Zipes, 2014).

Evidence of significantly longer QT intervals in HIV patients, when compared to uninfected individuals, precedes the advent of combination antiretroviral regimens (Cohen et al., 1991; Shahmanesh et al., 1991; Villa et al., 1995; Kocheril et al., 1997; Enakpene et al., 2015). Current literature The syndrome continues to be present despite greater effectiveness of newer antiretroviral classes (Villa et al., 1995; Ogunmola et al., 2015). Prevalence of QT prolongation is estimated to be 3 to 5 times higher in HIV and AIDS patients than in the HIV-negative population (Sani and Okeahialam, 2005). Moreover, regimens that include protease inhibitors may predispose HIV-infected individuals to QT interval lengthening due to cardiometabolic stress (Sani and Okeahialam, 2005; Chinello et al., 2007; Charbit et al., 2009; Fiorentini et al., 2012; Shavadia et al., 2012; Ogunmola et al., 2015). The persistence of cardiac manifestations associated with QT interval lengthening has therefore become an emergent concern in HIV-CVD treatment as prolongation of this interval is present across the age continuum and at nearly every stage of infection (Wongcharoen et al., 2014; McIntosh et al., 2017).

Cortical and subcortical brain regions that participate in modulation of heart rhythm exhibit the same susceptibility to the deleterious effects of aging and neurodegenerative disease as cognitive or emotional brain regions (Goldstein, 2003; Kaufmann and Biaggioni, 2003; Kaufmann et al., 2004). The central autonomic network (CAN) involves structures that regulate heart rate and blood pressure; e.g., the medial prefrontal cortex (MPFC), insula, anterior cingulate cortex (ACC), hypothalamus, periaqueductal gray, and brainstem regions including the nucleus of the solitary tract (NTS) and the rostral and caudal ventrolateral medulla (Matthews et al., 2004; Wong et al., 2007; Thayer and Lane, 2009). The ventral region of the medial prefrontal cortex (VMPFC) is of particular interest given its role in top-down coordination of sympathetic and parasympathetic response to autonomic maneuvers (Beissner et al., 2013). A neurovisceral integration model describes a network of structures including the anterior and posterior insula, dorsal and subgenual cingulate, and amygdala that are functionally connected to the ventral and orbitofrontal cortex and are thought to regulate adjustment of heart rate and blood pressure to psychological and physiological challenge (Thayer and Lane, 2000, Thayer and Siegle, 2002). Whether VMPFC activity leads or lags behind alterations in cardioautonomic activity has been debated. Granger causality analysis has been used to show that elevations in VMPFC activity precede decreases in skin conductance, a marker of sympathetic arousal (Zhang et al., 2013). Neuronal tract-tracing studies in animals confirm inhibitory and excitatory connections from VMPFC to cortical areas (e.g., insula) and to subcortical cardiorespiratory structures (Verberne and Owens, 1998). Parasympathetic and sympathetic effects of the VMPFC have been lateralized to left and right hemispheres, respectively, in both human (Wittling et al., 1998; Hilz et al., 2001) and animal (Terreberry and Neafsey, 1983, 1987; Neafsey et al., 1986) studies. Central control of cardioautonomic function may be of particular relevance to HIV+ individuals as thinning of bilateral medial frontal and insular brain regions has been reported in this population (Thompson et al., 2005; Kallianpur et al., 2012).

Resting-state functional connectivity (rsFC) is a technique that assesses the brain's intrinsic function by correlating the time course of spontaneous blood-oxygen-level-dependent (BOLD) activity in a particular seed region of interest (ROI) to signals from other areas. RsFC is a technique well-suited for exploration of functional neural networks (Biswal et al., 1995) and is useful for categorizing patient populations by neural phenotypes. This measure of intrinsic BOLD signal fluctuations is thought to index a property of functional brain organization indicative of behavioral or physiological characteristics (Hahn et al., 2011; Kim et al., 2011; Zhu et al., 2012; Baur et al., 2013). Resting state connectivity of the VMPFC has also been implicated in cardio-autonomic regulation. For example, greater resting-state functional connectivity of the left VMPFC has been related to higher vagal tone indexed by heart rate variability in the temporal domain (Ziegler et al., 2009). There are several reasons why lower rsFC of the VMPFC might relate to QTc interval length in persons with HIV. Compared to healthy controls, individuals infected with HIV show deficits in intrinsic brain connectivity across the HIV disease spectrum (Thomas et al., 2013; Herting et al., 2015). Moreover, marked HIV-related reductions in intra-network connectivity has been reported for the default mode network (DMN), of which the VMPFC is a major hub, as well as reduced inter-network connectivity with the salience network which is anchored by the anterior insula (Wang et al., 2011; Thomas et al., 2013). If these structures are indeed

involved in the regulation of sympathetic and parasympathetic tone then it is conceivable QTc interval length might reflect their functional connectivity. In addition, prolongation of the QTc interval in HIV+ individuals has been most consistently linked to cardio-metabolic disease comorbidity (Reinsch et al., 2009), antiretroviral therapy regimen (Chinello et al., 2007; Charbit et al., 2009; Shavadia et al., 2012), and CD4 decline (QaQa et al., 2010; Ige et al., 2014; Wongcharoen et al., 2014; Gaharwar et al., 2017). The aim of the current study was to determine the brain regions whose rsFC with the VMPFC corresponds to QTc interval length; whether these regions differ between HIV patients on stable antiretroviral therapy (ART) and HIV-negative comparison subjects; and whether these rsFC patterns vary as a function of CD4 count in the HIV+ patients. We hypothesized that (1) greater rsFC of the VMPFC with CAN structures, such as the anterior insula, cingulate cortex, and brainstem medulla, would correspond with shorter QTc interval length; (2) VMPFC connectivity with the CAN, as a function of QTc length, would be lower in HIV patients compared to healthy controls; and (3) connectivity between the VMPFC and CAN structures would be lower in HIV patients who had greater QTc interval length and lower CD4 count.

2. Methods

2.1. Participants

Resting-state functional magnetic resonance imaging (fMRI) data obtained for a subset of ART-treated HIV patients in the Hawaii Aging with HIV–Cardiovascular Disease (HAHC-CVD) cohort (Shikuma et al., 2012) were examined for cross-sectional associations between rsFC and cardio-metabolic data from the parent study. HIV-negative comparison subjects were included as well. HAHC-CVD participants were recruited through referrals from the clinic at the Hawaii Center for AIDS, community physicians, community advisory board members, and AIDS service organizations; and were eligible for the study if they were 40 years old, had a documented history of HIV infection, had been on stable antiretroviral therapy (ART) 3 months, and if they spoke English as their primary language and could understand and provide informed consent. Excluded from the HAHC-CVD study were individuals with a confirmed history of myocardial infarction, arrhythmias, and congestive heart disease. Other exclusion criteria were: (i) uncontrolled major affective disorder; (ii) active psychosis; (iii) loss of consciousness >5 min; (iv) factors precluding MRI (e.g., claustrophobia); and (v) any past or present condition (e.g., central nervous system infection, traumatic brain injury, stroke, substance abuse) deemed by the evaluating physician to introduce confounding variables. All study participants underwent a physical exam and neuroimaging, and provided details of their medical history with a focus on HIV disease and CVD events and risk factors. Nadir CD4 count, years since HIV diagnosis, and date of ART initiation were provided by subject self-report. Blood specimens were obtained, and plasma HIV RNA and CD4 cell counts performed by a local commercial Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Basic laboratory evaluations included a complete metabolic profile, CBC, high sensitivity (hs)-CRP, fasting glucose, insulin and lipids. HIV-specific labs included HIV-RNA viral levels and CD4 and CD8 counts. A physical examination, with a focus on CVD (including peripheral vascular disease) and neurologic evaluations, was completed. Height, weight, waist-to-hip ratio, pulse, and blood pressure were measured.

HIV-negative control subjects for the HAHC-CVD cohort were recruited from the same region (Hawaii) as the HAHC-CVD participants. The HIV-negative individuals were over 40 years old, spoke English as their primary language, had seronegativity verified by an enzyme-linked immunosorbent assay (ELISA), fulfilled the same exclusion criteria as the HAHC-CVD participants, and underwent MRI and similar clinical testing (non-HIV-related variables). IRB approval was obtained from the University of Hawaii and all participants provided written informed consent prior to study entry. In the present work, our comparison subjects comprised the subset of HIV-negative controls who had cardio-metabolic and resting-state fMRI data and were gender-matched to our HIV+ group.

2.2. Electrocardiography

A standard, supine 12-lead electrocardiogram (ECG) was obtained by a trained technician using a HP-playwriter Xli with autoanalyzer. All twelve leads were recorded simultaneously. Manual QT measurements were obtained by a single ECG interpreter blinded to clinical information about the participants. QTc was derived by correcting the QT measurements for heart rate using Bazett's formula (Ahnve, 1985). The QRS interval, an index of ventricular depolarization, was measured from the end of the PR interval to the end of the S wave.

2.3. Neuroimaging

Magnetic resonance imaging was performed on a 3.0-Tesla Philips Medical Systems Achieva scanner equipped with an 8-channel head coil (InVision Imaging, Honolulu). For each subject, a high-resolution anatomical volume was acquired with a sagittal T1-weighted 3D turbo field echo (T1W 3D TFE) sequence (echo time TE/repetition time TR = 3.2 ms/6.9 ms; flip angle 8°; slice thickness 1.2 mm with no gap; in-plane resolution 1.0 mm²; field of view 256 × 256 mm²; scan time = 10.2 min). Resting-state fMRI echoplanar imaging (EPI) BOLD data were acquired with the subjects' eyes closed and with whole-brain coverage (TR/TE = 1600 ms/22 ms with 262 time points; flip angle 70°; 3.5 mm isotropic voxels; 37 sagittal slices with no gap; scan time = 7.5 min).

2.4. Resting-state fMRI data preprocessing

Standard methods for preprocessing of the blood oxygen level dependent (BOLD) signal were implemented for the 4D time series using a modified version of a shell script generated by *afni_proc.py* (http://afni.nimh.nih.gov/pub/dist/doc/program_help/afni_proc.py.html) from AFNI. Images were skull-stripped and co-registered to the fourth time point of the time series data. The initial 3 time points were discarded to allow T₁ saturation. We then applied standard preprocessing methods which included despiking the time series data; slice time correction; motion correction; and smoothing with a 4mm full-width half-maximum Gaussian kernel. Data were filtered using a band-pass filter ($0.008 < f < 0.08$ Hz). At the motion correction stage, 6 demeaned rigid body motion profiles and their derivatives were calculated by the *enorm* and *outliers* commands and used to censor the data (Saad et al., 2012). Participants were excluded if they had more than 0.4 mm head movement, in any direction, and as a result had more than 20% of the time points censored following preprocessing of the resting-state fMRI data. HIV+ and HIV-negative groups did not differ in the proportion of TRs removed due to motion. Nuisance covariates (signals associated with deep white matter and with cerebrospinal fluid averaged over the ventricles) were also

computed. To remove confounding effects of physiological noise and participant movement, the time courses for white matter, cerebrospinal fluid, and six motion parameters were regressed out in a whole-brain linear model (Fox et al., 2009). Group-level connectivity maps were generated using t-tests of individual functional connectivity contrast images. A voxel-level uncorrected p-value threshold ($p < 0.001$) with a cluster size ≥ 20 voxels was used to control for multiple testing (Nichols and Hayasaka, 2003). The skull-stripped anatomical scan for each participant was coregistered with the EPI data and aligned to Montreal Neurological Institute (MNI)-152 template space using a 2-step symmetric normalization algorithm to maximize sensitivity in important brainstem and subcortical brain regions; i.e., the Automated Brainstem Co-registration (ABC) method (Napadow et al., 2006).

2.5. Region-of-interest selection

Coordinates for the left and right VMPFC were derived from a previous study examining structures associated with the modulation of parasympathetic tone during rest (Ziegler et al., 2009) and from meta-analytic findings on cortical autonomic regulation (Beissner et al., 2013). Fig. 1 shows a spherical mask with a 6-mm radius centered on the left VMPFC that was created using the Montreal Neurological Institute (MNI) coordinates of (MNI: x, y, z -12, 55, -3). An identical seed was set in the right VMPFC (MNI: x, y, z 12, 55, -3). The time series for the seed region was obtained by averaging all voxels within the seed across the resting-state scan.

2.6. Seed-based resting-state functional connectivity analysis

Each participant's residual 4D volumes were spatially normalized by applying the previously computed transformation to MNI-152 template at a 1.75 mm³ voxel space. The mean time series from each seed was extracted by averaging across 925 voxels in each VMPFC seed region of interest (ROI) for left and right hemispheres. Within each subject's native space, we then performed a correlation analysis for each ROI using the AFNI program 3dfim+. The analyses produced participant-level correlation maps of all voxels in the brain that were positively or negatively correlated with the VMPFC seed time series. The correlation maps were converted to Z-value maps using Fisher's r-to-z transformation to improve normality, and were corrected for degrees of freedom (time points after censoring) using the equation: $z = \log [(1 + r)/(1 - r)] \times ((n - 3))/2$, where n = degrees of freedom. Z-score maps were entered into second-level statistical analyses. These z-scores represent the magnitude of positive and negative rsFC between the VMPFC seed regions and the whole brain in a voxelwise fashion. Statistical maps were obtained by segmenting the mean normalized high resolution T1-weighted images of all subjects into gray matter, white matter and cerebrospinal fluid before comparing activation across the whole brain. All second level analyses were conducted using statistical parametric mapping software package SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>).

2.7. Group comparison of resting-state functional connectivity

Seed-based regression analyses were followed by comparison of rsFC between HIV+ and HIV-negative individuals. Unpaired two-sample t-tests were performed on the z-score maps derived from each seed ROI. For all analyses, a voxel-level family-wise error (FWE)

corrected threshold ($p < 0.05$) with a cluster size 20 voxels was applied. Because of the absence of group differences in QTc intervals the study may be somewhat underpowered to detect large effect sizes in rsFC; thus a minimal uncorrected threshold ($p < 0.001$) with cluster size of 20 voxels was applied for all analyses involving QTc interval. Statistical maps were overlaid on the MNI-152 template.

2.8. Statistical analysis of QTc interval

A multiple regression analysis was performed for the entire study sample using the statistical parametric mapping software package SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>). First, QTc interval was used as a covariate of interest in a regression model predicting rsFC with the left and right VMPFC seed regions based upon individual connectivity maps. In an alternative model, a whole-brain voxel-wise analysis of covariance (ANCOVA), using the full factorial option of SPM 12 tested for group differences in regions, whose rsFC to the VMPFC seed regions corresponded to QTc interval independently of HIV-related differences in functional connectivity. Significance threshold was defined as $p < 0.05$ (FWE-corrected) with more than 20 contiguous voxels per cluster for t-tests and a threshold of $p < 0.001$ (uncorrected) with more than 20 contiguous voxels for regression models. All models controlled for age.

2.9. Functional correlates of QTc interval in HIV patients

A separate regression model was tested in HIV+ individuals using QTc interval and CD4 count as covariates of rsFC with the VMPFC seed regions. We specifically searched for brain regions showing greater VMPFC rsFC corresponding with higher CD4 count and shorter QTc interval, as well as brain regions showing greater rsFC with lower CD4 counts and greater QTc intervals.

3. Results

3.1. Subject characteristics

HAHC-CVD participants with resting-state fMRI data and electrocardiogram recordings comprised 23 HIV-infected adults. The sole HIV+ female subject was excluded from analysis because of insufficient information on menstrual cycle (QT interval has been shown to vary as a function of estrogen level, which changes significantly with menstrual cycle and menopause status) (Haserath et al., 2000; Kadish et al., 2004; Gökçe et al., 2005). An additional 4 HIV+ individuals were excluded because of excessive head motion, leaving 18 HIV patients (all male) in the final analyses. Among the 46 HIV-negative individuals with resting-state scans and QTc data, we excluded 10 females (because of gendermatching) and 10 out of 36 males (because of head motion), so that the final comparison group consisted of 26 HIV-negative male subjects. One HIV+ and one HIV-negative participant met the diagnostic criterion for QT prolongation (QTc > 440 ms).

Demographic variables did not differ between HIV+ and HIV- participants (Table 1). The groups had comparable cardiometabolic profiles although HIV-negative individuals had higher cholesterol and triglyceride levels than the HIV+ group. Both groups evidenced comparable EKG measures. The median CD4 cell count for the HIV+ group was 457

cells/mm³, and 14 patients (78%) had undetectable HIV viral load (<50 copies/ml). There was a positive trend correlation between QTc interval and age ($r = 0.27$, $p = 0.07$) and a negative trend correlation between QRS interval length and age ($r = -0.29$, $p = 0.06$) for the entire study sample.

3.2. Group differences in rsFC

Fig. 2 displays rsFC of the left and right VMPFC as a function of HIV+ status. Tables 2 and 3 list the MNI coordinates, cluster sizes, z-scores and p-values (FWE-corrected) for brain regions showing significant rsFC with the left and right seed ROIs in subjects grouped by HIV serostatus. HIV-negative participants showed typical connectivity patterns within the DMN, with the most consistent connectivity observed in the bilateral precuneus and middle frontal gyrus. There was also a consistent pattern of rsFC observed between the VMPFC seed regions and the caudate nucleus. These connectivity patterns were FWE-corrected. Tables 4 and 5 report regions showing greater rsFC with the left and right VMPFC seed regions that were significantly greater ($p < 0.05$ uncorrected) in the HIV+ group (compared to HIV-negative). These tables reflect a pattern of greater VMPFC rsFC with the medial frontal gyrus, precuneus, and inferior parietal lobe in HIV-negative individuals. Conversely, compared to HIV-negative individuals, the HIV patients showed greater rsFC between the VMPFC seeds and regions within the posterior cingulate, posterior insula, and left dorsal cingulate gyrus.

3.3. QTc associations with rsFC

Fig. 3 shows that across both groups, rsFC between the VMPFC seeds and regions within the insula were associated with QTc intervals. Specifically, shorter QTc intervals were associated with greater rsFC between the left VMPFC and a cluster on 35 voxels in the left anterior insula ($x, y, z = -46 -4 2$), $Z = 3.38$, $p < 0.001$) (see Fig. 3a). Similarly, greater rsFC between the right VMPFC and a cluster of 34 voxels in the left anterior insula ($x, y, z = -44 -2 2$), $Z = 3.88$, $p < 0.001$ uncorrected) was associated with shorter QTc interval lengths (see Fig. 3b). Conversely, longer QTc interval length was associated with greater rsFC between the left VMPFC and two clusters of 93 and 48 voxels in the right posterior insula ($x, y, z = 48 -34 32$), $Z = 3.71$, $p < 0.001$ uncorrected) and ($x, y, z = 56 -40 24$), $Z = 3.58$, $p < 0.001$ uncorrected), respectively (see Fig. 3c). Longer QTc intervals were also associated with greater rsFC between the right VMPFC and three clusters of 82, 104, and 49 voxels centered around the posterior insula ($x, y, z = 56 -42 22$), $Z = 3.93$, $p < 0.001$ uncorrected), ($x, y, z = 48 -34 32$), $Z = 3.91$, $p < 0.001$ uncorrected) and ($x, y, z = 48 -24 32$), $Z = 3.58$, $p < 0.001$ uncorrected), respectively (see Fig. 3d).

3.4. Group-level regression effects of QTc on rsFC

Resting-state functional connectivity uniquely associated with QTc interval length was examined by a model that adjusted for HIV-related differences in rsFC with the VMPFC seed regions. Controlling for age and group-differences in rsFC, there were no brain regions in the HIV-negative group corresponding with longer QTc interval length that survived minimum threshold criteria ($p < 0.001$, $k = 20$ voxels, uncorrected). However, in HIV+ patients greater rsFC between the left VMPFC and several clusters centered a group of 117 voxels in the right posterior insula ($x, y, z = 50 -38 14$), $Z = 3.79$, $p < 0.001$) was associated

with longer QTc interval (see Fig. 3e). Similarly, longer QTc intervals in HIV+ individuals were associated with rsFC between the right VMPFC was 168 voxels in the right posterior insula (x, y, z = 50 -38 14), $Z = 3.54$, $p < 0.001$) (see Fig. 3f).

3.5. HIV+ group regression for CD4 count and QTc interval

Fig. 4 depicts brain regions showing rsFC with the VMPFC seed regions as a function of QTc interval length and CD4 count, within the HIV+ group. In the HIV + group shorter QTc interval length and greater CD4 count correlated with greater rsFC between the right VMPFC and a large cluster of 130 voxels in the caudate head/ventral striatum (x, y, z = 2 8 0), $Z = 4.05$, $p < 0.001$ uncorrected) as well as 86 voxels in the cerebellar vermis (x, y, z = -2 -42 -26), $Z = 3.82$, $p < 0.001$). Similarly, this profile of better immune function and lower QTc interval length correlated with greater rsFC between the left VMPFC and a cluster of 175 voxels in the caudate head (x, y, z = 0 8 0), $Z = 4.05$, $p < 0.001$), 55 voxels in the cerebellar vermis (x, y, z = -2 -38 -24), $Z = 3.53$, $p < 0.001$), and 21 voxels in the left precuneus region (x, y, z = -28 -52 12), $Z = 4.62$, $p < 0.001$). The model that investigated rsFC of the right VMPFC seeds correlating with lower CD4 count and greater QTc interval revealed a large cluster of 417 voxels in the right posterior insula (x, y, z = 54 -42 16), $Z = 3.52$, $p < 0.001$), 104 voxels in the left medial frontal gyrus (x, y, z = -16 52 2), $Z = 3.60$, $p < 0.001$), and 2 clusters of 188 and 125 voxels in the right dorsal cingulate region (x, y, z = 26 -20 30), $Z = 3.89$, $p < 0.001$) and (x, y, z = 2 -2 38), $Z = 3.31$, $p < 0.001$), respectively. The model that investigated rsFC of the left VMPFC seeds correlating with lower CD4 count and greater QTc interval revealed a cluster of 221 voxels in the right dorsolateral prefrontal cortex (x, y, z = 54 40 4), $Z = 3.98$, $p < 0.001$), 127 voxels in the right insula (x, y, z = 56 -40 18), $Z = 3.37$, $p < 0.001$), and 102 voxels in the left anterior temporal lobes (x, y, z = -54 24 -12), $Z = 3.64$, $p < 0.001$).

4. Discussion

A substantial body of literature has linked altered cortical and subcortical brain activation patterns to dysregulation of the heart cycle. Recently there has been increased interest in this “heartbrain axis”, whose neural circuitry can be elucidated by functional neuroimaging (Taggart et al., 2011). The current investigation sought to determine whether rsFC of a key cardio-autonomic structure, the VMPFC, differed between HIV+ and HIV-negative individuals and was associated with corrected QT interval length after adjustment for demographic, HIV and CVD risk factors.

The VMPFC seed region selected for this analysis not only represents a brain center for cardio-autonomic regulation but also represents a major hub within the default mode network (DMN). Reduced intra- as well-as inter-DMN connectivity has been reported in HIV+ patients compared with healthy controls (Thomas et al., 2013). Left and right hemisphere connectivity were examined separately because of a likely left-lateralized vagal influence over heart rate variability at rest (Verberne and Owens, 1998; Wong et al., 2007; Ziegler et al., 2009). The spatial organization of regions showing significant positive rsFC with the left VMPFC seed depicted in Fig. 2 (ventral ACC, posterior cingulate, temporal lobes, and parahippocampal cortex, along with the negative correlations found with inferior

parietal lobules, reflected typical DMN organization (Greicius et al., 2003; Uddin et al., 2009). The rsFC observed between the right VMPFC and ventral striatum in both groups has been replicated in other resting-state fMRI studies (Di Martino et al., 2008). Notably, HIV-negative individuals evidenced above-threshold rsFC with large clusters in the posterior cingulate cortex extending into the precuneus. These rsFC patterns are typical of the DMN (Uddin et al., 2009; FitzGerald et al., 2012). Sub-threshold contrasts revealed greater rsFC between the right and left VMPFC with large clusters within the right inferior parietal cortex and left superior temporal cortex respectively. The inferior parietal and superior temporal lobes are also identified as hubs in the DMN (Greicius et al., 2003) (Raichle et al., 2001; Buckner et al., 2008). Medial prefrontal cortex and associated DMN structures are particularly vulnerable to the effects of aging and neurodegenerative disease (Bluhm et al., 2008; Seeley et al., 2009; Koch et al., 2010; Sambataro et al., 2010). At least one study has reported HIV-associated neurocognitive impairment to be associated with lower connectivity between DMN structures at rest (Wang et al., 2011). In addition to these intra-network deficits HIV+ individuals show lower inter-network connectivity between the DMN and both central executive and dorsal attention networks at rest as a function of age and HIV-related neurodegeneration (Thomas et al., 2013, 2015).

Across the entire cohort greater rsFC between the VMPFC seed regions and left anterior insula was consistently associated with shorter QTc interval. Perhaps the best evidence of the involvement of the insula in the etiology of QTc prolongation comes from studies of cerebral infarctions. Because of proximity of the insular cortex to the middle cerebral artery, cumulative evidence from stroke patients suggests that impact to the anterior insula region is implicated in QT interval dispersion (Eckardt et al., 1999; Afsar et al., 2003; Lederman et al., 2014). These findings are in line with evidence that the left anterior insula exerts parasympathetic influence on cardiac regulation (Oppenheimer and Cechetto, 2016). Seminal work showed that direct stimulation of this region results in a slowing of heart rate and a decrease in blood pressure (Oppenheimer et al., 1992). Others have shown that inactivation of the left insula results in tachycardia and increased blood pressure response (Zamrini et al., 1990; Yoon et al., 1997; Hilz et al., 2001). Our findings are strengthened by co-activation of the left VMPFC and anterior insula that supports maintenance of high frequency HRV during emotional arousal (Lane et al., 2009).

There was also a consistent pattern of greater rsFC between bilateral VMPFC and the right posterior insula corresponding to longer QTc intervals across the entire cohort. Activation of the posterior insula has long been implicated in sympathetic/pressor responses. Critchley and colleagues reported elevated cerebral blood flow to the right posterior insula during periods of elevated mean arterial blood pressure during bouts of mental stress and isometric exercise challenge (Critchley et al., 2000). Animal research has shown that stimulation of the right posterior insular increased cardiac sympathetic tone independently of pulse, blood pressure or respiration (Oppenheimer et al., 1998). Similar observations have been made in humans following low body negative pressure with increased heart rate corresponding to the right posterior insula (Kimmerly et al., 2005).

We observed significant, albeit uncorrected, effects of higher CD4 count and lower QTc interval with bilateral VMPFC rsFC to the subgenual cingulate and caudate. Hypo-activation

of the ventral striatum has been linked with lower high frequency HRV during a stress reactivity (Holsen et al., 2012) and emotion regulation paradigm (Åhs et al., 2009; Lane et al., 2009). Given the role of the caudate and basal ganglia in behavioral inhibition, these findings have been interpreted as participation of the caudate head in the somatomotor regulation of cardiovascular tone during emotional arousal (Lane et al., 2009). In contrast, we found uncorrected correlations of lower CD4 count and greater QTc interval with VMPFC rsFC to the dorsal anterior cingulate and right posterior insula. Meta-analyses have implicated both of these structures in tasks involving sympathetic arousal (Beissner et al., 2013). Chang and colleagues observed that in subjects at rest, activation of the dorsal cingulate coincides with periods of elevated low frequency heart rate variability; i.e., an index for sympathetic arousal (Chang et al., 2013). Brain stimulation studies involving the posterior insula in rodents not only resulted in atrioventricular block, premature ventricular contractions, QT prolongation, along with elevated norepinephrine discharge (Oppenheimer et al., 1991). HIV patients with low CD4 and greater QTc interval length demonstrated higher functional connectivity between the left VMPFC seed and two large clusters in the right dorsolateral (DLPFC) and left ventrolateral prefrontal cortex (VLPFC). Dorsal and ventral regions of the lateral PFC have been implicated in the regulation of sympathetic arousal (Beissner et al., 2013). Experimental studies and animal models support PFC involvement in autonomic regulation (Van Eden and Buijs, 2000; Gabbott et al., 2005). Given the resting rather than task paradigm used to acquire the BOLD signal, activity in these structures may very well reflect the bottom-up signaling of sympathetic arousal at rest rather than the top-down regulation of autonomic tone (Groenewegen and Uylings, 2000). Finally, left VMPFC showed rsFC with a cluster of voxels within the dorsal brainstem medullary region in those with lower QTc intervals and higher CD4 counts. Blood pressure, heart rate variability, and baroreceptor sensitivity are largely regulated by medullary structures (Beissner et al., 2013). Specifically, vagal afferents from aortic baroreceptors and cardiorespiratory chemoreceptors terminate in the dorsomedial region of the NTS and in the paraventricular nucleus and hypothalamus where they provide pivotal input for regulation of heart rate and blood pressure (Mifflin, 2001; Boscan et al., 2002; Schreihöfer and Guyenet, 2002; Coote, 2005; Resstel and Correa, 2006; Gabbott et al., 2007; Mandel Schreihöfer, 2008).

4.1. Limitations

The absence of group differences in the QTc interval length was unexpected. The HIV+ and HIV-negative groups were similar across most sociodemographic, cardio-metabolic, and cardio-autonomic indices. Studies examining HIV-specific risk factors for QTc prolongation mainly implicate antiretroviral regimen and CD4 count (Chinello et al., 2007; Charbit et al., 2009; Shavadia et al., 2012; QaQa et al., 2010; Ige et al., 2014; Wongcharoen et al., 2014; Gaharwar et al., 2017). Although the sample of patients may be too small to extrapolate findings to the general HIV population, it should be noted that the sample mostly had an undetectable viral load, the average CD4 counts was in the mid-range of illness, i.e., 458.83 cells/mm³, and only 50% of the sample reported protease inhibitor use. Thus, it may be concluded that the HIV+ sample demonstrated relatively lower risk for QTc prolongation on account of disease-related markers. Nevertheless, HIV+ individuals did show greater dyslipidemia compared to HIV-negative controls, which has been associated with risk of

QTc prolongation (Cardoso et al., 2001; Robinson et al., 2003). We consider the present work a useful starting point for future investigations of resting-state functional connectivity in HIV-CVD comorbidity. The association found here between decreased CD4 count and weaker rsFC requires confirmation by larger studies, which may also reveal effects of other HIV-related factors. Future work may employ stronger magnetic fields and higher voxel resolution to examine brainstem nuclei involved in cardio-autonomic regulation (Bianciardi et al., 2015). It will be important for such research to address the multisymptomatic nature of HIV-CVD comorbidity and to detail the contributions of primary cardio-metabolic dysfunction and immunosuppression, and of secondary factors such as anti-retroviral regimen, to HIV-related autonomic dysfunction (Chow et al., 2006, 2011) and ventricular arrhythmias (Girgis et al., 1997). Finally, a considerable limitation of this study was the lack of cardiac or respiratory-based gating. Heart and respiratory rate are significant components of the perfusion-based artifacts and physiological noise present in resting-state data (Chang et al., 2009; Birn, 2012). Future studies will not only need to provide artifact correction but also causality analysis to determine the direction of the relationship between blood oxygen-level-dependent and cardioautonomic signatures.

5. Conclusions

To our knowledge, this is the first study linking QT interval to resting-state functional connectivity of the brain. Our findings may shed light on heart-brain interactions and provide new evidence of a neurogenic mechanism for QTc lengthening. Immune status in HIV-infected individuals may be related to intrinsic functional connectivity of brain structures supporting autonomic function. Neuroimaging research has begun to elucidate the functional outcomes of brain regions susceptible to HIV neuropathogenesis. Assessing the functional integrity and connectivity of neural networks involved with cardio-autonomic regulation may further help assess risk for cardiac events.

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HIGHLIGHTS

- A seed-based resting state functional connectivity (rsFC) of the ventromedial prefrontal cortex (VMPFC) was compared to QTc length.
- Increased rsFC between VMPFC and anterior insula was linked to shorter QTc intervals.
- Greater frontal-striatal connectivity was linked to higher CD4 and shorter QTc length in HIV+ patients.

Fig. 1.
Seed regions in right and left ventromedial prefrontal cortex.

Fig. 2.

Resting-state functional connectivity (rsFC) of the left (2a)* and right (2b)* ventromedial prefrontal cortex (VMPFC) in HIV-negative individuals, rsFC of the left (2c)* and right (2d)* VMPFC in HIV+ individuals, and the contrast in rsFC between HIV-negative and HIV+ individuals in the left (2e)** and right (2f)** VMPFC seeds. *Family-wise error corrected, **uncorrected.

Fig. 3. Resting-state functional connectivity of left VMPFC seed region (first, third and fifth row) and RVMPFC seed region (second, forth, and sixth row) with brain regions associated with low QTc interval (3a & 3b), high QTc interval 3c & 3d), and contrast of HIV+ > HIV- with high QTc interval (3e & 3f). All clusters >100 voxels, $p < 0.001$ uncorrected.

Fig. 4. Resting-state functional connectivity of left VMPFC seed region (4a and 4c) and right VMPFC seed region (4b and 4d) with brain regions associated with high CD4 and low QTc interval (4a & 4b); and low CD4 and high QTc interval (4c & 4d) in subsample of HIV+ individuals ($n = 18$). All clusters $k > 100$ voxels, $p < 0.001$ uncorrected.

Table 1
Median demographic and clinical characteristics for HIV+ and HIV-negative study participants.

Characteristics	HIV+	Q1, Q3	HIV-negative	Q1, Q3	p-value
Age (years)	51.7	[47.6, 56.2]	55.1	[49.8, 62.5]	NS
Male gender (%)	18	100.0	26	100.0	
Caucasian (%)	9.0	50.0	17.0	65.4	NS
Education (years)	14.0	[12.0, 16.0]	14.0	[12.8, 16.3]	NS
<i>Cardio-metabolic risk factors</i>					
Current smokers (%)	7.0	38.9%	11.0	42.3%	NS
Body mass index	25.1	[23.5, 26.8]	27.1	[23.4, 31.5]	NS
Systolic blood pressure (mm/Hg)	121.0	[107.8, 128.5]	119.5	[114, 130.5]	NS
Diastolic blood pressure	70.0	[66.5, 83.5]	71.0	[66, 79.3]	NS
Cholesterol	172	[160.5, 190]	201	[175, 235.5]	p < 0.001
High density lipoprotein	57.5	[49, 68.8]	56	[40.70.5]	NS
Triglycerides	61	[52, 93.3]	133	[72, 211]	p < 0.05
<i>Electrocardiogram</i>					
Heart rate (beats per minute)	66.5	[61.5, 73.5]	60	[55.5, 65.3]	NS
QRS (milliseconds)	94.0	[88.0, 102.0]	91.0	[86.0, 98.5]	NS
QTc (milliseconds)	412.0	[396, 423.3]	410.5	[395.5, 431.5]	NS
PR (milliseconds)	157.0	[145.0, 173.0]	167	[155.5, 195.0]	NS
<i>HIV disease status</i>					
Undetectable HIV RNA (%)	14.0	77.8%			
Current CD4+ count (cells/ μ l)	457.0	[318.5, 611.3]			
Nadir CD4+ count (cells/ μ l)	97.0	[44.5, 188.0]			
CD8_absolute	804	[490, 1335.5]			
Time on ART (years)	12.5				
Protease inhibitors (%)	50.0				

Table 2

Significant ($p < 0.05$) (FWE-corrected) regions of positive rsFC with left ventromedial prefrontal cortex in HIV-negative ($N = 26$) and HIV + individuals ($N = 18$).

	MNI x, y, z	Voxels	Z-value
<i>HIV-negative</i>			
L. Caudate/anterior cingulate	-10, 20, -6	27	6.41
L. Precuneus	-8, -64, 18	210	6.12
L. Middle Frontal Gyrus	-28, 26, 42	78	6.02
L. Uvula/L. Cerebellar Tonsil	-6, -60, -42	115	6.01
L. Superior Frontal Gyrus BA 8	-22, 22, 54	73	5.96
<i>HIV-positive</i>			
L. Superior Frontal Gyrus	-26, 40, 28	30	5.87
L. Inferior Frontal Gyrus	-28, 36, -20	21	5.61
R. Supramarginal Gyrus	68, -56, 22	77	5.46
R. Claustrum	-22, -16, -20	27	5.44

BA = Brodman area.

Table 3

Significant ($p < 0.05$) (FWE-corrected) regions of positive resting-state connectivity with right ventromedial prefrontal cortex in HIV– negative ($N = 26$) and HIV + individuals ($N = 18$).

	MNI x, y, z	Voxels	Z-value
<i>HIV-Negative</i>			
L. Caudate head	–12 20 10	3572	7.04
L. Precuneus	–8, –64, 10	204	6.13
L. Middle Frontal Gyrus	–26 26 40	30	5.84
L. Superior Frontal Gyrus	–14 72 22	78	6.02
R. Precuneus	4 –46 36	95	5.35
<i>HIV-Positive</i>			
L. Caudate Nucleus	–16 18 12	319	5.91

BA = Brodman area.

Table 4

Significant ($p < 0.001$) (uncorrected) regions of greater resting-state connectivity in HIV– negative ($N = 26$) versus HIV+ individuals ($N = 18$) within the left and right ventromedial prefrontal cortex.

	MNI x, y, z	Voxels	Z-value
<i>LVMPPFC Seed (HIV– > HIV+)</i>			
L. Inferior frontal gyrus	–54 42 –6	74	3.91
L. Inferior frontal gyrus	–58 18 8	31	3.90
R. Middle Frontal Gyrus	58 26 38	84	3.89
L. Inferior frontal/Superior Temporal	–52 20 –10	309	3.79
<i>RVMPPFC Seed (HIV– > HIV+)</i>			
L. Inferior Parietal Lobule	–64 –58 44	289	4.19
R. Inferior Parietal Lobule	36 –30 36	21	4.06
R. Posterior Cingulate	22 –50 18	52	4.02
R. Precuneus	24 –50 16	29	3.79

BA = Brodman area.

Table 5

Significant ($p < 0.001$) (uncorrected) regions of greater resting-state connectivity in HIV + individuals (N = 18) versus HIV- negative (N = 26) within the left and right ventromedial prefrontal cortex.

	MNI x, y, z	Voxels	Z-value
<i>LVMPFC Seed (HIV+ > HIV-)</i>			
R. Posterior Cingulate	20 -48 14	118	4.15
R. Posterior Insula	36 -30 36	22	3.56
R. Posterior Insula	38 -28 36	22	3.50
R. Caudate nucleus	16 24 8	24	3.45
<i>RVMPFC Seed (HIV+ > HIV-)</i>			
L. Inferior Frontal Gyrus	-58 18 8	526	4.01
L Dorsal anterior cingulate	-4 44 36	21	4.06
L. Inferior frontal gyrus	-54 42 -6	54	3.75
L. Dorsal Anterior Cingulate	24 -50 16	29	3.79

BA = Brodman area.