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Anterior Insula Activation During Cardiac Interoception Relates to Depressive Symptom Severity in HIV-Positive and HIV-Negative Postmenopausal Women

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ABSTRACT

Objective: This study aimed to determine whether subclinical symptoms of depression in postmenopausal women are associated with blood oxygen level–dependent (BOLD) activity within the anterior insula during cardiac interoceptive awareness and whether this association differs for persons living with the human immunodeficiency virus (PWH).

Method: Twenty-three postmenopausal (mean [standard deviation] age = 56.5 [4.8] years) and 27 HIV-negative women (mean [standard deviation] age = 56.4 [8.0]) underwent functional magnetic resonance imaging while performing a heartbeat detection task. BOLD activation within the bilateral anterior insula based on the contrast of a heartbeat detection condition with and without a distracting tone was entered along with age, HIV status, and psychological stress into two multivariate regression models with self-reported depressive symptom severity as the outcome.

Results: Depressive symptoms did not vary by HIV status, nor was there a main effect or interaction for PWH on insula BOLD activation. Depressive symptoms were positively associated with psychological stress for the left ($\beta = 0.310$, $t(49) = 2.352$, $p = .023$) and right brain models ($\beta = 0.296$, $t(49) = 2.265$, $p = .028$) as well as the magnitude of BOLD activation in the left insula ($\beta = 0.290$, $t(49) = 2.218$, $p = .032$) and right insula ($\beta = 0.318$, $t(49) = 2.453$, $p = .018$), respectively. Exploratory analyses revealed that greater magnitude of BOLD activation attributed to interoceptive noise (tone) was also correlated with self-reported distrust and preoccupation with interoceptive sensations.

Conclusions: Results support an active interference model for interoceptive awareness wherein greater BOLD signal in the anterior insula in the presence of distracting exteroceptive stimuli may reflect greater prediction error, a feature of depression.

Key words: cardiac interoception, HIV, prediction error, depression, active interference model.

INTRODUCTION

Understanding the etiology of depression for women living with the human immunodeficiency virus (HIV) is important for disease management. Persons living with HIV (PWH) are estimated to have two to three times greater risk of being diagnosed with major depressive disorder (MDD) compared with HIV-negative controls (1,2). Women with HIV are especially vulnerable to depression, in part, because of the chronicity of uncontrollable physiological and psychosocial stress (3–5). Compared with their male counterparts, women living with HIV are more likely to be diagnosed with MDD and report greater depressive symptom severity (6–8). Data from the Women’s Interagency HIV Study show that each additional year spent with an MDD diagnosis increases the risk of mortality by 72% (9). The clinical manifestation of depression is not solely germane to disease management in PWH. In the era of antiretroviral therapy (ART), greater depressive symptom severity was associated with a higher odds of mortality compared with those initiated on ART with minimal to no depressive symptoms

(10). Certain groups of women seem to be at greater risk for depression with clinical diagnoses two to four times more likely to occur during and immediately after the menopausal transition than during premenopause (11,12). Among multiethnic samples of community-dwelling midlife women, higher ratings of depressive symptoms were most closely predicted by early postmenopausal stage and cumulative life stress (13). Much of the increase in depressive symptoms reported with the menopause transition in PWH is attributed to cardiovascular and autonomic somatic complaints (e.g., hot flash activity) (14–16). Therefore, it is essential to identify

AFNI = Analysis of Functional NeuroImages, **BOLD** = blood oxygen level dependent, **CiA** = cardiac-interoceptive awareness, **H** = heartbeat detection task, **HT** = heartbeat detection while ignoring tone, **IA** = interoceptive awareness, **MAIA** = the Multidimensional Assessment of Interoceptive Awareness, **MDD** = major depressive disorder, **MNI** = Montreal Neurological Institute, **MRI** = magnetic resonance imaging, **PPG** = photoplethysmography, **PSS** = Perceived Stress Scale, **PWH** = persons living with HIV, **ROI** = region of interest, **T** = tone detection task

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the contributing factors and interactive effects of depressive symptoms in the psychosomatic function. However, the field has yet to investigate interoceptive awareness (IA) of cardiac signals in relation to depressive symptoms among postmenopausal PWH.

Individuals with abnormal levels of interoceptive sensitivity seem to be at increased risk for psychopathology. Blunted cardiac IA is associated with depression (17,18). Behaviorally, women with major depressive disorder (MDD) have poorer interoceptive accuracy on a heartbeat counting task (19). Although behavioral studies of interoception are altogether absent in PWH, ancillary evidence in individuals with alexithymia supports interoceptive deficits in this population. Alexithymia, that is, difficulty identifying and describing feelings, has been described as a general deficit in IA and sensibility (20). In PWH, alexithymia has been linked to biomarkers of inflammation, cardiovascular disease risk, and HIV disease progression (21–25). Individuals reporting higher levels of alexithymia are shown to perform worse on heartbeat counting tasks (26–28). Moreover, mindfulness awareness training not only reduces self-reported alexithymia but also increases interoceptive accuracy during a heartbeat counting task over time (29). Given the disturbances in IA in depression and the rates of depression in HIV, the dearth of studies investigating how IA relates to depression in PWH is surprising.

Women in the perimenopausal and postmenopausal transition period are particularly affected by vasomotor symptoms. Perceptions of aberrant heart muscle contractions in the chest, including hard beats, fast beats, irregular beats, and/or pauses, increase IA, challenge self-regulation, and increase somatic symptom burden (30,31). Severity of vasomotor symptoms, including hot flashes, heart palpitations, or changes in blood pressure during perimenopause and postmenopause, also predict depressive symptom severity (32,33). Indeed, strong associations are observed between severity of depressive symptoms reported in primary care patients and the extent to which bodily sensations are noticed, attended to, and trusted (34). Among women living with HIV, the menopausal transition is associated with reports of greater mood disturbance and somatic, that is, related to the body, symptom burden (35–38). In turn, frequency of symptoms and physical symptom burden consistently relate to mood disturbance and psychological distress in women living with HIV (39).

Computational models of interoception implicate prediction error in the manifestation of psychopathology. To maintain homeostasis, viscerosensory information is monitored and used to predict upcoming requirements (40,41). Interoception entails an active and iterative process of comparing the brain's anticipation of incoming sensory information with concurrent state. When the prediction error is relatively small or nonexistent, the actual state of the body coincides with that of top-down predictions. However, when these signals are decoupled, larger prediction error and distress may emerge (18,42). The anterior insula, an important hub within the salience network, is involved in predicting afferent interoceptive stimuli (43–45). In healthy adults, functional activation of the insula is a commonly detected using cardiac interoception paradigms ranging from the counting (46–49) to attending (50–53) and discrimination of heartbeats (54). A computational model of IA has been put forth, suggesting that the anterior insula plays a critical role in the receipt of cardiac interoceptive information and in the generation of top-down predictions for moment-to-moment conscious states (55,56). This active interference model for the role of the anterior insula in depression suggests that mismatch of predicted and

actual interoceptive state triggers allostatic compensatory mechanisms to restore the perceived loss of homeostasis. This increased anterior insula activity that signals detection of prediction error is thought to dampen over time, with this loss of sensitivity giving way to chronic ignoring or mislabeling of interoceptive stimuli and concomitant subsequent loss of homeostatic control (57). Indeed, compared with patients in remission and healthy controls, individuals with MDD show hyporesponsiveness of the anterior insula during a cardiac IA task suggesting a deficit in the interoceptive processing of these signals in the depressed state (58). Another study reported inverse associations between insula activity during heartbeats detection task and depressive symptom severity in persons with MDD (50). Altogether, these studies provide evidence implicating hypoactive anterior insula in the generation of predictive error from cardiac interoceptive signals.

Although no functional studies have examined IA in HIV, structural and neurochemical differences have been noted in the insula. Multiple studies have tested and confirmed that levels of HIV-1 DNA are inversely associated with insula volume in PWH (59,60). Most recently, evidence of structural alteration of the insula has been confirmed across several imaging parameters of cortical thinning, including the following: lower gray matter volume, gyrification index, and cortical thickness (61). For example, longitudinal data comparing the trajectory of whole-brain thinning in PWH versus HIV-negative controls reveal volumetric reduction of insula, tempoparietal, and cingulate regions (62). Serotonergic depletion in the insula is associated with an increased risk of depression in PWH (63–65). In addition, acute changes in serotonin can alter metacognitive insight into the reliability of judgments based on cardiac interoceptive information (66). Given the role of the anterior insula in IA and depression as well as neurobiological and psychosocial susceptibility to insula disruption and depression in PWH, a functional neuroimaging investigation of these interacting factors is warranted.

Despite the support for hypoactivation of anterior insula during cardiac IA in MDD, little is known about how this region functions in subclinical depressive states. Examining insula function in clinical populations may be confounded by behavioral and subjective aspects of depression as well as depression-related changes in insula structure, metabolism, and regional homogeneity (for a review, see Ref. (67)). Given evidence of structural alterations of the anterior insula and increased susceptibility to depression in PWH (1,2,21,59,60), the current study aimed to compare anterior insula activation to depressive symptoms as a function of HIV+ status in ethnically diverse community sample of postmenopausal women not currently diagnosed or treated for MDD. Based on a model of active interference, we hypothesize that during a cardiac IA task, persons with greater depressive symptom severity will evidence greater magnitude of blood oxygen level-dependent (BOLD) activity in the bilateral anterior insula when presented with a distracting external sound. Moreover, after adjusting for age and levels of perceived psychological stress, postmenopausal women living with HIV will evidence greater depressive symptoms as a function of bilateral insula activation.

METHODS

Participants

The study was conducted at the University of Miami. All recruitment procedures and consent were approved by the University of Miami Institutional

Review Boards. First, participants recruited from the greater Miami-Dade County area were screened via telephone interview. Postmenopausal women, that is, women with the absence of a menstrual cycle for 12 or more consecutive months, were recruited for the study. The inclusion of postmenopausal women coincides with the primary objectives of the original study, which was to investigate the association between inflammatory-immune and endothelial cell functioning and mood disturbance in the context of vagal and estrogen withdrawal in women of postmenopausal age that are chronically infected with HIV. The rationale of exploring neurobehavioral markers of IA as a secondary analysis in this sample is based on the observation that changes in somatic symptoms of the vasomotor nature are linked to the mood disturbance postmenopause (33). Exclusion criteria included the following: a) diagnosis of a cardiovascular disease or condition, cancer, kidney/liver disease, or type 1 or type 2 diabetes; b) history of a cerebrovascular accident or loss of consciousness; c) current psychiatric medication treatment or diagnosis of psychiatric illnesses including major depressive disorder; d) current smoker; e) metal implants or debris within the body; f) current pregnancy, hormone replacement therapy, menstruation, or breastfeeding, g) positive urine toxicology screen for cocaine, amphetamines, or opioid; and h) if HIV+, had any interruption or change in prescribed antiretroviral regimen within the last 6 months, met the criteria for exclusion; however, women not currently on ARTs were not excluded, provided there was no change in this status over the last 6 months. Positive test result for tetrahydrocannabinol was not exclusionary in the current study. However, there were no positive screens for tetrahydrocannabinol in the current sample. Current diagnosis or treatment of MDD or other *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) Axis I disorders was determined using a structured clinical interview instrument, that is, the Mini International Neuropsychiatric Interview (68). Individuals meeting the criteria for current MDD were excluded from participating in the study.

Of the 84 participants in the brain scanning portion of the study, a total of 50 participants (23 HIV+, 27 HIV-negative) completed the task and provided interpretable psychophysiological and behavioral response data (Table 1). Fifteen scans were aborted resulting in an incomplete scan sequence for one or both 7.5-minute cardiac interoception tasks. Eight participants provided insufficient behavioral response data for one or more blocks of heartbeat or tone detection trials during the IA task. Finally, the program for physiological noise correction failed for 11 participants because of excessive motion artifacts or otherwise uninterpretable photoplethysmography (PPG) signals.

TABLE 1. Demographics

	HIV-Positive (n = 23), Mean (SD) or n	HIV-Negative (n = 27), Mean (SD) or n
Age, y	56.5 (4.82)	56.4 (8.0)
Years postmenopausal	8.9 (11.3)	9.0 (10.7)
Hispanic (n)	9.5	20.8
Black (n)	85.7	75.0
White (n)	4.8	4.2
BDI total score	10.5 (11.6)	12.8 (12.2)
Perceived stress	19.5 (2.6)	19.3 (2.9)
MAIA noticing	3.5 (1.1)	3.2 (1.3)
MAIA not distracting	2.5 (1.5)	3.1 (1.1)
MAIA not worrying	2.6 (0.7)	2.7 (1.0)
MAIA attention regulation	2.8 (1.5)	3.1 (1.2)
MAIA emotional awareness	3.6 (1.4)	3.6 (1.1)
MAIA self-regulation	3.4 (1.6)	3.5 (1.2)
MAIA body listening	3.2 (1.6)	2.8 (1.2)
MAIA trusting	3.8 (1.5)	3.9 (1.2)

SD = standard deviation; BDI = Beck Depression Inventory; MAIA = Multidimensional Assessment of Interoceptive Awareness.

TABLE 2. HIV+ Group Disease Characteristics

	Mean (SD) or n
Years with HIV	18.3 (9.4)
Years on antiretrovirals	11.34 (10.5)
On cART (n)	82.1
NRTI	0
NNRTI	28.6
PI	19.0
NtRTIs	9.5
INIs	25.0
Fusion inhibitors	0
Undetectable viral load (n)	66.7

SD = standard deviation; cART = combination antiretroviral therapy; NRTIs = Nucleoside reverse transcriptase inhibitors; NNRTIs = Non-nucleoside reverse transcriptase inhibitors; PIs = Protease Inhibitors; NtRTIs = Nucleotide reverse transcriptase inhibitors; INIs = HIV Integrase Inhibitors.

Neuroimaging data were collected between October 2017 and January 2020. Participants were asked to refrain from exercise or alcoholic consumption within 24 hours before the appointment and from drinking caffeinated beverages on the morning of the scan. Laboratory studies were drawn from the HIV-positive individuals to determine CD4 count (in cells per cubic milliliters) and detectability of HIV-1 RNA. HIV-1 viral load was determined using an in vitro nucleic acid amplification test (AMPLICOR HIV-1 Monitor Test; Roche Diagnostics, Branchburg, New Jersey) with ultrasensitive methods (range, 50–750,000 HIV-1 RNA copies/ml) and repeated with standard methods to determine if viral load met the upper detection limit (range of 400 copies/ml to 10 million copies/ml). Date of HIV diagnosis, current ART regimen, and length of duration of ART treatment at the time of the questionnaire were collected (Table 2).

Paradigm

An IA paradigm was adopted from Zaki and colleagues (54) wherein participants were instructed to monitor and respond to cardiac interoceptive (i.e., heartbeat) stimuli in the presence or absence of an auditory exteroceptive (i.e., tone) stimuli or simply monitor and detect the auditory tones. During the *heartbeat monitoring with tone* condition (HT), participants were instructed to make a response each time they felt their heartbeat while ignoring tones. During the *heartbeat monitoring* condition (H), participants were instructed to make a button press response, as quickly as possible, each time they felt their heartbeat in the absence of tones. During the *tone monitoring* condition (T), participants were prompted to make a button press each time they heard a tone.

During the practice session, each participant’s resting heart rate was determined so that tones could be presented at that participant’s heart rate, $H_r \pm 25\%$ random variance to simulate the natural variability in resting heart rate. For example, if a given participants’ resting heart rate was 60 beats/min, they would hear one tone every 1.00 ± 0.25 seconds.

Each task was presented in six 30-second blocks across two 7.5-minute functional runs. Participants were prompted to respond to visual and auditory prompts before the beginning of each of the cardiac IA blocks. Using an LCD Hyperion Magnetic Resonance Imaging (MRI) Digital Projection System, instructions were presented on a black background using white writing and viewed through a mirror mounted on the head coil. Each block was preceded by a 2-second visual presentation of the phrase “rate heart beat” or “rate tones,” indicating which task they should perform during that block. Blocks were separated by a fixation cross, presented for 3 ± 1 s. Biopac physiological recording systems were used to collect heart rate using a PPG and respiration rate using a respiratory transducer.

A standard protocol was implemented to familiarize study participants with the cardiac IA task and the MRI environment (e.g., scanner noises associated with the different pulse sequences) using a mock scanner outside

of the MRI suite. Before entering the MRI environment, participants were provided noise canceling headphones (Avotec, Inc.; Silent Scan SS-3300 Hearing Protection, Communication and Music System) to attenuate scanner noise during the practice (mock MRI) and real MRI sessions. All participants further underwent a verbal and tone auditory check before engaging in the heartbeat detection task while in the scanner.

Measures

Depression

Symptoms of depressive symptoms were assessed using the Beck Depression Inventory II (69). The Beck Depression Inventory II is a clinically robust 21-item self-report questionnaire. Individuals' items are rated on a 4-point scale indicating degree of severity, with items rated between 0 (not at all) and 3 (extreme form of symptom). Although not intended for diagnostic purposes, the following cutoffs are recommended for determining symptom severity: minimal = 0–13, mild = 14–19, moderate = 20–28, and severe = 29–63. This measure demonstrated good internal consistency ($\alpha = .84$).

Stress

Severity of psychological stress was assessed using the 14-item Perceived Stress Scale (PSS) (70). The scale measured how often individuals appraised situations in their lives as being stressful on a scale of 0 (never) to 4 (very often). Positive items were reverse scored, and items were summed to create a total PSS score. This measure demonstrated good internal consistency ($\alpha = .81$).

Multisource Interoceptive Awareness Questionnaire

The Multidimensional Assessment of Interoceptive Awareness (MAIA) is a 32-item self-report of IA (71). Five dimensions: a) awareness of comfortable, uncomfortable, and neutral body sensations; b) attitude of body awareness; c) quality of attention to somatic sensation; d) mind-body integration; and e) not distracting or worrying are measured by a eight subscales, including noticing, not distracting, not worrying, attention regulation, emotional awareness, self-regulation, body listening, and trusting (71). As an exploratory aim, the bivariate correlation of each of these subscales with the study variables was analyzed to determine whether the self-report indices of IA correspond to behavioral markers of interoception in relation to the other study variables. Subscales of the MAIA show good internal consistency with Cronbach α values ranging from $\alpha = .66$ to $\alpha = .87$.

Behavioral

During the H and HT conditions, individuals pressed the button when detecting their heartbeat. Accurate responses were recorded if the button press occurred within the biological response time allowable within the interbeat interval (≥ 120 milliseconds). Hit rate for each block of the H and HT conditions was calculated as number of accurate button presses divided by the total number of heartbeats detected by PPG signal. Response latency was determined by taking the time of the registered PPG signal and subtracting the time of the subsequent button press.

To test the null hypothesis that the hit rate and response latency did not vary across the H, HT, and T conditions, a repeated-measures analysis of variance was performed. Violations in the Mauchly test for sphericity necessitated Greenhouse-Geisser correction.

Photoplethysmography

PPG uses a transducer to measure total hemoglobin content in the superficial vasculature of the skin. The amplitude of the PPG signal reflects blood volume and its pulsatile variations with the cardiac cycle (72). PPG signals were sampled at 1000 Hz using a Biopac's AcqKnowledge software connected to the MP 150 digitizer system and PPG100C-MRI transducer attached to the participant's left index finger and (Biopac Systems Inc., Goleta, California). The PPG signal was synchronized to the MRI scanner trigger.

MRI Acquisition

MRI was performed on a GE MR750 3.0T MR scanner and 32-channel head coil capable of performing functional and structural scans in humans. In two 7.5-minute blocks, functional T2*-weighted echo planar images with BOLD contrast were acquired parallel to the AC-PC plane in bottom-up interleaved order using the following settings: 24 slices per volume; slice thickness, 3 mm; field of view, 240 mm²; matrix, 96 × 96; spatial resolution, 2.5 × 2.5 × 3 mm³; echo time, 25 milliseconds; repetition time, 2000 milliseconds; and flip angle, 50degrees. The initial five nonequilibrium volumes of each functional run were discarded from further analyses. High-resolution T1-weighted anatomical images were also acquired for everyone using a magnetization-prepared rapid gradient echo sequence (thickness, 1 mm; field of view, 256 mm²; matrix, 256 × 256; repetition time, 9.2 milliseconds; echo time, = 3.7 milliseconds; flip angle, 12 degrees). Before analysis, MRI data were visually inspected for warping, head coverage, blurring, and signal artifacts (including ringing, striping, ghosting, or signal loss; see http://fcon_1000.projects.nitrc.org/indi/enhanced/qc.html).

Functional MRI Preprocessing and Single-Individual Analysis

Before functional MRI analysis, the RETROICOR program was used for physiological noise correction to minimize global changes in BOLD signal within the brain because of low-frequency fluctuations in cardiac rate (73,74). This step was intended to enhance the signal of conscious cardiac processing and reduce the noise associated with afferent signaling of heart rate. Cardiac noise correction involved first removing the time-locked cardiac artifacts and then removing the low-frequency respiratory cardiac effects using methods previously described by Chang and Glover (74). Specifically, the heart rate time series was calculated as the inverse of the average interbeat interval using a 6-second sliding window. This time series was then convolved with the cardiac response function, and the resulting waveform is simultaneously regressed out of each voxel's time series using multiple regression.

The fMRI data were preprocessed using the Analysis of Functional NeuroImages (AFNI) software package (75), version AFNI_17.3.00. DICOM images were reconstructed into AFNI's *.BRIK format. Processing steps were generated with `afni_proc.py`. We used the following blocks: despiking, tshift (default), align, tlrc, volreg (default), blur (default), and regress (default). Frames were first despiked and slice-timing corrected. All the functional images of each run were realigned to the third functional image of that run. During the volume registration step, six motion parameters (roll, pitch, yaw, dS, dL, dP) were derived and demeaned, and derivatives were specified. These parameters were included in the regression. Functional images were coregistered to the structural image. Echoplanar images were normalized to a high-resolution Montreal Neurological Institute (MNI-152) atlas template followed by manual inspection to confirm successful alignment. Outliers were generated for the volume-registered data set based on whether a given time point greatly exceeded the mean number of voxel outliers for the time series and were subsequently removed using the `regress_censor_motion` function. A Gaussian filter (4-mm full-width half-maximum) was used for spatial blurring. A mask was created using the 3dAutomask algorithms. Voxels were resampled into 2.5-mm isotropic space. The .BRIK files were converted to NIFTI using the AFNI `3dAFNItoNIFTI` command so that these outputs could be used for second-level exploratory analyses in SPM-12.

First-level design matrices for each participant were estimated within the general linear model using AFNI. Events were modeled by a standard hemodynamic response function. The onset times were documented for each of the task conditions, which included the cued events (HT, H, T). Only responses recorded within 2 seconds of the trials were included. Using the 3dDeconvolve function, the impulse response function was first estimated and convolved with the stimulus time series to yield the estimated results. A generalized additive model regression was selected for the basis function because this model is more robust to stimuli that is brief (<2 seconds) and of relatively same length, that is, tone and heartbeat. The β weights derived from this approach represent the peak height of a

generalized additive model curve (approximately 12 seconds) found in the data (Cox, 1996). Effects for condition (HT, H, T) relative to baseline were computed using previously demeaned, cardiac noise-reduced, and normalized time series data for each voxel of the bilateral anterior insula. We focused on the contrast (H – HT) to best approximate activity germane to the discrimination of cardiac interoceptive information because each of the conditions in this contrast has interoceptive components. As outlined by Zaki and colleagues (54), examining this contrast provides a conservative estimate of anterior insula activity related to interoceptive attention when there is a need to filter out external distracters.

Regions of Interest

β Estimates of BOLD activity associated with button response during the HT, H, and T conditions relative to baseline were extracted from the anterior insula. The left and right anterior insula masks were adopted from a previous study implicating these structures as a key hub in the integration of afferent and efferent cardioautonomic signals (76). In that study, the anterior insula region of interest (ROI) was manually drawn by trained investigators on MRICron using a high-resolution T1 MNI template (ch2better.nii; <http://www.mccauslandcenter.sc.edu/mricro/mricron/stats.html>). The total volume of both ROIs was 15,664 mm³. The center of mass for the left anterior insula ROI was at MNI $x = 39.3$ mm, $y = 16.1$ mm, and $z = -0.8$ mm, whereas the right anterior insula ROI was at MNI $x = -35.3$ mm, $y = 16.6$ mm, $z = 0.3$ mm.

Statistical Analysis

Data screening included calculating descriptive statistics, intercorrelations between study variables, and variable distributions, and evaluating normality. No log transformations were required for variables departing from normality. Bivariate correlations were evaluated (two-tailed) and included primary and secondary (MAIA) study variables (Table 3). β Weights indicating BOLD activity to the H – HT contrast were extracted from left and right anterior insula ROIs were entered into two separate regression models, as independent variables, characterizing the main effect for activity in those ROIs on the dependent variable depressive symptoms. Controlling for the covariates of age and perceived level of psychological stress each model first tested the additive and then the interactive effect for the independent variables of HIV+ serostatus and BOLD activation to the H – HT contrast for both left and right anterior insula. To assess the statistical significance of the left and right insula models of cardiac IA, a Bonferroni correction of $\alpha = .025$ (e.g., $\alpha = .05/2$) was applied to each regression model. All analyses were conducted in SPSS version 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Macintosh, Version 27.0; IBM Corp., Armonk, New York).

RESULTS

Behavioral

As shown in Figure 1, the main effect for condition type on response hit rate was significant ($F(2,96) = 88.87, p < .001, \eta_p^2 = 0.649$). Participants detected a lower number of heartbeats without the tone (H mean = 35.3%) as compared with the tone distractor (HT mean = 65.5%) or just the tone by itself (T mean = 75.4; p values $< .001$). There was also a statistical difference between H and HT conditions ($p < .001$). However, there was no effect for HIV group status on hit rate accuracy across tasks ($F(1,48) = 0.420, p > .05$). The condition by HIV serostatus interaction was also significant ($F(2,96) = 5.37, p = .01, \eta_p^2 = 0.101$). In the tone condition, HIV+ participants also showed lower hit rates (mean = 68.4%) compared with HIV-negative women (mean = 82.4%; $F(1,48) = 5.632, p = .022$). However, this interactive effect was not observed for the H ($F(1,48) = 0.808, p = .373$) and HT conditions ($F(1,48) = 0.165, p > .05$).

As a key node within the salience network, during interoception, the anterior insula plays a role in differentiating low-fidelity or “noisy” from

TABLE 3. Bivariate Associations Between Study Variables (Two-Tailed)

Variable	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1 Age	-0.18	-0.24	0.11	0.13	-0.06	0.18	-0.04	0.17	0.02	-0.05	0.07	0.21	-0.08	-0.08
2 PSS	0.36**	0.04	0.08	0.08	0.29*	-0.19	-0.01	0.02	0.30*	0.10	0.05	-0.02	-0.09	-0.19
3 BDI-II		0.29*	0.31*	0.31*	0.12	-0.57	-0.29*	0.01	0.17	0.03	0.01	-0.01	0.37**	0.29*
4 BOLD left al			0.95**	0.21	0.21	-0.17	-0.26	0.26	0.33*	0.33*	0.30*	0.47**	0.12	0.23
5 BOLD right al				0.14	0.14	-0.19	-0.29*	0.16	0.25	0.024	0.22	0.42**	0.09	0.27
6 MAIA noticing						-0.23	-0.02	0.54**	0.68**	0.63**	0.51**	0.33*	-0.21	-0.20
7 MAIA not distracting							0.41**	-0.29*	-0.31*	-0.12	-0.24	-0.04	-0.15	-0.24
8 MAIA not worrying								0.03	0.08	0.10	0.03	-0.05	0.11	-0.25
9 MAIA attention Regulation								0.71**	0.68**	0.77**	0.41**	0.11	-0.13	
10 MAIA emotional awareness								0.71**	0.63**	0.53**	0.01	-0.12		
11 MAIA self-regulation											0.74**		-0.01	-0.25
12 MAIA body listening												0.49**	0.05	-0.16
13 MAIA trusting												0.53**	0.09	-0.03
14 MAIA disability														0.44**
15 MAIA pain scale														

PSS = Perceived Stress Scale; BDI = BDI-II = Beck Depression Inventory II; BOLD = blood oxygen level dependent; Multidimensional Assessment of Interoceptive Awareness; al = anterior insula.

*.05 level (two-tailed).

** .01 level (two-tailed).

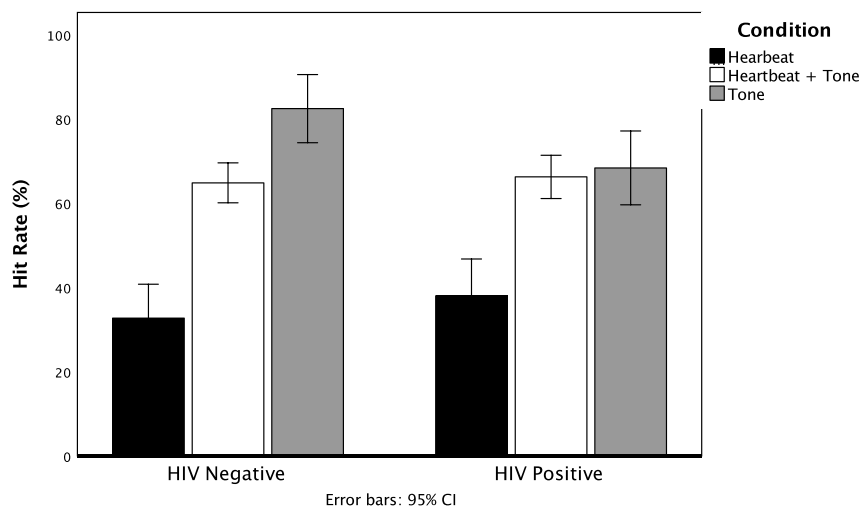


FIGURE 1. Comparison between HIV+ and HIV-negative controls of the mean hit rate during each of the interoceptive task conditions. CI = confidence interval.

high-fidelity signals that carry more predictive information. However, whereas response latency for both heartbeat (584.83 milliseconds) and heartbeat + tone (597.82 milliseconds) conditions was shorter for HIV+ women compared with controls (646.23 milliseconds) and (635.94 milliseconds), respectively, latency of response to the tone was longer for HIV+ women (639.75 milliseconds) compared with controls (546.19 milliseconds; condition by HIV serostatus interaction: ($F(2,96) = 12.13, p < .001, \eta_p^2 = 0.202$; Figure 2).

ROI Regression Models

For illustrative purposes, BOLD activation for each condition, as well as the contrast of interest, is depicted for the combined sample in MNI space (Figure 3). These functional activation maps are depicted at an unthresholded p value of .05. As mentioned in the Methods section, these maps were provided for visual purposes and do not reflect the primary analytic approach; that is, rather than being a dependent outcome variable, the parameter estimates generated from the H – HT contrast were used in a multivariate model

as independent predictors of depressive symptoms for the entire group. This constrained any test of the assumption differences in functional activation germane to HIV-associated covariance with depressive symptoms.

Separate linear regression models that analyzed the effect of HIV+ serostatus, BOLD activation, age, and psychological stress on depressive symptoms were significant in both the left ($F(4,49) = 3.677, p = .011$) and right ($F(4,49) = 4.01, p = .007$) anterior insula. HIV+ status was not associated with depression in the left ($\beta = -0.01, p > .05$) and right ($\beta = -0.01, p > .05$) models. BOLD activity linked to the H – HT contrast was associated with greater depressive symptoms in the left ($\beta = 0.290, t(49) = 2.218, p = .032$) and right ($\beta = 0.318, t(49) = 2.453, p = .018$) anterior insula models. These models explained 24.6% (left) and 26.3% (right) of the variance in depressive symptom severity. An interaction term between HIV+ status and BOLD activation of the anterior insula was specified for each model. This term was not significant for both the left ($\beta = -0.036, t(49) = -0.166, p > .05$) and right ($\beta = -0.202, t(49)$

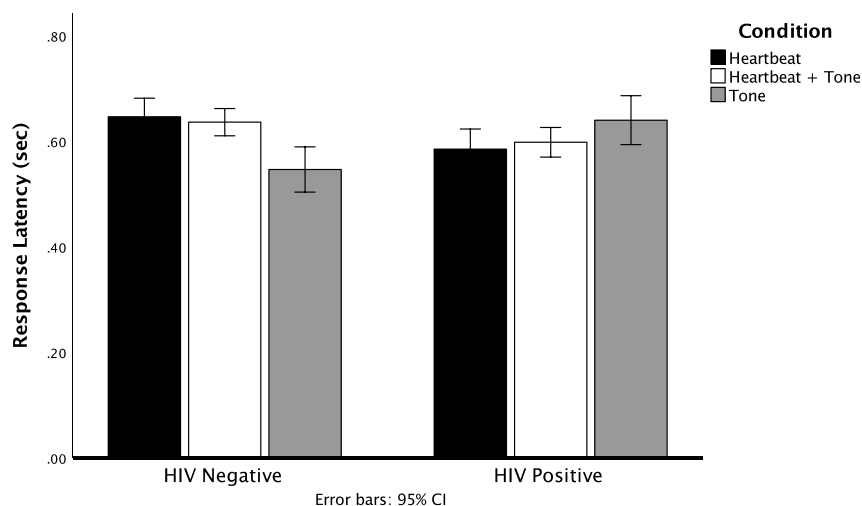


FIGURE 2. Comparison between HIV+ and HIV-negative controls of the mean response latency during each of the interoceptive task conditions. CI = confidence interval.

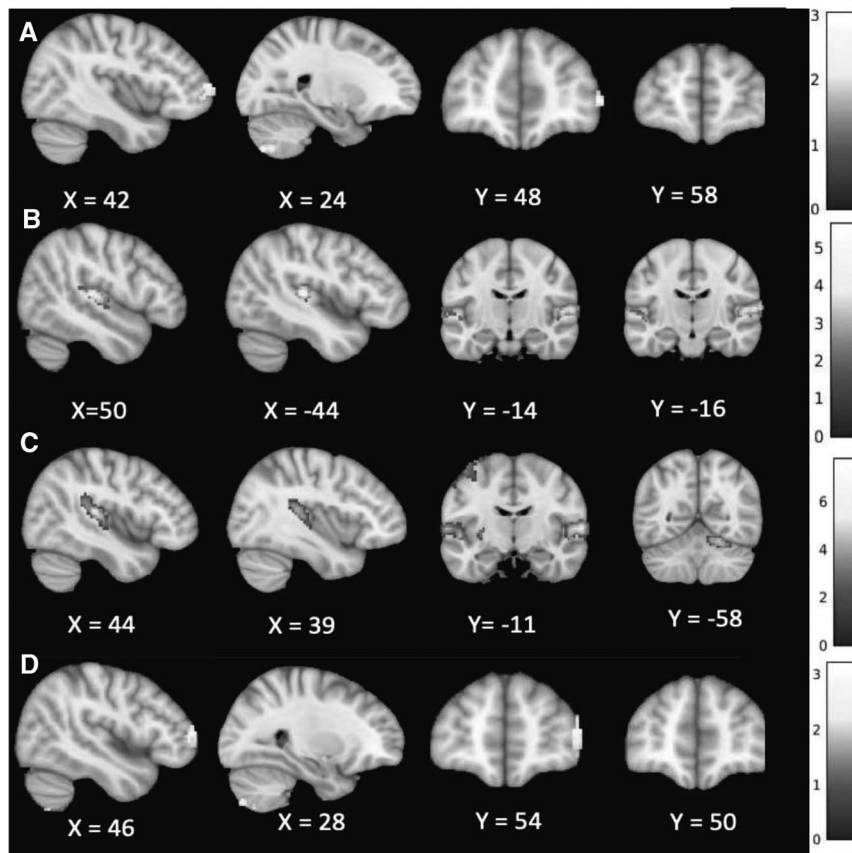


FIGURE 3. BOLD activations observed during (A) heartbeat detection, (B) heartbeat detection plus tone, (C) tone detection, and (D) contrast of conditions A and B. BOLD = blood oxygen level dependent.

$= -0.696, p > .05$) anterior insula models. Age was not associated with depressive symptoms in the left ($\beta = -0.222, t(49) = -0.167, p = .10$) and right anterior insula models ($\beta = -0.232, t(49) = -1.759, p = .085$). Perceived psychological stress was also related to depressive symptoms in the left ($\beta = 0.310, t(49) = 2.352, p = .023$) and right ($\beta = 0.296, t(49) = 2.265, p = .028$) anterior insula models.

Exploratory Analysis

As shown in Table 3, self-reported measures of IA reported on the MAIA not worrying subscale were associated with the primary independent and dependent variables. Less worrying about interoceptive sensations was associated with lower depressive symptom severity ($r = -0.29, p = .041$) as well as less BOLD activation isolated during cardiac interoception in the right anterior insula ($r = -0.29, p = .038$) and at the trend level for the left anterior insula ($r = -0.26, p = .066$). In contrast, self-reported trust of interoceptive signals was associated with greater activation in both the right ($r = 0.34, p = .017$) and left anterior insula ($r = 0.41, p = .003$).

DISCUSSION

In the current study, accuracy during heartbeat detection, with and without the presence of a distracting tone, as well as self-reported IA were comparable between postmenopausal PWH and HIV-negative controls. After accounting for age, HIV-serostatus, and levels of perceived psychological stress, bilateral anterior insula activation related to greater depressive symptom severity. The interaction for HIV+ serostatus with BOLD activity was not significant. How-

ever, positive correlations were observed among depressive symptoms, BOLD activity associated with heartbeat detection, and self-reported worry attributed to the awareness of interoceptive signals. These findings should be contextualized by the exclusion of persons currently diagnosed with, or treated for, MDD from participating in this study.

Compared with HIV-negative controls, postmenopausal PWH were faster to detect their heartbeat both with and without the presence of a distracting tone. The validity of these behavioral response findings may be ambiguous given the interindividual variability in methods used to detect heartbeats. Indeed, high levels of performance may be achieved during heartbeat detection tasks by participants estimating, rather than feeling, their heartbeat (77–79). Thus, it is unclear whether the shorter response latencies observed during heartbeat detection reflect greater attentional allocation to cardiac IA. However, the finding of lower tone hit rate in the HIV+ group is supported by studies reporting longer latency, lower target discrimination, and reduced electrocortical amplitude to auditory oddball stimuli in PWH compared with HIV-negative controls (80,81). Given that this study is the first to compare cardiac IA as a function of HIV+ serostatus, future replication is needed.

Greater anterior insula activation for H – HT was associated with depressive symptoms severity. The anterior insula functions as a major hub for the integration of interoceptive stimuli in conjunction with top-down appraisals (51,82,83). The effect for BOLD activity may be explained by the active interference model for interoception awareness in depression. In accordance with this model, greater

anterior insula activity during cardiac IA reflects large prediction error (i.e., greater mismatched state) and may compromise self-regulatory capacity (18). Furthermore, assigning negative appraisals to interoceptive signals (i.e., “there is something wrong with my heart”) contributes to prediction error, which may further challenge self-regulation and contribute to depressive affect. Greater cardiac IA coinciding with negative appraisals may reflect a neurobehavioral susceptibility for depressive symptom severity in midlife to older adult women. Post hoc analyses revealed that higher levels of the worried and distracted subscale of the MAIA were associated with severity of depressive symptoms. Moreover, women endorsing being less worried by attention to interoceptive stimuli showed lower activity in the left and right anterior insula isolated to the H – HT contrast. Hence, our data suggest that an inability to match interoceptive stimuli with top-down appraisals may enhance this prediction error in a manner that prompts worry or preoccupation with cardiac signals, further contributing to depressive symptom severity.

An interaction was expected between BOLD activity and HIV status given previous findings of neurobehavioral dysfunction in PWH. For example, advancing age is known to put HIV+ women are at increasing risk for developing MDD compared with HIV-negative controls (9). Persons with severe depression show reduced anterior insula BOLD activity during cardiac IA compared with moderately depressed persons (50,58). Using single-photon emission computerized tomography imaging in a sample of adult PWH reporting elevated levels of apathy, volumetric reductions of the insula were observed, and there was an association between hypoperfusion of the bilateral anterior insula and the severity of apathy (84). Meanwhile, others have reported HIV-related volumetric deficits of the insula (59,60). It is unclear whether these structural abnormalities previously reported in PWH translate directly to functional brain changes due to the independent and interactive effects of aging, HIV disease progression, and substance abuse cerebrovascular function (85). Moreover, although PWH show lower calibrated BOLD responses than healthy controls, these responses are much more variable because of aberrant coupling between the rate of cerebral blood flow and oxygen consumption (86). Although perceived psychological stress was a salient predictor of depressive symptoms exposure to other factors concomitant with the etiology of depression within this demographic such as exposure to unstable housing, low education, trauma, drug use, and violence, are likely coincidental for both HIV+ and HIV-negative women recruited for the study (87–89). Ultimately, larger samples are needed to detect what may be a small effect for HIV+ serostatus on activity within the anterior insula during cardiac IA. However, a recent study examining the association between interoceptive sensibility and mental health symptoms in women living with HIV found that, although lower levels of psychological distress tracked with higher levels of interoceptive sensibility and body trusting self-reported interoceptive accuracy did not vary as a function of HIV+ status (90). Coinciding with our findings, this study supports the absence of a neurobehavioral deficit in IA among PWH.

Other neurobehavioral mechanisms for depression have been described in PWH. Among those most commonly studied include stress-mediated neuroinflammatory signaling, altered monoaminergic and glutamatergic transmission throughout reward pathways, and neurodegenerative processes ensuing from the proliferation of HIV-proteins GP-120 and Tat (91). HIV seems to also have an affinity for frontostriatal brain regions with alterations often

coinciding with symptoms of apathy and depression (92–97). Our null findings for a unique neurobehavioral correlate for depressive symptom severity in the anterior insula of PWH during cardiac IA is surprising given that this region was among the only cortical areas showing significantly lower serotonin transporter binding in comparison to HIV-negative controls (63–65).

Given the cross-sectional study design, temporal precedence of functional brain changes on the manifestation of depressive symptoms cannot be inferred. Studies comparing longitudinal trajectories or effects for behavioral interventions on depression are required to elucidate the role of the anterior insula in the etiology of depression. It is also important to note that 12% of the total sample endorsed at least one lifetime depressive episode before the study. Thus, the current findings do not speak to the complete absence of lifetime MDD but do support what others have shown to be comparable levels of anterior insula activation between nondepressed and those in remission during heartbeat interoception (47). Sample size was another important limitation for the current study, and future studies should look to encompass a more heterogeneous sample. However, it has been demonstrated that the detection of heartbeats with synchronous or asynchronous tones is reliably and most optimally determined using 40 to 60 trials in samples as small as $n = 25$ (98).

CONCLUSIONS

Given that anterior insula hypoactivity during cardiac IA is a feature of MDD, our findings beg the question of why greater activation of this region is positively associated with depressive symptom severity in a subclinical sample. First, it must be reiterated that, although studies have primarily focused on insula activity associated with attending to the heartbeat, the contrast used to predict depressive symptoms in the current study reflects the activity associated with the processing of a distractive exteroceptive tone. According to the active interference model, this increased exteroceptive noise leads to prediction errors generated from unreliable interoceptive signals (17). Playing a specific role is the insula and its ability to integrate interoceptive or exteroceptive stimuli for homeostatic purposes and in doing so produce a sense of material self within a predictive coding framework (83). Given the specificity of anterior insula to IA, noisy or low fidelity signals not derived from bodily state are poorly differentiated from cardiac interoceptive afferents that carry information about more predictive outcomes. With respect to the role of anterior insula in the etiology of depression, Paulus and Stein (18) and Paulus et al. (99) posit that noisy afferent interoceptive information reflects a partial failure of the cognitive control apparatus to differentiate predictive from nonpredictive signals. According to this model, individuals at risk for depression process a greater ratio of noise to signal within the anterior insula during heartbeat interoception. This prediction error results in uncertainty for the future self in relation to the external world and over time may lead to altered self-awareness, avoidance, and behavioral withdrawal.

We interpret the current findings to suggest that, during IA, the neural representation of a distracting tone in the anterior insula reflects the additional noise associated with the dual processing of distracting exteroceptive stimuli. In the anterior insula, individuals at greater risk for depression exhibit lower signal-to-noise ratio of cardiac interoceptive afferents during IA. Given that lower exteroceptive noise was related to less self-reported worry about and greater trust of interoceptive sensations further supports the consequence of predictive error in the increased risk of depression.

Within an active interference framework, this study provides support for a relationship between exteroceptive processing during IA and increased risk of depression in postmenopausal women regardless of HIV status.

Future studies should also examine HIV-associated biotypes that could potentially modify the observed associations between cardiac IA and depressive symptom severity. Given that PWH treated with ARTs in advantaged countries are often able to achieve undetectable viral load status and CD4+ cell recovery, there has been a shift in attention to other HIV biotypes such as humoral and cellular inflammation status also shown to be predictive of HIV-associated mood disturbance and neurocognitive impairment (100–103). Functional imaging studies reveal that both cognitive and interoceptive task performance and corresponding activity in mid-insula and anterior-insula do vary as a function of change in levels of peripheral inflammation (104,105). Given recent findings showing that the relationship between depression severity and insula activity during an interoceptive task varies as a function of peripheral levels of the proinflammatory cytokine interleukin 6 (106), future studies may wish to examine the interactive effect of inflammatory burden and different stages of HIV disease severity on interoceptive processes in PWH and whether this may mitigate effects on depressive symptom severity or treatment response.

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