MEDITATION AND AEROBIC EXERCISE ENHANCE MEMORY AND MENTAL HEALTH IN WOMEN LIVING WITH HIV

By

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ABSTRACT OF THE DISSERTATION

Meditation and aerobic exercise enhance memory and mental health in women living with HIV

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Human Immunodeficiency Virus (HIV) infects the body, including the brain. After being infected with HIV, people often experience additional traumas, along with symptoms of mental illness related to stress, depression and anxiety. In this study, women with HIV (*n* = 37) were assessed for posttraumatic cognitions (Posttraumatic Cognitions Inventory), ruminative thoughts (Ruminative Responses Scale), perceived stress (Perceived Stress Scale), depressive symptoms (Beck Depression Inventory) and anxiety symptoms (Beck Anxiety Inventory) with self-report questionnaires. Mental health symptoms were highly correlated with one another within individuals. An exploratory factor analysis was performed on responses to the five questionnaires to determine which items related most highly to a common underlying construct, and how these symptoms vary and relate to interoception. Measures of mental health loaded highly and consistently onto one factor and accounted for 66% of the variance in the data. Women that were more representative of the trait captured by this principal factor (i.e., those with higher factor scores) reported that they were less able to sense their bodily sensations

and less able to regulate thoughts and feelings when assessed with the Multidimensional Assessment of Interoceptive Awareness. Thus, women who reported poor awareness of bodily sensations were experiencing greater numbers of trauma-related and ruminative thoughts, as well as feelings of stress, depression and anxiety. Although interoceptive sensitivity did not relate to interoceptive accuracy, accuracy was positively related to recognition memory, indicating women who could better detect their heartbeats were likewise better at remembering everyday information. These results suggest that women with HIV may respond especially well to interventions that target processes of learning and memory. In particular, they might benefit from a combined mind and body intervention that enhances awareness of emotional states as they emerge in the body, along with tools to regulate maladaptive thoughts and feelings.

Mental and Physical (MAP) Training targets the brain and the body through a combination of 30 minutes of focused-attention meditation and 30 minutes of aerobic exercise. The following pilot study tested whether six weeks of MAP Training would enhance hippocampal-dependent processes of learning and memory (assessed with the Behavioral Pattern Separation task) and reduce mental health symptoms (assessed with self-report questionnaires) in women with HIV ($n = 18$). After six weeks of combined meditation and aerobic exercise training, participants performed better during a pattern separation task related to discrimination learning. They reported fewer ruminative thoughts, depressive symptoms, less perceived stress and fewer posttraumatic cognitions. Reductions in rumination and depression persisted at six months post-training. Heart rate variability, interoceptive accuracy and interoceptive sensibility did not change after six weeks of combined meditation and aerobic exercise. These data support the combination of meditation and aerobic exercise as an effective add-on treatment to address cognitive and mental health challenges faced by women living with HIV.

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Introduction

Over one million adults in the United States are living with human immunodeficiency virus (HIV) (CDC, 2020). Left untreated, HIV ultimately develops into acquired immune deficiency syndrome (AIDS), which is deadly (CDC, 2020). Antiretroviral therapies allow people with HIV to live longer and better quality lives without developing AIDS (Nachega et al., 2011), but many suffer from the psychological stress of living with a chronic disease. The prevalence of mental illness in people with HIV is high, with rates as high as 74% for depression, 37% for suicide ideation and 19% for generalized anxiety disorder (Beer et al., 2019; Orza et al., 2015).

Women with HIV are twice as likely to experience trauma compared to women without HIV (Gielen et al., 2007; Machtinger et al., 2012; Wyatt et al., 2002). Many continue to experience trauma throughout their lifetime and develop trauma-related symptoms as a result. Fifty-five percent of women with HIV are victims of intimate partner violence and 42% meet full criteria for posttraumatic stress disorder (PTSD) (Machtinger et al., 2012; Martinez et al., 2002). Rumination is the tendency to engage in repetitive thoughts, which are oftentimes autobiographical, negative and about the past, and can emerge as a result of trauma (e.g., Millon, Chang, & Shors, 2018). Women with HIV are more likely to ruminate, and experience higher perceived stress and depression as a result (Nightingale et al., 2010; Yanes et al., 2012).

The trauma of living with a chronic disease such as HIV impacts the relationship between mental and physical health outcomes (Gore-Felton & Koopman, 2008; Ivanova et al., 2012; Looby et al., 2018). For example, women with HIV report feeling anxious about their HIV status, which consequentially impacts their sleep, appetite and ability to concentrate (Schulte et al., 2018). Anxiety and depressive symptoms reduce adherence to medication, which in turn compromises physical health (Hart et al., 2008; Schönnesson et al., 2007; Willie et al., 2016). Therefore, it is important to determine how mental and physical health interact potentially to compromise health status in people living with HIV.

Interoception refers to the mental awareness of the body's physiological state and thus depends on the interaction between mental and physical processes. In particular, cardiac interoception refers to the awareness of one's own heartbeat. Even though the heart beats approximately 100,000 times a day, we are generally unaware of it. This awareness relies on distributed signals from receptors and neural networks, including those related to temperature, pain, visceral sensations and activation of the autonomic nervous system. Three common dimensions of interoception have been proposed and include interoceptive accuracy, sensibility and awareness (Garfinkel et al., 2015; Garfinkel & Critchley, 2013). Interoceptive accuracy refers to the objective measure of detecting or tracking body sensations, such as heartbeats, whereas interoceptive sensibility measures subjective interoception through self-report. Interoceptive awareness is defined as a person's confidence in or beliefs about their own interoceptive accuracy or sensibility (Garfinkel & Critchley, 2013). Some studies support at least partial independence of these dimensions. There is some evidence that trauma can reduce interoceptive sensibility (Payne et al., 2015; van der Kolk, 2006), whereas cognitive processes related to learning and memory can enhance it (Pollatos et al., 2007). Research on interoceptive processes are limited for people living with HIV. If anything, the data suggest that people with HIV/AIDS are more aware of their body sensations (Gonzalez et al., 2001, 2016). But again, the data are limited.

In other populations, trauma-related thoughts co-occur with symptoms of depression and anxiety. For example, we recently reported that trauma-related cognitions and ruminations are highly related and coalesce within women with sexual violence history, regardless of PTSD diagnosis (Millon et al., 2018). Whether similar relations exist in women living with HIV is unknown. There is evidence that brooding ruminations and lower interoceptive accuracy accounts for depression and anxiety-related distress in young adults (Lackner & Fresco, 2016), but these interactions and relationships have not been analyzed in women with HIV.

The present study analyzed relationships among mental health outcomes, such as depression and anxiety, with cognitive processes involving memory, and their association with interoception, both with respect to sensibility and accuracy. Interoceptive accuracy of the heart was measured using a heartbeat tracking task (Garfinkel et al., 2015; Rae et al., 2020; Schandry, 1981). Interoceptive sensibility was defined here as beliefs about bodily sensations assessed through self-report with the Multidimensional Assessment of Interoceptive Awareness (Mehling et al., 2012, 2018). (Since its original publication in 2012, Mehling and colleagues have acknowledged that the construct of interoceptive awareness was designed to measure what is now more commonly identified as interoceptive sensibility (Mehling et al., 2018)). First, we used factor analyses to detect the potential contribution of trauma-related and ruminative thoughts, reported levels of perceived stress, and depressive and anxiety symptoms to a central construct of mental health. It was hypothesized that mental health symptoms would be highly correlated within individuals, and that higher numbers of mental health symptoms would be related to lower interoceptive sensibility. Second, we examined the relationship between interoceptive sensibility and accuracy. It was hypothesized that women who reported that they were more aware of their body's physiological state would be more accurate at tracking their heartbeats. Third and finally, we investigated the relationship between interoceptive accuracy and recognition memory. It was hypothesized that women with HIV who were more accurate at tracking their own heartbeats would also be more accurate at remembering and recognizing previously-viewed information.

Method

Participants

Thirty-eight female participants (95% Black/African-American, 2.5% Latina, 2.5% White) between the ages of 22-68 years (M_{age} = 45 years) living with HIV participated in this study. Participants were recruited from the François-Xavier Bagnoud (FXB) Center, Rutgers University Hospital and St. Clare's Housing

Program in Newark, NJ, where individuals with HIV come for counseling and medical treatment.

Procedure

Participants were provided with information about the study and written informed consent was obtained in accordance with the Declaration of Helsinki. This study was carried out in accordance with the recommendations of the Institutional Review Board at Rutgers University. All research staff were certified by the Collaborative Institutional Training Initiative (CITI) for Human Subjects Research. Participants completed self-report questionnaire measures of trauma history, trauma-related cognitions, ruminative thoughts, perceived stress, depression, anxiety, and interoception (outlined below). After completing questionnaire measures, participants completed a memory recognition task on a computer. Following the memory task, participants completed the heartbeat tracking task during electrocardiography (ECG) recording.

Life Events Checklist. The history of traumatic events was assessed with the self-report Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013). The LEC assesses exposure to 16 events related to stress and trauma, including natural disasters, transportation accidents, physical and/or sexual assault, and serious injury.

Posttraumatic cognitions: The frequency and type of posttraumatic cognitions were assessed with the Posttraumatic Cognition Inventory (PTCI; Foa, Ehlers, Clark, Tolin, & Orsillo, 1999). The PTCI is a 33-item questionnaire composed of three subscales: thoughts associated with the extent to which one negatively views oneself (i.e., blameworthy, isolated, unreliable), others (i.e., untrustworthy), and the world (i.e., dangerous). The purpose of the PTCI is to assess the person's reaction to the event after time has passed and includes items such as "*I have to be on guard all the time*," "*I feel like I don't know myself anymore*," and "*I feel isolated*." We altered the prompt to ask participants about their thoughts and feelings related to "*the most stressful event of your life*." This way, women with no trauma history could also report their thoughts and feelings related to a very stressful past event.

Ruminative thoughts: The frequency and type of ruminative thoughts were assessed with the Ruminative Responses Scale (RRS; Treynor, Gonzalez, & Nolen-Hoeksema, 2003). The RRS measures how often a person engages in specific thoughts related to sadness. The RRS contains 22 items including: "*think about how alone you feel*," "*think about how hard it is to concentrate*," or "*think about "why do I always react this way?*'" Items are scored on a scale from 1 (almost never) to 4 (almost always). The RRS is scored as a summation of responses (min 22; max 88) as well as according to three subscales: (1) depressive ruminations, which relate to the rehearsal of depressive events, (2) brooding ruminations, which are often non-adaptive and emotion-laden, and (3) reflective ruminations, which are not as maladaptive but self-focused (Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013; Shors, Millon, Chang, Olson, & Alderman, 2017). Healthy young adults self-report rumination scores of approximately 42-44, women with sexual violence history report rumination scores of approximately 54, and depressed individuals report rumination scores of approximately 60 (Millon et al., 2018; Nolen-Hoeksema, Larson, & Grayson, 1999; Shors et al., 2017).

Perceived Stress: Perceived stress was assessed with the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). The PSS assesses a person's self-reported ability on how well she has handled events from the past month. The PSS contains 10 items such as "*In the last month, how often have you felt nervous and stressed?*" and "*In the last month, how often have you felt that you were on top of things?*" Items are scored on a scale from 0 (never) to 4 (very often). PSS scores ranging from 0-13 are considered low perceived stress, 14-26 indicate moderate perceived stress, and 27-40 indicate high perceived stress.

Depressive symptoms: The severity of depressive symptoms was assessed with the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996). The BDI contains 21 items related to feelings of sadness, satisfaction, guilt and changes in appetite/weight/interest in sex. Items are scored on a scale from 0 (not at all) to 3 (most severe). BDI scores from 0-13 indicate minimal depression, 14-19 indicate mild depression, 20 and above indicate moderate to severe depression (Beck et al., 1996).

Anxiety symptoms: The severity of anxiety symptoms was assessed with the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988). The BAI contains 21 items and has been used in clinical populations to assess anxiety: 14 items relate to somatic symptoms of anxiety and 7 items assess cognitive and subjective features of anxiety and panic. Items are scored on a scale from 0 (not at all) to 3 (most severe). BAI scores less than 10 indicate minimal anxiety, 10-19 indicate mild to moderate anxiety, and greater than 20 indicate severe anxiety. Prior large-scale studies report BAI scores ranging from 11 to 19 in people with social phobia, panic disorder and generalized anxiety disorder (Muntingh et al., 2011).

Interoceptive sensibility: Interoceptive sensibility was assessed with the Multidimensional Assessment of Interoceptive Awareness Version 2 (MAIA-2; Mehling et al., 2018). The MAIA-2 contains 37 items related to the awareness of bodily sensations, including pain or discomfort, the connection between bodily sensations and emotional states, the ability to regulate distress, and viewing one's body as safe and trustworthy. Items are scored on a scale from 0 (never) to 5 (always). The MAIA-2 has 8 subscales corresponding to noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening, and trusting. Higher MAIA scores overall indicate better interoceptive sensibility.

Recognition memory: Recognition memory was assessed with the Behavioral Pattern Separation Task, also known as the Mnemonic Discrimination Task (Stark et al., 2013). The task took approximately 20 minutes. During the first phase of the task, participants were asked to categorize 128 common objects as "indoor" or "outdoor" with a button press (encoding phase). Immediately following encoding, participants were given a surprise recognition test in which they were shown repetitions of previously-viewed objects (64 targets) and novel objects (64 foils). Participants were asked to categorize the items as "old" or "new" with a button press. Recognition memory scores were calculated as the percent of familiar objects correctly rated as "old" minus the percent of new objects incorrectly rated as "old" (i.e., hits minus false alarms). Higher recognition memory scores indicated better recognition memory ability.

Interoceptive accuracy: Interoceptive accuracy was measured with the heartbeat tracking task (Rae et al., 2020; Schandry, 1981) while recording ECG. One electrode was attached to the participant's right wrist, one to the left ankle, and the ground electrode was also attached to the right wrist. Participants sat upright in a chair with their feet flat on the floor. During the task, participants were asked to sit facing the wall (away from the researcher) and to minimize movement. She was instructed to silently count her own heartbeats, without taking her pulse, when verbally signaled to start and stop by the researcher. At the stop signal, the participant reported the number of heartbeats counted. Six trials were conducted with randomized durations of 25, 30, 35, 40, 45 and 50 seconds and a 10-second break between trials.

ECG data were collected from the wrists using a J&J Engineering C2+ physiograph. Raw ECG data were imported to WinCPRS® (Absolute Aliens Oy, Turku, Finland) or ARTiiFACT (Kaufmann et al., 2011) to extract time intervals between R-R waves (one heartbeat to the next) or interbeat intervals. Reported heartbeats ($n\text{beats}_{\text{reported}}$) were compared to the actual number of heartbeats recorded from the interbeat intervals during ECG ($n\text{beats}_{\text{real}}$). Accuracy scores during the heartbeat tracking task were scored according to two different formulas, depending on whether the person substantially overestimated or underestimated their heartbeats (Garfinkel et al., 2015; Rae et al., 2020).

People typically underestimate their number of heartbeats. The following "standard accuracy" formula was used for underestimators (i.e., participants who did not estimate more than twice the number of actual heartbeats):

$$1 - (|n\text{beats}_{real} - n\text{beats}_{reported}|)/(n\text{beats}_{real})$$

In addition to the formula above, a second formula ("alternative accuracy") was used for overestimators (i.e., participants who substantially overestimated the number of actual heartbeats). The average of the reported and actual beats in the denominator was used to mitigate overestimation:

$$1 - (|n\text{beats}_{real} - n\text{beats}_{reported}|)/((n\text{beats}_{real} + n\text{beats}_{reported})/2)$$

The average accuracy score across all six trials was calculated for each individual. Only one participant substantially overestimated her heart rate, so her data was calculated according to the alternative accuracy formula. All other participants' interoceptive scores were calculated according to the standard accuracy formula, per Rae et al. (2020).

Data analyses

Statistical tests were performed using IBM SPSS Statistics. Correlational analyses were performed between five dependent measures of mental health (scores from the PTCI, RRS, PSS, BDI and BAI) within individuals. Three participants were missing either questionnaire, heartbeat tracking or recognition memory data; sample sizes are reported accordingly with results below. An exploratory factor analysis was performed to determine the existence of a shared common construct among the dependent measures of mental health. Correlational analyses between factor scores and self-reported interoceptive sensitivity, as well as interoceptive accuracy and recognition memory were performed within individuals to determine additional relationships (n = 35). We also report descriptive statistics (i.e., means and standard errors) for interoceptive sensibility and its subscales (MAIA scores).

Results

History of traumatic events

Out of 38, 13 women (34%) reported no history of sexual or physical assault. Twenty-three women (61%) reported a history of physical and/or sexual assault according to the LEC-5. Data were missing from two women (5%) who did not disclose their trauma history. Differences in mental health outcomes were assessed according to women who reported trauma exposure (n = 23) compared to those who did not (n = 13). Trauma-related thoughts (PTCI scores) significantly differed between women with a history of physical and/or sexual assault (*M*: 106, *SE*: 7) compared to women with no history of assault (*M*: 80, *SE*: 9), $t(33) = -2.36$, $p < 0.05$. Differences in PTCI subscale scores according to assault history were also analyzed. Women with assault history significantly differed from those without on negative thoughts about the world, $t(33) = -2.21$, $p < 0.05$, and self-blame, $t(33) = -3.67$, $p = 0.001$, but not negative thoughts about the self, $p > 0.05$.

Women did not differ on RRS, PSS, BDI, or BAI scores when grouped according to history of physical and/or sexual assault, $p > 0.05$. We were interested in the relationship of mental health outcomes in women living with HIV, regardless of trauma history, and how these outcomes were related to each other. In addition, we were not able to separate the sample further due to lack of power. Therefore, for the following analyses, dependent outcomes were analyzed from the entire group of women living with HIV, regardless of trauma history.

Relationships among mental health outcomes

Group means and standard errors of trauma-related thoughts (as assessed with the PTCI), rumination (as assessed with the RRS), perceived stress (as assessed with the PSS), depression (as assessed with the BDI), and anxiety (as assessed with the BAI) are shown in Figure 1A-E. Correlational analyses indicated that mental health outcomes were moderately to highly correlated (Table 1). Numbers of trauma-related thoughts were highly correlated with numbers of ruminative thoughts, $r = 0.77$, $p < 0.001$, $n = 36$ (Figure 1F), and moderately correlated with reported levels of perceived stress, $r = 0.44$, $p < 0.01$, $n = 37$ (Figure 1G) and symptoms of depression $r = 0.52$, $p = 0.001$, $n = 36$ (Figure 1H), but not with symptoms of anxiety, $r = 0.31$, $p > 0.05$, $n = 36$. Ruminative thoughts were highly correlated with reported levels of perceived stress, $r = 0.69$, $p < 0.001$, $n = 37$ (Figure 1I), and symptoms of depression, $r = 0.79$, $p < 0.001$, $n = 37$ (Figure 1J) and anxiety, $r = 0.61$, $p < 0.001$, $n = 37$ (Figure 1K). Reported levels of perceived stress were highly correlated with symptoms of depression, $r = 0.62$, $p < 0.001$, $n = 37$ (Figure 1L) and moderately correlated with symptoms of anxiety, $r = 0.43$, $p < 0.01$, $n = 37$ (Figure 1M). Finally, symptoms of depression and anxiety were highly correlated in women with HIV, $r = 0.63$, $p < 0.001$, $n = 37$ (Figure 1N).

Subtypes of ruminative thoughts

All three subtypes of ruminative thoughts (depressive, brooding and reflective) were moderately to highly related to trauma-related cognitions, perceived stress, depression and anxiety. Depressive ruminations highly correlated with trauma-related cognitions, $r = 0.71$, $p < 0.001$, perceived stress $r = 0.70$, $p < 0.001$, depressive symptoms $r = 0.79$, $p < 0.001$, and anxiety symptoms $r = 0.62$, $p < 0.001$. Brooding ruminations also highly correlated with trauma-related cognitions, $r = 0.74$, $p < 0.001$, perceived stress $r = 0.68$, $p < 0.001$, depressive symptoms $r = 0.68$, $p < 0.001$, and anxiety symptoms $r = 0.50$, $p < 0.01$. Reflective ruminations correlated slightly less strongly with other mental health outcomes than depressive and brooding subtypes but correlations were still quite significant. Reflective ruminations significantly correlated with trauma-related cognitions, $r = 0.63$, $p < 0.001$, perceived stress $r = 0.44$, $p < 0.01$, depressive symptoms $r = 0.64$, $p < 0.001$, and anxiety symptoms $r = 0.50$, $p < 0.01$.

Exploratory factor analysis of mental health outcomes

An exploratory factor analysis was used to determine potential shared construct(s) accounting for the variance in mental health symptoms. The five dependent measures of mental health (PTCI, RRS, PTCI, BDI, BAI) were entered into the factor analysis. Questionnaires loaded highly and consistently onto a primary factor (Eigenvalue 3.30), which accounted for 66% of the variance in the sample. A Scree plot of components extracted from the factor analysis and corresponding Eigenvalues indicated a primary factor with an Eigenvalue above 3

(Figure 2A). Exploratory factor analysis was used to assign each person a factor score. These scores were normally distributed, as indicated by a non-significant Shapiro-Wilk test of a null of normality ($p > 0.05$) and skewness and kurtosis values of 0.07 and -0.46 respectively.

Mental health outcomes and interoception

Means and standard errors from MAIA subscales are reported in Table 3. Correlations were performed among the factor scores of mental health and self-reported interoceptive sensibility (MAIA scores). Within each individual, mental health factor scores related inversely to overall interoceptive sensibility ($r = -0.40$, $p < 0.05$, $n = 35$) (Figure 2B), and only related to one subscale measure of interoceptive sensibility (self-regulation). Mental health factor scores inversely correlated with self-reported levels of self-regulation $r = -0.40$, $p < 0.05$, $n = 35$ (Figure 2C). These data suggest that women who endorsed greater numbers of maladaptive symptoms related to mental health (indicated from factor scores) also reported decreased ability to sense their bodily sensations and regulate thoughts and feelings related to these sensations (as assessed with the MAIA).

The relationship between mental health factor scores and interoceptive accuracy scores (assessed with the heartbeat tracking task) was not significant ($p > 0.05$). The relationship between interoceptive sensibility (MAIA scores) and interoceptive accuracy was also tested. Interoceptive sensibility and interoceptive accuracy did not significantly relate within individuals, $p > 0.05$ (Figure 3A).

Interoception and memory

Interoceptive accuracy scores from the heartbeat tracking task were highly variable and ranged from 4% to 93% accuracy (*M*: 56%, *SE*: 4%). Twelve people (a third of the sample) had scores of 50% or lower on the heartbeat tracking task, indicating that they were not performing better than chance. Recognition memory scores (assessed with the Behavioral Pattern Separation Task) were highly variable and ranged from -0.11 to 0.97 (*M*: 0.54, *SE*: 0.05). Negative scores on recognition memory result when a person incorrectly rates new objects as “old” more frequently than correctly rating familiar objects as “old.” According to this criterion, two people had negative recognition memory scores. The relationship between interoceptive accuracy and recognition memory was analyzed. Interoceptive accuracy was moderately correlated with scores of recognition memory ($r = 0.37$, $p < 0.05$), indicating women with HIV who were more accurate at tracking their heartbeats were also more accurate at identifying previously-viewed information (Figure 3B).

Discussion

In the present study, we examined thoughts and symptoms related to trauma and mental health in women infected with HIV, many of whom had been HIV positive for years, even decades. Sixty-one percent of women living with HIV reported a history of physical or sexual abuse, or both. These women reported significantly greater numbers of trauma-related thoughts compared to women with HIV without a similar history (who were asked to report their thoughts on a very stressful event from their past) ($p < 0.05$). In particular, women with trauma history and HIV reported greater numbers of negative cognitions related to self-blame and the world compared to women without trauma history and HIV. The data support prior findings from others indicating women with trauma history report greater numbers of trauma-related thoughts related to viewing the world as dangerous and blaming oneself for the event or one's reactions since the event (e.g., Millon et al., 2018; Startup, Makgekgenene, & Webster, 2007). These data suggest that, within women living with HIV, a history of trauma elicited higher numbers of trauma-related thoughts related to self-blame and the world, but not necessarily negative thoughts about the self. To our knowledge, this was the first use of the Posttraumatic Cognition Inventory in women with HIV, many of whom had a history of trauma.

Despite high numbers of trauma-related thoughts, women living with HIV and a history of interpersonal trauma did not have a greater tendency to ruminate, perceive greater levels of stress, or report more symptoms related to anxiety and depression compared to women with HIV who did not have a similar history ($p > 0.05$). Regardless of trauma history, women reported moderate levels of trauma-related and ruminative thoughts and perceived stress, as well as moderate levels of depressive and anxiety symptoms (Figure 1). Self-reports were moderately high with means of 95 for the number of trauma-related thoughts and 45 for the number of ruminative thoughts. These numbers are somewhat lower than scores reported by women with sexual violence history and no HIV in a young adult college-aged sample (Millon et al., 2018). However, a third (33%) of those women met diagnostic criteria for PTSD and reported higher numbers of trauma-related and ruminative thoughts compared to women without PTSD, which likely accounted for higher scores than our current sample of women with HIV. We did not assess diagnostic criteria related to mental disorders in this study. Self-reported levels of perceived stress were moderate (mean of 18), as were symptoms of depression (mean of 16) and anxiety (mean of 13). While exhibiting higher than “normal” levels, the majority of women in our study would not meet diagnostic criteria for a mood disorder, but nevertheless were suffering from depressive and anxious thoughts on a daily basis.

There was considerable variability for all measures among individuals, ranging from very low to high levels for each of the five measures, suggesting that some individuals were experiencing more mental health symptoms than others. Moreover, and as in other studies, these self-report measures tended to correlate with one another, in part because they ask similar types of questions. The correlation between trauma-related and ruminative thoughts was highly and significantly correlated ($r = 0.77$) (Figure 1F). Trauma-related thoughts moderately correlated with perceived stress ($r = 0.44$) and depressive symptoms ($r = 0.52$) (Figures 1G-H). Of all mental health outcomes, numbers of ruminative thoughts were correlated most strongly with other measures. In addition to trauma-related thoughts, rumination was also highly related to reported levels of perceived stress ($r = 0.69$), symptoms of depression ($r = 0.79$) and anxiety ($r = 0.61$) (Figures 1I-K). Depressive, brooding and ruminative subtypes of thoughts were highly related to other outcomes of mental health (p’s < 0.01). These data suggest that the presence of ruminative thoughts might be a common contributor to other mental health symptoms, though we are not able to determine causality. Perceived stress was more strongly correlated with symptoms of depression (r = 0.62) than anxiety (r = 0.43), but the relationship to anxiety was still moderately high (Figures 1L-M). Also, symptoms of depression and anxiety were highly correlated with each other (r = 0.63; Figure 1N), which is generally consistent with other studies (Morrison et al., 2002). Overall, women with HIV who were experiencing mood-related symptoms were also experiencing higher levels of perceived stress related to the ability to cope and handle unexpected events, irritations and everyday difficulties.

Individual differences in mental health outcomes

In 2010, the National Institutes of Health presented the Research Domain Criteria (RDoC), in order to outline research foci that centered on domains of functioning shared across diagnostic criteria of mental illness (Insel et al., 2010). These guidelines arose from concerns about the efficacy of pharmacological treatments for mental illness, as well as the use of diagnostic categories that did not necessarily capture underlying etiology or treatment response (Insel et al., 2010). To this end, clinicians and basic science researchers wanted to include information on neurobiological and behavioral mechanisms of mental illness. However, psychological assessments of dysfunction are still prevalent and tend to focus on symptoms specific to discrete categories of illness (Van Dorn et al., 2016). To this end, factor analyses are a promising analytical tool to detect commonalities across measures and uncover shared symptoms across different mental states.

Few studies exist; those that do report positive or negative affective states, and/or externalizing or internalizing behaviors shared across diagnoses (Black et al., 2019; Pezzoli et al., 2017; Van Dorn et al., 2016). However, little is known about how dysfunctional thoughts and feelings manifest and potentially coalesce in subclinical populations; and furthermore, how traditional measures of purportedly distinct constructs might ask similar types of questions and measure overlapping dysfunctional states.

An exploratory factor analysis was performed on five dependent measures of mental health (trauma, rumination, perceived stress, depression, anxiety). This process identified which symptoms accounted for the most variance in the data, and thus might be accounting for other symptoms that were observed. Our goal was to reduce the number of dependent measures as they were highly related (Table 1) and compute a score of mental health for each participant to assess differences across individuals. The five questionnaires loaded highly and consistently onto a primary factor and explained 66% of the variance in the data (Table 2). The women reported moderate, subclinical levels of mental health symptoms (Figure 1); yet those who reported higher numbers of thoughts related to trauma and rumination were experiencing greater perceived stress, and more depressive and anxiety symptoms. Thus, these symptoms were highly related within individuals, and in part, might share physiological mechanisms. Previously, we have reported that symptoms related to trauma, anxiety and depression highly coalesce in women with sexual violence history, regardless of PTSD status (Millon et al., 2018). Importantly, we are not claiming that depression, anxiety and stress are the same phenomena, but rather that they may overlap. Identifying commonalities across mental health assessments can in part help to understand the boundaries of diagnostic categories, some of which might be superficial. Ultimately, locating commonalities across dysfunctional states can improve self-report assessments of mental health to better capture a person's physiological and psychological state. To our knowledge, this is the first demonstration of implementing a factor analysis to target a central construct of mental health in women with HIV.

More than any questionnaire, items related to ruminative thoughts mapped most consistently and to the greatest degree onto a common underlying construct from the factor analysis; the scores from the rumination questionnaire (RRS) accounted for as much as 94% of the variance in the primary factor, which again, we are interpreting as mental health. The RRS assesses to what degree a person has the tendency to rehearse thoughts repetitively, which are oftentimes negative and about the past. These thoughts are highly related to depressive symptoms, particularly in women (Nolen-Hoeksema et al., 1999; Shors et al., 2017). These data suggest that ruminative thoughts were accounting for much of the variance in the data related to mental health and were most related to other outcomes of trauma-related thoughts, perceived stress, depression and anxiety. These data were consistent with the correlational analyses (Figures 1F-N); ruminative thoughts were strongly correlated with scores of trauma, perceived stress, depression and anxiety, and more so than the other measures were correlated with one another (Figures 1F, 1I-K). Ruminative subtypes were also highly related to other mental health outcomes. The factor analysis further indicated that items from the Beck Depression Inventory (BDI) loaded highly onto the primary factor and accounted for 87% of its variance. The BDI assesses feelings of sadness or guilt, thoughts related to suicide, and changes or difficulty with sleep, appetite, concentration and fatigue. Prior research indicates depressive symptoms and fatigue are highly related in women living with HIV (Voss et al., 2007). Our data suggest that women who had a greater tendency to ruminate were also reporting physiological symptoms related to impaired sleep, concentration and fatigue.

Two scales related to stress, the Perceived Stress Scale and the Posttraumatic Cognitions Inventory (PTCI), both loaded highly onto the primary factor and accounted for 75% of its variance. These data indicate that, in addition to ruminating on past events, some of which were traumatic, participants continued to feel high levels of stress and nervousness in the present, which contributed to feeling overwhelmed and impacted daily function. PTCI data indicated a general negative view of the self and one's feelings or reactions, as well as feeling alienated from others (Foa et al., 1999). As mentioned, to our knowledge this is the first report of trauma-related thoughts in women with HIV. We did not assess these cognitions in women without HIV so we are not able to determine the degree to which living with HIV is accounting for trauma-related thoughts. Also, we did not ask participants to describe their most stressful event. However, similar assessments indicated that 36% of this population considered the HIV diagnosis a trauma in and of itself (Olley et al., 2005). The presence of negative thoughts and feelings related to the self in women with HIV, regardless of trauma history, suggests that they are experiencing ongoing stress, some of which is potentially related to their compromised health status. Finally, items from the Beck Anxiety Inventory related highly to the primary factor and accounted for 73% of its variance. These items assessed feelings of numbness, nervousness and fear, as well as being unable to relax or breath. Collectively, these data indicated that the five questionnaires related to mental health were highly related and were measuring similar thoughts and symptoms in women with HIV.

Self-regulation related to mental health

We hypothesized that women with higher numbers of mental health symptoms would report that they were less aware of their body. This prediction was generally supported by the data. Interoceptive sensibility was measured via self-report with the Multidimensional Assessment of Interoceptive Awareness (Mehling et al., 2018). Total MAIA scores correlated with factor scores of mental health within individuals, indicating women who had higher numbers of mental health symptoms also felt less aware of their own bodily sensations (Figure 2B). We further analyzed the relationship between mental health factor scores and MAIA subscales, because the responses on subscales were variable and are oftentimes reported as indicators of separate processes related to interoception (Calì et al., 2015; Mehling et al., 2012). Responses to one subscale of the MAIA, that of self-regulation, moderately correlated with mental health scores (Figure 2C). This subscale measures the ability to regulate psychological distress by attending to bodily sensations (Mehling et al., 2012). Items include, *"When I bring* *awareness to my body I feel a sense of calm", "I can use my breath to reduce tension",* and *"When I am caught up in thoughts, I can calm my mind by focusing on my body/breathing."*

Without overinterpreting these findings, it is nonetheless helpful to consider the context in which the MAIA was developed, Initially, Mehling and colleagues attempted to isolate the conscious detection of bodily sensations (in their words, a "nonjudgmental awareness"). In doing so, they sought to avoid conflating this construct with maladaptive worry or anxiety about bodily sensations; maladaptive feelings can include hypervigilance, pain catastrophizing or anxiety sensitivity (which is believing anxiety symptoms to be dangerous and being consequently afraid of these feelings). Accordingly, the MAIA attempts to measure adaptive interoceptive processes that occur along the midpoint of a continuum, with maladaptive hyperawareness on one end, and a complete lack of awareness, which is also maladaptive and oftentimes characterizes dissociative states, at the other end. At both extremes, (either an absence or abundance of) bodily awareness is unhealthy, and is associated with stress, trauma, and psychopathology more broadly. A healthy, adaptive level of conscious awareness of one's bodily signals (and how these signals relate to one's thoughts and feelings) is a balance between extremes, and this is what the MAIA was developed to capture. It is noted that we do not report physiological outcomes in this study, nor did we assess interoceptive sensibility in women without HIV. However, means obtained from our data ranged from approximately 2.5 to 3.5 (reported in Table 3). These numbers are consistent with those reported by individuals without HIV

(Mehling et al., 2012), suggesting that women living with HIV are not necessarily reporting less awareness of feelings in their bodies.

Interoceptive accuracy and interoceptive sensibility

We had predicted that women who were more accurate at tracking their heartbeats would report increased levels of interoceptive sensibility. The data indicated that accuracy and sensibility were not related within individuals (Figure 3A). Total scores on the MAIA averaged around 25 and widely varied from 8 to 37 (Table 3). Interoceptive accuracy scores were also highly variable and ranged from 4% to as high as 93%. Though not significant, the relationship between accuracy and sensibility was slightly negative, indicating that women who were more able to track their own heartbeats also reported being less aware of their bodily signals; this relationship was driven in particular by two women who were more than 75% accurate at tracking their heartbeats but reported very low scores of interoceptive sensibility. Others have reported similar negative results (e.g., Calì et al., 2015; Khalsa et al., 2008). It is thought that interoceptive sensibility measures not only a person’s ability to track their bodily signals (which is what the heartbeat tracking task is designed to capture), but also broader processes related to how well a person feels able to regulate these signals (Ceunen et al., 2013; Garfinkel et al., 2015). For example, people with panic disorder, higher numbers of anxiety symptoms, or increased anxiety sensitivity are more accurate at tracking their heartbeats (Domschke et al., 2010). Conversely, people high in anxiety report less interoceptive sensibility assessed with the MAIA (Mehling et al., 2018). Our data partially align with prior findings; women who reported greater numbers of mental health symptoms, some of which were related to anxiety, reported less overall interoceptive sensibility. These same women also felt less able to regulate their thoughts and feelings compared to women with fewer mental health symptoms.

Women with HIV who were more accurate at tracking their heartbeats did not report greater (or fewer) numbers of mental health symptoms. Interoceptive accuracy did not relate to factor scores of mental health, even though women who endorsed difficulties regulating their bodily signals reported feeling more stressed, anxious and depressed, and were more likely to ruminate. Thus, the behavioral interoception data did not support what was indicated through self-report. Women who reported less awareness of their bodily signals did not necessarily perform worse on the heartbeat tracking task. And likewise, women who reported more sensitivity to their bodily signals via self-report were not able to detect their heartbeats more accurately. Nor did the ability to detect one's heartbeats relate to symptoms of mental health. These findings were somewhat surprising as others have reported decreased interoceptive accuracy in people with trauma history (Schaan et al., 2019) as well as an effect of arousal and mood on performance (Dunn et al., 2007; Dunn, Galton, et al., 2010; Dunn, Stefanovitch, et al., 2010). However, most of these other studies tested interoceptive processes in clinical samples, and the women in our study were not assessed for mental disorders. Women with HIV reported moderate levels of mental health symptoms, indicating the majority would likely not meet diagnostic criteria for mental illness (Figure 1). One study did test these relationships in a nonclinical sample of young adults. They reported that ruminations of the brooding subtype related to lower interoceptive accuracy, and this relationship accounted for depressive symptoms and anxiety-related distress (Lackner & Fresco, 2016). Ruminations (regardless of subtype) did emerge from our factor analysis as accounting for the greatest number of mental health symptoms in our sample; however, overall symptoms did not relate to the ability to track bodily signals, despite the fact that women with fewer symptoms *reported* that they were more sensitive to their bodily signals (on the MAIA). Thus, the relationship between interoception and self-report is more complex, at least in women with HIV.

Collectively, these data suggest that interoceptive accuracy and sensibility are overlapping yet distinct phenomena, supporting prior data from others (Ceunen et al., 2013; Garfinkel et al., 2015). The ability to track one's heartbeats has been used an index of processes related to how a person experiences and regulates one's thoughts and feelings, though the data are not entirely straightforward (Barrett et al., 2004). Traditionally, interoception has been described theoretically as a mechanism that accounts for individual differences in emotions and how people likewise think about their feelings (e.g., Mehling et al., 2018). More recently, theories have attempted to specify the range of interoceptive processes, only some of which relate to emotion. Data from neuroscientific studies have helped to clarify the science of interoception, both in terms of the phenomena itself and how to measure it. Recent models implicate sensory-motor cortices, in addition to the insular cortex and subcortical areas (e.g., Barrett & Simmons, 2015; Craig, 2009; Khalsa, Rudrauf, Feinstein, & Tranel, 2009).

Interoceptive accuracy and memory

Interestingly, women who were accurate at tracking their heartbeats were more accurate at detecting information that they had previously seen (termed “recognition memory”) (Figure 3B). Thus, individuals who were more sensitive or attentive to the sensations of their heartbeat, and thus were more accurate at tracking them at rest, were better able to recall previously-viewed information related to everyday objects. These data partially align with a previous study, indicating people with higher interoceptive accuracy perform better on a recognition memory task (Pollatos et al., 2007). Their study required that people recognize previously-viewed pleasant or unpleasant scenes. People who were more accurate at tracking their heartbeats felt more aroused while rating emotional scenes (indicated with an increase in heart rate). Those individuals also were more accurate at recognizing unpleasant scenes compared to people who were less accurate at tracking their heartbeats (Pollatos et al., 2007). However, they were not more accurate in remembering “neutral” information. The objects in our recognition task were not affectively salient (or highly arousing) and did not contain social information. In light of these prior findings, our data suggest that interoceptive accuracy might relate more broadly to the ability to learn and remember information or events, regardless of the arousal level of the information being viewed. Furthermore, behavioral measures of interoception might be driven by processes related to attention and arousal that also influence the ability to recognize and remember information from the environment.

Conclusions

Women with HIV experience general mental and physical challenges related to living with a chronic disease (e.g., Gore-Felton & Koopman, 2008; Ivanova et al., 2012; Looby et al., 2018; Schulte et al., 2018). Here we report a specific relationship between the physiological detection of one's heartbeat and cognitive processes of learning and memory, although without a detectable relationship to self-reported symptoms of mental health. In turn, women with fewer dysregulated thoughts and emotions reported greater ability to sense and regulate their own bodily sensations. Moreover, these data indicate that women with HIV were living with a high degree of stress and were experiencing traumatic thoughts and ruminations on past events and depressive states. These thoughts and feelings were meanwhile accompanied by symptoms of depression and anxiety that more than likely impacted their ongoing physiological health and well-being. When these corresponding measures of mental and physical health were subjected to factor analyses, all measures loaded highly and consistently onto a primary factor. Across individuals, greater mental and physiological difficulties related to less emotional regulation. Thus, women living with HIV stated they felt generally unable to regulate their physiology, which became represented as an emotional response. However, women who could better detect their bodily sensations were likewise better at remembering everyday information. Based on our findings and others, women with HIV may respond especially well to activities that target both the brain and the body via processes of learning and memory. In particular, they might benefit from a combined mind and body intervention that enhances awareness of feelings as they emerge in the body, along with tools to regulate maladaptive thoughts generated by the brain.

Chapter 2: Mental and Physical (MAP) Training with meditation and aerobic exercise enhances mental health and cognition in women with HIV

Introduction

Prevalence of HIV

Nearly 38 million people are living with HIV worldwide (WHO, 2020). Within the United States, women of color are disproportionately affected by HIV and represent 80% of new diagnoses (CDC, 2020). HIV indirectly damages neurons via the activation of white blood cells and subsequent release of proinflammatory cytokines (Kaul et al., 2001). These toxins cause excitotoxicity in the brain, which can lead to neurodegeneration (Kaul et al., 2001; Kovalevich & Langford, 2012). HIV is present in brain tissue even in people receiving antiretroviral therapy (Asahchop et al., 2017) and the consistent regimen of drugs compromises the immune and nervous systems. As a result, people with HIV experience deficits in central and peripheral nervous system function. Living with the virus also takes a psychological toll.

Mental health in people with HIV

The prevalence rates of mood and trauma disorders are substantially higher in women with HIV as compared to women in the general population (Beer et al., 2019; Bing et al., 2001; Wagner et al., 2012). Some women with HIV report psychological problems prior to diagnosis, albeit of lower numbers; other mental health problems arise in response to social isolation and stigma (Orza et al., 2015).

Mental health difficulties related to HIV are compounded by trauma. Women with HIV are twice as likely to experience trauma compared to women without HIV and more than 30% report that the diagnosis is a trauma in and of itself (Gielen et al., 2007; Machtinger et al., 2012; Olley et al., 2005; Wyatt et al., 2002). Trauma can occur early in life long before a diagnosis or relate to how a woman becomes infected with the virus. Exposure to traumatic events can lead to an increased tendency to ruminate and greater levels of perceived stress and depression in women with HIV (Nightingale et al., 2010; Yanes et al., 2012).

The psychological trauma of living with a chronic disease such as HIV impacts physical health (Gore-Felton & Koopman, 2008; Ivanova et al., 2012; Looby et al., 2018). Women with HIV report feeling anxious about their HIV status, which consequentially impacts their sleep, appetite and ability to concentrate (Schulte et al., 2018). Anxiety and depressive symptoms in turn reduce adherence to medication (Hart et al., 2008; Schönnesson et al., 2007; Willie et al., 2016). Socioeconomic factors can exacerbate these effects. For example, food insecurity (and anxiety of its uncertainty) increases the risk of developing GAD or PTSD in women with HIV (Whittle et al., 2019). Given the interactions between mental and physical health outcomes, it is important to treat both mental and physical health in people living with HIV.

Cognitive deficits related to HIV

The hippocampus is a brain region that is necessary for select learning processes and is used in the formation of new memories. Upon autopsy, people who had HIV had higher concentrations of the virus in their hippocampus compared to other areas of the brain, including the cortex (Wiley et al., 1998). While alive, people with HIV express deficits in hippocampal structural integrity (Gongvatana et al., 2014), which can become more pronounced as the virus progresses. Higher levels of mitochondrial DNA damage are associated with reduced hippocampal volume in people with HIV (Kallianpur et al., 2016). Trauma history in women with HIV exacerbates these effects; women with HIV and trauma history had greater reductions in hippocampal volume, and these alterations were associated with deficits in learning and memory compared to women with HIV and no trauma history as well as women without HIV or trauma (Spies et al., 2016).

A key aspect of recognizing and remembering events is the ability to differentiate between patterns or events that are different and spaced across time. This process is called discrimination learning and involves the hippocampus (e.g., Squire, Zola-Morgan, & Chen, 1988; Bennett, Stark, & Stark, 2019). Discrimination learning allows for the storage of new memories in comparison to previously-stored information related to episodic events (Stark et al., 2013; Yassa & Stark, 2011). Pattern separation is a type of discrimination learning that is often used to describe a computational process in the hippocampus that transforms similar inputs into distinct, non-overlapping outputs (Marr, 1971; McClelland et al., 1995). Laboratory studies have further associated this type of learning with newly generated neurons in the dentate gyrus of the hippocampus (e.g., Clelland et al., 2009; Drew et al., 2010; Snyder et al., 2005). Although studies indicate that people with HIV often express deficits in recognition memory related to the hippocampus (Castelo et al., 2006; Maki et al., 2009), it is not known whether and if so how, HIV impacts discrimination learning and/or pattern separation in this population.

Current interventions for HIV

There are few interventions for HIV, other than those that are aimed at reducing transmission (Adimora & Auerbach, 2014; Crepaz et al., 2014). Some focus on targeting social contextual factors linked to HIV/AIDS that provide people living with the virus access to clean syringes, health care and stable housing, as poverty increases the risk of acquiring HIV (Adimora & Schoenbach, 2005). These multifaceted programs address the epidemic of HIV/AIDS but do not directly treat the psychological and physiological impact of living with the virus. The behavioral health interventions that do exist have focused on physical training, including aerobic exercise, or mental training with meditation or mindfulness techniques, but rarely both. Sixteen weeks of aerobic exercise improved cardiovascular fitness (as measured by maximum oxygen output) in women with HIV (Dolan et al., 2006), while twelve weeks reduced depressive symptoms (Neidig et al., 2003), and 24 weeks reduced perceived stress (MacArthur et al., 1993). Exercise interventions also improve quality of life in people with AIDS (Galantino et al., 2005). Mindfulness techniques reportedly reduced perceived stress and depression (Hecht et al., 2018; Rodkjaer et al., 2017). Mindfulness Based Stress Reduction (MBSR), an 8-week course that teaches people sitting meditation, body scan techniques and how to eat slowly and mindfully, reduced the physical side effects of antiretroviral therapy (Duncan et al., 2012). Stress management and relaxation techniques improved quality of life and reduced anxiety, depression and pain (Ramirez-Garcia et al., 2019). Ten weeks of Tai Chi improved quality of life and reduced psychological stress (Robins et al., 2006). A 10-wk cognitive behavioral program that emphasized stress management techniques significantly improved emotional coping skills but not quality of life (McCain et al., 2008). Furthermore, the effects do not necessarily persist. Twelve sessions of yoga and meditation improved health-related quality of life, but these effects did not persist six weeks later (Brazier et al., 2006).

Overall, interventions for people living with HIV that address the physiological or psychological consequences of HIV rarely target both, even though people with HIV express a desire for a more comprehensive program. For example, patients who received talk therapy and take-home assignments reported a willingness to engage in physical activity (Rosen et al., 2017). Thus, there is a need for approaches that simultaneously target both the brain and body for people living with HIV. People with HIV also report being confused by esoteric terms like “mindfulness” or “body scan” (which are used in MBSR) (Rosen et al., 2017), preferring behavioral tools that can be implemented as small-scale changes (such as walking more throughout the day) (Cioe et al., 2018). They also prefer programs that do not include “HIV” in the title. Given these responses, there is clearly a need for health-focused interventions that incorporate techniques that are easy to understand and simple to implement for people living with HIV.

Mental and Physical (MAP) Training

Mental and Physical (MAP) Training is a brain fitness program that targets the brain and the body through a combination of 30 minutes of focused-attention meditation and 30 minutes of aerobic exercise (Shors et al., 2014). Clinical studies indicate that the program, when practiced over weeks, enhances mental and physical health in a variety of human populations. For example, women with sexual violence history who engaged in six weeks of MAP Training reported fewer numbers of ruminative and stress-related thoughts, as well as greater self-worth (Millon et al., 2018; Shors et al., 2018; Shors & Millon, 2016). In another study, women who were homeless and had substance dependence reported significant decreases in anxiety after eight weeks of MAP Training. They also had greater VO_2, which is a physiological measure of cardiovascular health (Shors et al., 2014). MAP Training decreased depression in men and women with major depressive disorder, while increasing synchronized brain activity during tests for cognitive control (Alderman et al., 2016). The combination of meditation and exercise training is particularly effective at decreasing numbers of ruminative thoughts in various populations (Alderman et al., 2016; Lavadera et al., 2020; Shors et al., 2017, 2018). Most importantly, the combination of meditation and aerobic exercise is more effective than doing either activity alone (Shors et al., 2018). Collectively, these data indicate the broad psychological, physiological and neurocognitive benefits of MAP Training.

In this set of studies, we tested whether a combination of meditation and aerobic exercise would enhance hippocampal-dependent processes of learning and memory in women with HIV. It was hypothesized that a 6-wk regimen would enhance discrimination learning, as measured during a pattern separation task, in women living with HIV. In addition, it was hypothesized that the combination would enhance mental health outcomes related to rumination, depression, perceived stress, trauma and anxiety in women with HIV.

Method

Participants

A power analysis was performed using G-Power Software to determine the optimal number of participants for the study. A sample of 36 was necessary to obtain an effect size of 0.25 for an analysis of variance within-subjects test (alpha = 0.05). 38 adult women living with HIV (M_{age} = 45 years, *range* 22-68 years, 95% Black/African-American, 2.5% Latina, 2.5% White) were recruited from the François-Xavier Bagnoud (FXB) Center, Rutgers University Hospital and St. Clare's Housing Program in Newark, NJ, where individuals with HIV come for counseling and medical treatment. On their first visit, participants were provided information about the study and informed consent was obtained. Following the initial assessment, participants were scheduled for combined meditation and aerobic exercise training sessions. These sessions occurred once per week for six weeks in a group setting at FXB Center or St. Clare's. Attendance was taken at each group session. Upon completing six weeks of meditation and aerobic exercise training, participants returned to the original testing location at St. Clare's or FXB Center for a post-training assessment. Outcome measures were collected before and after the 6-wk training program. Participants who completed exercise and meditation training were asked to complete a follow-up questionnaire online at three and six months after training to determine long-term efficacy.

Training participants (*n* = 19) were compensated $100 for completing pre- and post-training assessments and six weeks of meditation and exercise training. They were provided an additional $20 for 3-mo follow-up testing and $20 for 6-mo follow-up testing. No-training controls (*n* = 9) who were not able to participate in exercise and meditation training sessions and only completed initial and follow-up assessments were paid up to $60. Ten women did not complete a second test session and therefore were omitted from data analyses; two of those were unable return because of COVID-19 and were compensated $60. The other eight women dropped out of the study after initial testing (adherence rate 79%).

Materials

The history of traumatic events was assessed with the Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013). The frequency and type of ruminative thoughts were assessed with the Ruminative Responses Scale (RRS; Treynor et al., 2003). The severity of depressive symptoms was assessed with the Beck Depression Inventory (BDI; Beck et al., 1996). Perceived stress was assessed with the Perceived Stress Scale (PSS; Cohen et al., 1983). Posttraumatic cognitions were assessed with the Posttraumatic Cognitions Inventory (PTCI; Foa et al., 1999). The severity of anxiety symptoms was assessed with the Beck Anxiety Inventory (BAI; Beck et al., 1988). See Chapter 1 for full details on questionnaires.

Procedure

Before and after training, participants completed self-report measures of trauma history, ruminative thoughts, depressive symptoms, perceived stress, posttraumatic cognitions and anxiety symptoms. After the questionnaires, participants completed the Behavioral Pattern Separation (BPS) task (Stark et al., 2013) on a computer, also known as the Mnemonic Similarity Task. The task took approximately 20 minutes. The BPS task assessed the ability to discern the difference between previously-viewed everyday objects (i.e., pattern separation). During the first phase of the task, participants were asked to categorize 128 common objects as “indoor” or “outdoor” with a button press (encoding phase). Immediately following encoding, participants were given a surprise recognition test in which they were shown repetitions of previously-viewed objects (64 targets), objects similar but not identical to those in the prior set (64 lures), and novel objects (64 foils). Participants were asked to categorize the items as “old”, “similar”, or “new” with a button press. There were two versions of the BPS task; the instructions were the same but the types of household images that were displayed differed. Participants completed version A prior to training and version B after training.

MAP Training Intervention

Following the initial assessment, participants completed six weeks of MAP Training. Each MAP session began with 20 minutes of silent seated meditation, followed by 10 minutes of very-slow walking mediation, ending with 30 minutes of aerobic exercise. The MAP Training session can be easily remembered as SIT, WALK, SWEAT, described below.

SIT: Participants first engaged in 20 minutes of focused attention (FA) meditation (Lutz et al., 2008). During FA meditation the focus of attention was on the breath. In traditional meditation circles, FA meditation is most similar to Zen meditation. During the seated session, participants were asked to sit on the floor on a meditation pillow or in a straight-backed chair. They were instructed to place their hands in their lap, with their thumbs slightly touching, and asked to close their eyes if they felt comfortable, or gaze at the floor a few feet in front of them. The participants were instructed to focus their attention on their breath, noticing as the air travelled into and out of their body. In particular, participants were instructed to focus their attention on the space between the end of one exhale and the beginning of the next inhale. They were instructed to start counting these spaces in time, beginning at one. If and when a person lost count, the person was instructed to begin their counting again at one. The brain training component of this type of meditation was the process of learning to concentrate on the breath, forgetting, and then remembering, over and over again. The 20-min session was conducted in complete silence until a standardized bell rang (using a meditation app), which indicated to participants that the 20 minutes were over.

WALK. When the bell rang, participants were instructed to stretch out their legs, and stand up slowly for walking meditation. Walking meditation served to get the blood flowing to the legs prior to aerobic exercise. During this session, participants engaged in 10 minutes of very-slow walking meditation. Participants walked slowly in a circle, with their arms clasped loosely behind their back. They were instructed to gaze at their feet while walking slowly. The meditation was still a focused-attention meditation, but now the focus of attention was on the feet. In particular, the participants were instructed to focus their attention on each part of the foot as it touched the floor, from the heel of the foot to the ball of the foot, to each toe, and notice the weight of the body as it shifted from one foot to the other. Again, as their attention drifted from the point of focus, participants were instructed to notice the interruption in concentration, and return their attention to their feet. The 10-min walking session was also conducted in complete silence until a standardized bell rang (using a meditation app).

SWEAT. Immediately following the 30-min meditation session (sitting and walking), participants began 30 minutes of aerobic exercise. Participants engaged in a group aerobic exercise class to music, with kicking, jumping, and lunges to get the heart rate up to 60-80% of their maximum (220 minus age). After 25 minutes of aerobic exercise, participants took their own heart rate, which was followed by a 5-min cool down. This ended the MAP Training session.

Data analyses

All data analyses were conducted with IBM SPSS Statistics. Questionnaire data were incomplete from two participants. Repeated measures analyses of variance and paired t-tests were conducted to determine whether RRS, BDI, PTCI, PSS, and BAI scores measured at the second assessment significantly varied from scores at initial assessment (alpha level 0.05) in those who trained (n = 18) and no-training controls (n = 8). Percent accuracy scores to novel, old and similar items were computed from the BPS task. The recognition memory score was calculated as percent of familiar objects correctly rated as “old” minus percent of new objects incorrectly rated as “old” (i.e., hits minus false alarms). Higher recognition memory scores indicated better recognition memory ability. Paired sample t-tests were performed to determine whether post-training scores related to novelty detection, recognition memory and pattern separation significantly varied after training as compared to prior to training. Participants with recognition memory scores above 80% prior to the intervention (n = 8) were analyzed on pattern separation ability with the “BPS score” (calculated as difference between the percent of similar objects correctly rated as “similar” minus the percent of novel objects incorrectly rated as “similar”). Higher BPS scores indicated greater pattern separation ability. Negative BPS scores resulted when the person incorrectly categorized more novel objects as “similar” than did correctly categorize similar objects as “similar.”

Results

Trauma history and mental health outcomes

Twenty-seven women reported their history of traumatic life events according to the Life Events Checklist. Eighteen women (67%) reported a history of physical and/or sexual assault; nine women (33%) reported no history of physical and/or sexual assault. There was a significant group by time interaction for both ruminative thoughts (assessed with the RRS) and depressive symptoms (assessed with the BDI). A repeated measures analysis of variance indicated a significant 19% decrease in ruminative thoughts in the meditation and aerobic exercise group post-training (*M*: 40, *SE*: 3) versus pre-training (*M*: 49, *SE*: 4), [$F_{(1, 24)} = 17.37$, $p < 0.0001$, partial $\eta^2 = 0.42$] (Figure 4A), compared to no-training controls (pre: *M*: 35, *SE*: 5; post: *M*: 41, *SE*: 5). A repeated measures analysis of variance indicated a significant 41% decrease in depressive symptoms in the meditation and aerobic exercise group post-training (*M:* 11, *SE*: 2) versus pre-training (*M*: 19, *SE*: 2), [$F_{(1, 24)} = 4.83$, $p < 0.05$, partial $\eta^2 = 0.17$] compared to no-training controls (pre: *M*: 11, *SE*: 3; post: *M*: 11, *SE*: 3) (Figure 4B).

Perceived stress (assessed with the PSS) significantly decreased by 22% in the training group after six weeks of training with meditation and aerobic exercise (*M*: 14, *SE*: 2) compared to prior to training (*M*: 18, *SE*: 2), $t(17) = 5.13$, $p < 0.0001$, Cohen's $d = 1.20$ (Figure 4C). In contrast, PSS scores did not significantly change in no-training controls between initial (*M*: 17, *SE*: 2) and follow-up testing six weeks later (*M*: 14, *SE*: 3), $p > 0.05$.

Posttraumatic cognitions (assessed with the PTCI) significantly decreased by 17% in the training group after six weeks of training with meditation and aerobic exercise (*M*: 86, *SE*: 7) compared to prior to training (*M*: 104, *SE*: 8), $t(17) = 2.94$, $p < 0.01$, Cohen's $d = 0.71$ (Figure 4D). In contrast, PTCI scores did not significantly change in no-training controls between initial (*M*: 82, *SE*: 14) and follow-up testing six weeks later (*M*: 71, *SE*: 10), $p > 0.05$.

Anxiety symptoms (assessed with the BAI) decreased by 33% in the training group after six weeks of training (*M*: 10, *SE*: 2) compared to prior to training (*M*: 15, *SE*: 3), and trended towards significance $t(17) = 2.07$, $p = 0.05$, Cohen's d =

0.48 (Figure 4E). Numbers of anxiety symptoms did not significantly change in no-training controls between initial (*M*: 7, *SE*: 2) and follow-up testing six weeks later (*M*: 8, *SE*: 3), $p > 0.05$.

Ruminative thoughts, depressive symptoms and levels of perceived stress were assessed three months ($n = 17$) and six months ($n = 6$) following the end of training in those women who trained. Follow-up surveys indicated decreases in ruminative symptoms were sustained and remained significant at six months after training (*M*: 36, *SE*: 5), $t(5) = 2.89$, $p < 0.05$, Cohen's $d = 1.17$, but not at three months (*M*: 42, *SE*: 3), $p > 0.05$; still, the numbers of ruminative thoughts had decreased by 16% at three months and by 27% at six months post-training compared to prior to training (Figure 5A). Follow-up surveys indicated decreases in depressive symptoms were sustained and remained significant up to six months after training; levels of depressive symptoms were 49% lower at three months (*M*: 10, *SE*: 2), $t(16) = 3.79$, $p < .01$, Cohen's $d = 0.89$ and 59% lower at six months (*M*: 8, *SE*: 3), $t(5) = 3.57$, $p < .05$, Cohen's $d = 1.51$ compared to before training (Figure 5B). Follow-up surveys of PSS scores in those who trained indicated decreases in perceived stress were 16% lower at three months (*M*: 16, *SE*: 2) and 25% lower at six months (*M*: 13, *SE*: 3) compared to prior to training but these decreases at follow-up did not reach significance ($p > 0.05$) (Figure 5C).

Memory outcomes

Responses to novel, old and similar items from the Behavioral Pattern Separation Task are reported in Table 4. Novelty detection accuracy scores did not significantly change after meditation or aerobic exercise training (*M*: 0.63, *SE*: 0.05) compared to before training (*M*: 0.70, *SE*: 0.04), $t(18) = 1.37$, $p > 0.05$. Pattern separation accuracy, as assessed by the percentage of correct responses to similar items, prior to training (*M*: 0.32, *SE*: 0.05) significantly increased after six weeks of meditation and aerobic exercise training (*M*: 0.38, *SE*: 0.04), $t(18) = -2.33$, $p < 0.05$, Cohen's $d = 0.57$ (Figure 6B). Pattern separation accuracy scores did not significantly change in women who did not train when assessed six weeks apart, $p > 0.05$.

Participants who performed at 80% accuracy or higher on recognition memory prior to any training were selected for further analyses ($n = 8$) to detect individual differences in discrimination learning after the meditation and aerobic exercise program. Recognition memory scores did not significantly change after training (*M*: 0.83, *SE*: 0.02) compared to before training (*M*: 0.88, *SE*: 0.02), $t(7) = 1.70$, $p > 0.05$ in this subgroup. Pattern separation scores assessed prior to training (*M*: -0.02, *SE*: 0.08) significantly increased after training (*M*: 0.10, *SE*: 0.10), $t(7) = -2.53$, $p < 0.05$, Cohen's $d = 0.89$ (Figure 6C). There were no relationships between pattern separation scores and mental health outcomes (*p*'s > 0.05).

Discussion

Mental health outcomes related to MAP Training

The present intervention study assessed the effects of combined meditation and aerobic exercise on mental health and cognitive functioning in women living with HIV. The intervention is known as Mental and Physical (MAP) Training and is trademarked as MAP Train My Brain™. The program combines “mental training” with 30 minutes of silent meditation and “physical training” with 30 minutes of aerobic exercise. After six weeks, participants reported significantly fewer ruminative thoughts, depressive symptoms, less perceived stress and fewer trauma-related thoughts (Figures 4A-D).

Rumination is the tendency to engage in repetitive thoughts, which are oftentimes autobiographical, negative and about the past. People who ruminate tend to analyze recent events to determine why they feel unmotivated or depressed, and often think about how sad they feel (Nolen-Hoeksema et al., 1999, 2008). In the following study, meditation and aerobic exercise training decreased the numbers of ruminative thoughts by 19% in women who trained for six weeks and the reduction in rumination was highly significant (Figure 4A). Rumination is highly related to depression, particularly in women (Nolen-Hoeksema et al., 1999; Shors et al., 2017). Consistent with this relationship, depressive symptoms were similarly decreased after MAP Training, by as much as 41% in women who trained (Figure 4B). Furthermore, the effects of training on depression and rumination persisted up to six months after training (Figures 5A-B).

Perceived stress, the ability to handle everyday events and stressors, is also highly related to rumination and depression. In other studies, women with HIV who reported more perceived stress reported a greater tendency to ruminate; and rumination accounted for the association between reported perceived stress and depression (Yanes et al., 2012). Similarly here, women who reported a greater tendency to ruminate also reported higher levels of perceived stress and depressive symptoms (Millon and Shors, under review). And similarly, perceived stress decreased by more than 20% after training. The reduction was sustained up to several months later but did not reach statistical significance (Figure 5C).

Rumination oftentimes emerges in women with trauma histories, though it is not known whether the tendency to ruminate precedes the traumatic event and exacerbates trauma symptoms or arises after (Halligan et al., 2006; Michael et al., 2007; Shors & Millon, 2016). Sixty-seven percent of women with HIV in this study reported a history of physical or sexual assault or both. These high prevalence rates are supported by data from others indicating women with HIV are twice as likely to experience trauma compared to non-HIV women (Gielen et al., 2007; Machtinger et al., 2012; Wyatt et al., 2002). The tendency to ruminate has traditionally been thought of as a trait that is more or less stable among individuals, rather than a state (Shors et al., 2017). However, we have consistently documented a significant reduction in ruminative thoughts after combined meditation and aerobic exercise training in various populations, including women with sexual violence history (Shors et al., 2018, 2017, 2014). We also have previously documented that the numbers of ruminative thoughts are highly related to trauma-related thoughts in women with trauma history and collectively these thoughts reduce after six weeks of meditation and aerobic exercise training (Shors et al., 2018). The data reported here support these prior findings. Women with HIV who reported higher numbers of trauma-related thoughts also reported a greater tendency to ruminate (Millon and Shors, under review), and these types of thoughts reduced significantly after six weeks of training. Overall, these data indicate that the combination of meditation and aerobic exercise is effective at reducing ruminative and trauma-related thoughts, as well as depressive symptoms in women with HIV, some of whom had a history of physical or sexual trauma.

These reductions in mental health symptoms are consistent with other studies using a similar training program. We have previously documented that six to eight weeks of MAP Training significantly reduced depressive symptoms and ruminative thoughts in young adults with major depressive disorder (Alderman et al., 2016), reduced anxiety in young mothers with trauma histories who were recently homeless (Shors et al., 2014), and reduced trauma-related and ruminative thoughts in young adult women with sexual violence history (Shors et al., 2018). Importantly, we have demonstrated that the combination of silent meditation and aerobic exercise is more effective at reducing ruminations and thoughts related to trauma than either activity alone (Shors et al., 2018). We have further documented that eight weeks of MAP Training enhanced quality of life and reduced perceived stress in first- and second-year medical students (Lavadera et al., 2020).

Learning and memory outcomes related to MAP Training

MAP Training was developed out of neuroscientific studies that documented physical training with aerobic exercise increases the number of new neurons in the hippocampus and effortful mental training enables these cells to survive past the time that they would normally die (Curlik & Shors, 2013; Curlik et al., 2013; Curlik & Shors, 2011; Millon & Shors, 2019; Shors et al., 2014). The process of generating new cells in the adult mammalian brain is known as neurogenesis and was discovered in the 1960's (Altman & Das, 1965). Since its discovery, multiple studies have provided evidence for neurogenesis in the hippocampus, and the role of these new neurons in processes of learning and memory (Cameron et al., 1995; Cameron & Gould, 1994; Drew et al., 2010; Gould et al., 1997; Gould et al., 1999; Niibori et al., 2012; Seo et al., 2015; Shors et al., 2001; Shors et al., 2012; Snyder et al., 2005). Importantly, it is not practical to verify neurogenesis in the human brain while someone is alive (e.g., Millon & Shors, 2019). However, findings on neurogenesis inspired our lab to develop a brain fitness program that trained the brain with effortful mental learning (through meditation) and aerobic exercise.

Here we report enhanced hippocampal-dependent learning and memory after six weeks of combined meditation and aerobic exercise in women with HIV (Figure 6). To our knowledge, this is the first indication of improved learning and memory function in people with HIV after six weeks of meditation and aerobic exercise. Hippocampal-dependent learning and memory was measured as pattern separation ability related to discrimination learning and assessed with the Behavioral Pattern Separation (BPS) task. Stark and colleagues developed the BPS task to identify neural correlates of pattern separation related to discrimination learning in humans (Stark et al., 2013, 2019). The BPS task has been used numerous times in behavioral and neuroimaging studies to assess alterations in recognition memory and pattern separation related to healthy aging, mild cognitive impairment, and even hippocampal damage. Importantly, recognition memory does not necessarily require discrimination learning (or pattern separation). People who are able to perform recognition memory tasks are not always able to complete tasks of discrimination learning. Recognition memory and pattern separation both involve the ability to differentiate between familiar and novel information; however, pattern separation also requires the ability to discriminate between highly overlapping yet distinct information or events. Recognition memory is relatively stable across the lifespan, but pattern separation ability declines with age. For example, healthy older adults perform worse on a behavioral pattern separation task compared to younger adults but are not impaired on recognition memory (Stark et al., 2013).

In laboratory studies, pattern separation has been associated with neurogenesis in the hippocampus (Clelland et al., 2009). Low-dose irradiation was used to reduce neurogenesis in the mouse dentate gyrus (i.e., reduce numbers of immature and proliferating hippocampal neurons). Two months after irradiation, mice were tested on an eight-arm radial maze task. This spatial memory task required that animals select the arm that had not been previously presented from a choice of two arms. (The two choices randomly rotated throughout the eight arms during the task). The task measured pattern separation ability by determining whether mice were able to differentiate between the locations that were closer in space versus farther apart. Irradiated mice were impaired at differentiating between arms in closer proximity versus arms located farther apart (Clelland et al., 2009). Irradiated mice also were tested on a second task that measured spatial discrimination ability using a touch screen. Mice were required to choose between two of five locations that were increasingly farther apart in space, and were deficient on locations that were closer in space (Clelland et al., 2009). This study was one of the first to demonstrate that neurogenesis in the mouse dentate gyrus of the hippocampus is potentially involved in discrimination learning related to spatial information (Clelland et al., 2009). In humans, activity in bilateral hippocampi predicted discrimination learning in young adults during functional magnetic resonance imaging (Klippenstein et al., 2020). Data from lesion studies in humans provide further support that discrimination learning requires the hippocampus, while recognition memory does not. That is, people with hippocampal deficits were able to perform a recognition memory task but impaired in discrimination learning (Kirwan et al., 2012).

In the present study, women who improved on pattern separation after meditation and aerobic exercise training did not necessarily improve on novelty detection or recognition memory. However, it is important to note that novelty detection and recognition memory did not change as a result of practice (even though new objects were used for the repeated testing procedure). We did not have the opportunity to assess pattern separation or recognition memory in people without HIV; therefore, we are not able to determine the impact of HIV on discrimination learning, prior to any intervention. Other reports suggest that people with HIV are impaired on recognition memory compared to people without HIV (Castelo et al., 2006; Maki et al., 2009). Two studies used functional magnetic resonance imaging to detect changes in hippocampal function related to recognition memory in people with HIV. Both reported that people with HIV exhibited reduced blood oxygenation (a marker of brain activity) in the hippocampus to remembered versus forgotten scenes compared to people without HIV. People with HIV were also less able to differentiate between familiar and novel information behaviorally (Castelo et al., 2006). In our study, as a group, women with HIV were performing on par with healthy adults on pattern separation and novelty detection, when compared to studies of healthy younger and older adults (Stark et al., 2013). And after training, pattern separation scores significantly improved. These data indicate that meditation and aerobic exercise training is perhaps interacting with hippocampal-dependent processes, such as neurogenesis, to increase pattern separation learning in women with HIV.

Behavioral interventions for HIV

Prior behavioral health interventions for people living with HIV have focused on physical training, including aerobic exercise or resistance training, or mental training, such as meditation or mindfulness techniques, but rarely both. This is despite the fact that mental and physical health difficulties arise to a greater degree in people living with HIV than people without HIV (e.g., Orza et al., 2015). In addition, mental health symptoms, such as anxiety and depression oftentimes interact with physiological symptoms related to the virus that negatively impact physical health (e.g., Voss et al., 2007). Interventions for people with HIV are not always feasible for participants. A recent meta-analysis of 45 studies reported that current health interventions for people living with HIV/AIDS are rarely integrated into existing services at a single site where clients are already receiving treatment (Chuah et al., 2017). In addition, the majority of interventions for HIV tend to target men who have sex with men rather than women or African-American populations (Crepaz et al., 2014). Our study focused on women living with HIV, the majority of whom identified as African-American and were living below the poverty line in Newark, NJ. All women were currently attending group counseling sessions and continued to do so throughout the MAP sessions. We viewed MAP sessions as an adjunct to their ongoing counseling and medication regimes. Participants learned about the brain and simple behaviors that could be incorporated into their life to enhance overall mental and physical health. (It should be noted that no-training controls also were enrolled in their usual counseling sessions throughout the study and had access to resources normally available to them at these sites).

Putative mechanisms engaged during MAP Training

Previously, the combination of meditation and aerobic exercise has been more effective than either activity alone in reducing ruminative and trauma-related thoughts for women with trauma history (Millon et al., 2018). These data suggest a synergy between the two activities beyond that experienced by either alone. At the start of the meditation session, participants were instructed to focus their attention on the breath and begin counting their breaths after each exhale. They also were instructed that when thoughts arose during the silence, they should not follow the thought or attach emotions to the thought. Thoughts occurred, potentially related to past negative events, traumas or depressed states, but they did so presumably when the body was calm, and the context was safe. In this way, we interpret meditation as an indirect form of exposure therapy, whereby a person learned to let negative thoughts go, and this was potentially facilitated by the calm state of the autonomic nervous system. Likewise, and immediately following meditation, the person safely experienced an elevation in heart rate during aerobic exercise, in the absence of negative thoughts and feelings. We further speculate that aerobic exercise consolidates the effortful learning engaged in meditation through increased blood flow to the brain. It is thus possible that this particular combination of meditation and aerobic exercise might serve to decouple negative thoughts and feelings that oftentimes are accompanied by an increased physiological response felt in the body during fearful or anxious states, and are particularly severe in people with trauma histories (Shors et al., 2018). Overall, MAP Training may be especially effective in this population, as more than two thirds reported a history of physical and/or sexual trauma and moderate levels of anxiety.

The women in this study reported that they had difficulties sensing and regulating bodily sensations prior to the intervention (Millon and Shors, under review). Women with trauma oftentimes find it difficult to attend to inner sensations (e.g., van der Kolk, 2006), and report negative attitudes towards their bodies (Sack et al., 2010; Wenninger & Heiman, 1998). Women with HIV likewise report that they view their body in a negative way, which decreases quality of life (Huang et al., 2006). Various body-oriented therapies have attempted to enhance body awareness in women with trauma (e.g., Porges, 1995; Price & Hooven, 2018; van der Kolk et al., 2014), including those that utilize meditative practices (de Jong et al., 2016; Farb et al., 2015). But the data are mixed as to what extent current meditative practices on their own enhance body awareness and emotional regulation, and whether these practices impact learning (Khalsa et al., 2019; Treves et al., 2019). To date, those inventions that successfully target mental health do not report an effect on cognition. A meta-analysis of exercise interventions for trauma populations reported aerobic exercise reduced maladaptive arousal but the impact on cognition had not been widely tested (Hegberg et al., 2019). We propose here that the combination of aerobic exercise and meditation might be particularly effective in enhancing the ability to discriminate bodily signals in women living with the chronic stress of HIV. Furthermore, the enhancement in discrimination learning might enable longer-term mental health benefits.

We did not assess mechanisms through which meditation and aerobic exercise facilitated enhanced mental health and cognition in women with HIV. Changes in mental and cognitive outcomes did not correlate within individuals and therefore, it is difficult to determine how these processes are interacting with respect to training. The decreases in thoughts and feelings related to rumination, depression, perceived stress and trauma might have facilitated the ability to discriminate between similar sets of information or vice versa. Either way, it seems likely that the increase in discrimination during pattern separation is mediated by learning processes that are activated during the intervention. For example, during silent meditation, one learns how to discriminate each breath from subsequent and prior breaths by counting them. Thoughts and feelings occur during meditation that are oftentimes negative and about the past. As they arise, a person learns how past events are remembered by the brain and to recognize that they are different from what is experienced in the present. Likewise, during aerobic exercise, participants learn how to take their heart rate by counting their heartbeats. Breaths and heartbeats are physiological events that are discrete in time but also highly overlapping, and thus learning about them might enhance discriminative ability. Participants are instructed to take their heart rate at the end of the 30-min silent meditation and again after 25-min of aerobic exercise, prior to the 5-min cool down. In this way, participants learn that the heart naturally slows down or speeds up depending on one's activity and behavior and can be experienced in a healthy and safe manner.

MAP Training was translated from neuroscience studies suggesting that mental training with learning and physical training with aerobic exercise increases neurogenesis in the hippocampus. Laboratory studies in rodents report that pattern separation is dependent on hippocampal neurogenesis in the adult mammalian brain (Clelland et al., 2009). HIV might impede neurogenesis in humans by infecting neural progenitor cells and neural stem cells, which can develop into adult neurons (e.g., Lawrence et al., 2004; Putatunda et al., 2018). For example, HIV is present in neural progenitor cells identified postmortem from brain tissue in children who had died of AIDS (Schwartz et al., 2007). HIV-associated dementia can exacerbate the effects of the virus on neurogenesis. At autopsy, people who developed HIV-associated dementia had fewer neural progenitor cells in hippocampal tissue compared to people who lived with HIV but did not develop dementia (Krathwohl & Kaiser, 2004).

In the present study, novelty detection and recognition memory were not enhanced by the training program whereas pattern separation improved. To our knowledge this is the first study to report an increase in pattern separation related to discrimination learning as a result of a combined meditation and exercise intervention. Suwabe and colleagues have documented enhanced pattern separation related to discrimination learning following aerobic exercise in healthy young adults. An acute bout of 10 minutes of exercise enhanced pattern separation ability in young adults (Suwabe, Hyodo, Byun, Ochi, Yassa, et al., 2017), and aerobic fitness mediated the effect (Suwabe, Hyodo, Byun, Ochi, Fukuie, et al., 2017). In addition, 10 minutes of exercise increased functional connectivity between hippocampal and cortical regions, and the magnitude of enhanced connectivity predicted behavioral memory improvement in young adults (Suwabe et al., 2018). These findings are striking as pattern separation was enhanced after only 10 minutes of exercise but the study population were young adults without HIV, and therefore it is hard to compare to our data. The women in our study participated in 30 minutes of aerobic exercise weekly for six weeks. We did not test changes in discrimination learning over the course of six weeks, and thus we are not able to determine the necessary dose of training, so to speak, to elicit the effects observed. We employed six weeks of training based on our other studies that have documented improvements in cognition and mood; we also sought to make the training effortful to enable learning to occur (Curlik & Shors, 2013; Millon & Shors, 2019). The increase in pattern separation reported here may relate to an increase in neurogenesis after MAP Training. However, it is not practical to detect neurogenesis in the human brain while someone is alive. Therefore, although the present data are consistent with interpretations of rodent studies, we cannot determine whether or not an increase in neurogenesis is related to the enhanced performance during the pattern separation task observed behaviorally.

Only a few studies exist on neurocognition and exercise in people with HIV and those that do have relied on self-report and male populations. Men with HIV who indicated they regularly exercised through self-report, performed better on a motor speed task compared to men who did not report that they exercised (Honn et al., 1999). Adults with HIV (74% male) who reported that they regularly exercised exhibited less neurocognitive impairment related to working memory compared to adults with HIV who did not exercise (Dufour et al., 2013). In both of these studies, exercise was assessed with self-report. One study did utilize an exercise intervention but cognition was assessed with self-report. Men with HIV reported fewer cognitive problems after a randomized control trial of weekly aerobic and resistance training over six months (Fillipas et al., 2006). Cognition was assessed via a survey of health-related quality of life rather than processes specific to learning and memory such as those reported here. Few, if any, aerobic exercise interventions for people with HIV document enhanced learning and memory after training.

Irrespective of neurogenesis, many studies report that either aerobic exercise or meditation can induce changes in the hippocampus (e.g., Millon & Shors, 2019). One of the first studies reported that three months of aerobic exercise increased cerebral blood volume in the dentate gyrus of the hippocampus, which related to similar changes in mice (Pereira et al., 2007). Several reviews report either increased right or left hippocampal volume after aerobic exercise (Firth et al., 2018; Li et al., 2017). Others have documented that increased hippocampal volume related to greater aerobic fitness (measured as increased oxygen consumption) as well as increased performance on a memory-related task in older adults (Jonasson et al., 2017). Fitness also appears to protect against volume loss in the hippocampus. Exercise training increased hippocampal volume and spatial memory in older adults and reversed age-related volume loss by one to two years (Erickson et al., 2011). People who meditate also exhibit changes in hippocampal neural activity and/or blood flow. In one study, novice meditators were instructed on how to meditate while in a scanner, and blood flow to the hippocampus increased after just four days of training (Zeidan et al., 2014). People with mild cognitive impairment who practiced MBSR for eight weeks expressed more functional connectivity between hippocampal and cortical regions and less hippocampal atrophy compared to those with mild cognitive impairment who did not practice MBSR (Wells et al., 2013). These effects persist with age. Older adults with mild cognitive impairment who practiced meditation for 12 weeks expressed increased hippocampal volume compared to age-matched controls (Fotuhi et al., 2016). In our study, we did not assess hippocampal volume, and thus cannot confirm or deny these types of associations. However, the MAP Training program used in our study was not especially time-consuming and only persisted for 6 weeks. It seems likely that changes in the brain, including the hippocampus, would be more evident at the cellular and neurophysiological level.

Conclusions

Women with HIV who engaged in six weeks of combined meditation and aerobic exercise training exhibited significant enhancements in learning and memory processes related to discrimination learning, and experienced substantial reductions in mental health symptoms related to depression and perceived stress. Furthermore, women reported fewer numbers of ruminative and trauma-related thoughts after training, most of whom had experienced past physical and/or sexual traumas. Overall, the combination of silent meditation and aerobic exercise is an effective therapy for women who live each day with the physiological, psychological and cognitive effects of a chronic disease that impacts the health of the brain and body.

Chapter 3: Regulatory processes after meditation and aerobic exercise in women with HIV

Introduction

HIV not only attacks the immune system but also crosses the blood-brain barrier to infect the brain (Kaul et al., 2001). Consequently, people living with HIV experience deficits in autonomic nervous system function (e.g., Rogstad, Shah, Tesfaladet, Abdullah, & Ahmed-Jushuf, 1999). The autonomic nervous system allows for communication between the brain and the heart and regulates essential physiological processes such as heart rate, blood pressure and respiration. Fluctuations in heart rate reflect a system that can respond adaptably to physical activity or stress when necessary (e.g., Shaffer & Ginsberg, 2017). These fluctuations are measured as variations in time between successive heart beats and are known as heart rate variability or HRV. HRV has been used to categorize impairments in autonomic function, but it is not sufficient as a stand-alone measure of health.

The autonomic nervous system consists of sympathetic and parasympathetic branches and both regulate cardiac function. HRV is typically assessed according to time and frequency domains (Sayers, 1973; Shaffer & Ginsberg, 2017; Task Force, 1996). Common time measures are the standard deviation of normal beat-to-beat intervals or SDNN and root-mean-squared of standard deviation normal-to-normal or RMSSD (units in milliseconds). Frequency domain statistics are based on power spectral analyses that provide the variance in heart rhythms explained by periodic oscillations of heart rate at various frequencies (e.g., Stein & Kleiger, 1999). Thus, HRV can be quantified according to the power in specific frequency bands or energy distributed per unit time. In a healthy heart, the parasympathetic system predominates at rest. Likewise, the parasympathetic system is thought to mediate both low (0.04-0.15 Hz) and high-frequency (0.15-0.4 Hz) HRV, as these frequencies are blocked by cholinergic antagonists (Akselrod et al., 1981; Billman, 2013; Reyes del Paso et al., 2013; Shaffer & Ginsberg, 2017). The sympathetic system has minimal effects on high-frequency HRV, with potential effects on the low end of the low-frequency range (Billman, 2013). There is disagreement as to what the ratio of low-frequency to high-frequency HRV purportedly measures. Early reports of low-/high-frequency cited the ratio as a measure of autonomic balance between sympathetic and parasympathetic branches (Pagani et al., 1984, 1986). However, more recently this has been called into question as an oversimplification (Billman, 2013; Reyes del Paso et al., 2013). Now it is thought that both low- and high-frequency HRV predominately are indicative of parasympathetic function. HRV analyses can provide insight into the parasympathetic and sympathetic modulation of heart rate, as well as broader systems such as the baroreflex, which regulates blood pressure (Goldstein et al., 2011; Shaffer & Ginsberg, 2017). Thus overall, HRV should be considered not a measure of autonomic balance but rather an index of multiple regulatory systems (Lehrer & Eddie, 2013).

The following study targeted the brain and the body in women with HIV with a brain fitness program known as Mental and Physical (MAP) Training. Now trademarked as MAP Training My Brain™, the intervention combines 30 minutes of focused-attention meditation and 30 minutes of aerobic exercise in weekly sessions (Shors et al., 2014). Prior clinical studies indicate that the program, when practiced over weeks, enhances mental health and neurophysiology in a variety of human populations. In particular, we have reported that eight weeks of MAP Training significantly increased VO_2, which is a measure of aerobic fitness, in women with high levels of anxiety and trauma histories (Shors et al., 2014). We have also documented enhanced synchronized brain activity related to cognitive control in young men and women with major depressive disorder who engaged in eight weeks of MAP Training (Alderman et al., 2016). Therefore, we determined that MAP Training might be especially effective in improving physiological and psychological health in women with HIV. It was hypothesized that heart rate variability, interoceptive accuracy and interoceptive sensitivity would be enhanced after six weeks of MAP Training with meditation and aerobic exercise in women with HIV.

Method

Participants

Approximately 15 adult women living with HIV (M_{age} = 45 years, *range* 23-58 years) were recruited from the François-Xavier Bagnoud (FXB) Center, Rutgers University Hospital and St. Clare's Housing Program in Newark, NJ, where individuals with HIV seek counseling and medical treatment. Participants were tested on outcomes at an initial test session and at follow-up six weeks later. Immediately after the initial test assessment, participants were scheduled for combined meditation and aerobic exercise training. Training occurred once per week for six weeks in a group setting at FXB Center or St. Clare's Housing Program offices in Newark. Participants were compensated $100 for completing initial and follow-up assessments and six weeks of training.

Measures

Interoceptive sensibility was assessed with the Multidimensional Assessment of Interoceptive Awareness Version 2 (MAIA-2; Mehling et al., 2018). Interoceptive accuracy was measured with the heartbeat tracking task (Schandry, 1981) while recording electrocardiography (ECG). (See Chapter 1 for full details of interoceptive measures). HRV was assessed while recording ECG during a 5-min rest period. Levels of carbon dioxide output were measured simultaneously during the 5-min period with capnometry.

Procedure

Interoceptive accuracy scores were calculated across six trials by comparing the number of actual heartbeats measured with ECG compared to the number of heartbeats reported by the participant (Garfinkel et al., 2015; Rae et al., 2020). See Chapter 1 for details on how scores were computed. Immediately following the heartbeat tracking task, HRV and CO_2 output were measured for a 5-min period at rest. During the rest period, participants were instructed to breath normally and count their breaths to themselves. If they lost count, they were instructed to begin counting again at one. The researcher alerted participants that they would be asked for the highest number of breaths counted at the end of the session. When the researcher verbally cued the participant, she began counting in silence until the researcher instructed the person to stop 5 minutes later. The researcher recorded the number of breaths the participant counted. Upon completion of the breathing task, electrodes were removed.

MAP Training Intervention

Each one-hour MAP session began with 20 minutes of silent seated meditation, followed by 10 minutes of very-slow walking mediation, ending with 30 minutes of aerobic exercise. The full intervention protocol is outlined in Chapter 2.

Data analyses

ECG data were collected from the wrists using a J&J Engineering C2+ physiograph. Capnometry was collected with a Better Physiology capnograph. Raw ECG data were taken from the wrists and digitized at 1024 samples per second. Raw ECG data were imported to WinCPRS® (Absolute Aliens Oy, Turku, Finland) or ARTiiFACT (Kaufmann et al., 2011) to extract time intervals between R-R waves (one heartbeat to the next) or interbeat (IBI) intervals. IBI data were output at 4 samples per second. Several HRV time- and frequency-domain measures were analyzed from the beat-to-beat intervals obtained during ECG using Kubios HRV Software (Tarvainen et al., 2014): the standard deviation of normal-to-normal (SDNN), root-mean-squared of standard deviation normal-to-normal (RMSSD), very-low frequency power (msec^2), low-frequency power (msec^2), high-frequency power (ms^2) and the ratio of low-/high-frequency HRV. HRV measures were not normal and thus were log transformed. The two highest values of CO_2 were averaged for each 30-sec epoch within each person's 5-min recording, yielding ten values prior to training and ten values after training. The standard deviation of the ten values was analyzed prior to and after training to determine within subject changes related to six weeks of meditation and aerobic exercise training. All statistical tests were performed with IBM SPSS Statistics. Paired sample t-tests were performed to determine whether outcomes significantly varied after training as compared to before.

Results

Interoceptive outcomes related to MAP Training

Interoceptive accuracy, as measured with heartbeat tracking scores, did not significantly change after six weeks of silent meditation and aerobic exercise training (*M*: 60%, *SE*: 5%) compared to before training (*M*: 58%, *SE*: 5%), $t(17) = -0.40$, $p > 0.05$ (Figure 7A). Interoceptive sensibility, as measured with the MAIA, did not significantly change after six weeks of silent meditation and aerobic exercise training (*M*: 25.73, *SE*: 1.55) compared to before training (*M*: 23.45, *SE*: 2.07), $t(17) = -1.34$, $p > 0.05$ (Figure 7B). Self-regulation subscale scores of the MAIA slightly increased after six weeks of training (*M*: 3.43, *SE*: 0.33) as compared to prior to training (*M*: 2.69, *SE*: 0.42) and approached significance but did not reach the alpha threshold, $t(17) = -2.05$, $p = 0.06$ (Figure 7C).

Physiological outcomes related to MAP Training

HRV analyses were analyzed in women who engaged in six weeks of combined silent meditation and aerobic exercise training. None of the HRV measures changed significantly after training. Group means, standard deviations, standard errors of means and effect sizes of HRV outcomes are reported in Table 5. Paired sample t-tests indicated that standard deviation of normal-to-normal values did not significantly change after six weeks of training, $t(14) = -0.38$, $p > 0.05$, Cohen's $d = 0.09$. Root mean squared of normal-to-normal values did not significantly change after six weeks of training, $t(14) = -0.26$, $p > 0.05$, Cohen's $d = 0.06$. Very-low frequency power (ms^2) did not significantly change after training, $t(14) = 0.80$, $p > 0.05$, Cohen's $d = 0.21$. Low-frequency power (ms^2) did not significantly change after training, $t(14) = -0.38$, $p > 0.05$, Cohen's $d = 0.09$. High-frequency power (ms^2) did not significantly change after training, $t(14) = 0.49$, $p > 0.05$, Cohen's $d = 0.13$. The ratio of low-/high-frequency HRV did not significantly change after training, $t(14) = -0.89$, $p > 0.05$, Cohen's $d = 0.23$. The standard deviation of CO_2 did not significantly change after training, $t(15) = 0.91$, $p > 0.05$. The total number of breaths counted during the 5-min rest period did not significantly differ before as compared to after training, $t(10) = -0.27$, $p > 0.05$. Finally, Pearson correlations indicted that HRV outcomes were not significantly associated with interoceptive outcomes either before or after meditation and aerobic exercise training, p's > 0.05.

Discussion

Heart rate variability related to aerobic exercise and meditation

The following study tested the effect of six weeks of combined silent meditation and aerobic exercise on physiological health as assessed with heart rate variability (HRV) in women living with HIV. The intervention is known as Mental and Physical (MAP) Training and combines 30 minutes of silent meditation with 30 minutes of aerobic exercise. Six weekly training sessions did not significantly alter HRV in women with HIV. HRV is typically used as an indicator of health, as people who are more aerobically fit have higher HRV (e.g., De Meersman, 1993), whereas low HRV is a risk factor for heart disease and all-cause mortality (Kleiger et al., 1987; Tsuji et al., 1994; Vaishnav et al., 1994). Multiple studies have reported that increased aerobic fitness is related to increased HRV, and this is observed across the lifespan, though HRV does decrease with healthy aging (e.g., Reardon & Malik, 1996). For example, post-menopausal women who regularly endurance trained (quantified as running an average of 32 miles per week) had significantly higher HRV compared to women who did not regularly exercise (Davy et al., 1996).

Few studies have successfully enhanced HRV in the short-term. This can be partially explained by the fact that measures are fairly stable within individuals and typically do not change with short-term behavioral modifications (Davy et al., 1997). Those intervention studies that do exist report changes in HRV after multiple training sessions, many more than the six sessions of training reported here. For example, one study reported changes in HRV after combined aerobic and resistance training performed five times a week for four weeks in sedentary middle-aged women (Masroor et al., 2018). The changes reported were in both time- and frequency-domain measures: four weeks of training increased high-frequency HRV and SDNN and decreased low-frequency and low-/high-frequency HRV in women who previously had not exercised (Masroor et al., 2018).

Several groups have reported differences in HRV related to meditation but most of these studies tested outcomes in people grouped by meditation experience who were not exposed to interventions. Furthermore, the effects are often observed during the meditative state, rather than at rest after completing an intervention. An early study by Lehrer and colleagues (1999) measured HRV in experienced practitioners of Zen meditation. HRV significantly increased within the low-frequency range but decreased in the high-frequency range during “tanden” or slow breathing (Lehrer, Sasaki, & Saito, 1999). These data are supported by other reports in people who were regular practitioners as well as novice meditators. One study reported low-frequency HRV increased during meditation in people who regularly meditated, and high-frequency HRV and the ratio of low-/high-frequency HRV decreased after meditation, as compared to paced breathing (Léonard et al., 2019). Novice practitioners of Zen meditation also exhibited increased low-frequency HRV and decreased high-frequency HRV during meditation (Cysarz & Büssing, 2005). However, the results across studies are mixed. People with no meditation experience exhibited decreased low-frequency HRV and a decreased ratio of low-/high-frequency HRV during a 20-min Zen meditation session (Wu & Lo, 2008). Young adults who listened to a 20-min recording of a guided body scan used in MBSR exhibited greater high-frequency HRV while meditating, measured as respiratory sinus arrhythmia, as compared to people who sat at rest or engaged in progressive muscle relaxation (Ditto et al., 2006). Again, few studies have successfully enhanced HRV with meditative interventions. One group did test the effects of meditation on HRV with a randomized control trial in people with mild to moderate depression, and reported significant decreases in depressive symptoms as assessed with the Hamilton Scale, but no change in HRV (Ionson et al., 2019).

A few early studies that targeted aerobic fitness with exercise in people with HIV reported enhanced oxygen consumption after training but did not measure HRV (e.g., MacArthur et al., 1993; Perna et al., 1999; Stringer, Berezovskaya, O'Brien, Beck, & Casaburi, 1998). However, one study did report that people with HIV who were aerobically fit had higher high-frequency HRV compared to those who were not aerobically fit, and HRV measures did not significantly differ from those without HIV who were also aerobically fit (Spierer et al., 2007). In this same study, people with HIV had greater baroreflex sensitivity as compared to people without HIV (Spierer et al., 2007). To our knowledge, very few interventions have attempted to enhance HRV in people living with HIV. Those that do incorporate aerobic exercise. One recent study reported a significant increase in SDNN in people living with HIV following eight weeks of aerobic exercise, practiced three times a week, which is substantially longer than our intervention reported here (Quiles et al., 2020). However, the same study reported no differences in frequency-domain measures of HRV after exercise (Quiles et al., 2020). Another study assessed HRV prior to, during and after a 20-min treadmill exercise (performed at 60% of maximum oxygen intake) (Borges et al., 2012). People with

HIV exhibited lower SDNN and low- and high-frequency HRV at rest, as well as significantly less low- and high-frequency HRV following exercise compared to controls (Borges et al., 2012). It is hard to compare our data to others who have assessed HRV in HIV populations as there are so few studies. The SDNN and low-frequency HRV measures reported in our study here were lower than those reported by Borges and colleagues (2012); however, that study assessed 10 males and only 3 females with HIV. For the most part, men have higher HRV than women (e.g., Koenig & Thayer, 2016) though reported sex differences in HRV are also mediated by age (Stein et al., 1997). The SDNN values in our study were also lower than those reported by Quiles and colleagues (2020), both before and after their aerobic exercise intervention. In our study, we did not measure HRV in people without HIV so we are not able to report on the impact of HIV on HRV; however, others have reported decreased low- and high-frequency HRV in people with AIDS, and these indices are lower even compared to people without HIV but with heart disease (Neild et al., 2000).

Heart rate variability and MAP Training

Here we report no change in time and frequency-domain measures of HRV in women with HIV who engaged in six weeks of MAP Training with meditation and aerobic exercise. CO_2 output also did not change after training. We hesitate to conclude that aerobic exercise and meditation training do not enhance HRV, as others have reported either practice alone has physiological effects. Previously, we have reported neurophysiological changes after eight weeks of MAP Training practiced twice weekly. For example, MAP Training enhanced oxygen consumption in women with a history of trauma and anxiety (Shors et al., 2014), and also enhanced synchronized brain activity related to cognitive control in young adults with major depressive disorder (Alderman et al., 2016). And thus, given these changes in brain physiology and cardiovascular fitness, it seems likely that MAP Training also targets the autonomic nervous system, but we were not able to detect changes after only six weekly sessions. Prior studies from our lab provided training sessions twice a week for eight weeks, which is substantially more frequent than the six sessions reported here. Furthermore, the women in this study were living with the physical effects of a chronic virus that was quite likely impacting cardiovascular health, and thus might not have been responsive physiologically to sessions practiced only weekly.

Heart rate variability related to HIV

How exactly HIV disrupts autonomic modulation of the heart is not entirely clear but both sympathetic and parasympathetic components seem to be dysregulated. People with HIV often live with resting heart rates above 100 beats per minute or tachycardia (Freeman et al., 1990). HRV also appears to be disrupted in this population following stress exposure. For example, sympathetic reactivity to stress was heightened in people with HIV when measured with a stress test during ECG and reduced at rest (Correia et al., 2006). There is also evidence that HIV inflames and degenerates sympathetic nerve fibers as the virus progresses, thereby potentially reducing sympathetic activity. For example, one study examined the morphology of sympathetic nerve cells in the spinal cord in people who had died of AIDS; postmortem examination showed inflammation in cervical sympathetic nerve cells as well as neural degeneration (Chimelli & Martins, 2002).

People with HIV also exhibit reduced high-frequency HRV as well as a reduced ratio of low-/high-frequency HRV compared to people without HIV (Borges et al., 2012; Correia et al., 2006; McIntosh, 2016). These data might indicate compromised vagal function, though measures are indirect. In addition, vagal function might be compromised via immune system activation. HIV significantly increases proinflammatory cytokines (Naitoh et al., 1988), which have been shown to suppress parasympathetic activity when experimentally induced in healthy adults without HIV (Lehrer et al., 2010). Collectively, these data suggest, that in people with HIV, the parasympathetic system perhaps is not modulating sympathetic control of the heart either following a stressor or at rest, thereby leading to a higher resting heart rate and lower HRV. Finally, HIV might lead to dysfunction in the baroreflex system (Brownley et al., 2001; Brownley & Hurwitz, 2003), though the findings are mixed (Rogstad et al., 1999). In both studies, the baroreflex was measured with the Valsalva maneuver where participants exhaled into a mouthpiece attached to a pressure gauge. People with HIV had an intact baroreceptor reflex; however, those individuals with lower stroke volume had larger increases in heart rate; thus, HIV might impact the relationship between resting cardiac function and the baroreceptor reflex (Brownley et al., 2001). The second study reported that people with AIDS did not differ from healthy controls when assessed during the Valsalva maneuver, but there was a trend towards greater changes in blood pressure with respect to controls (Rogstad et al., 1999). In our study, we did not assess the baroreceptor reflex or other measures of HRV in people without HIV, and thus it is difficult to determine how exactly HIV might be impacting HRV.

Heart rate variablity, self-regulation and interception

Initial theories of HRV have defined it as a measure of autonomic balance (e.g., Pagani et al., 1986, 1984), but this simplification has been called into question more recently (Reyes del Paso et al., 2013). In fact, HRV should be thought of as an index of multiple control systems that mediate not only heart rate but also blood pressure and body temperature (e.g., Lehrer and Eddie, 2013). Neuroimaging research has provided further evidence that HRV is one player in a larger framework of regulatory processes implicated in stress, disease and overall health (Thayer & Lane, 2000, 2009). Regional blood flow to specific areas of the brain, including both cortical and subcortical areas implicated in emotion regulation, have been associated with HRV within individuals. For example, high-frequency HRV has been associated with increased blood flow to medial prefrontal brain regions, as measured with positron emission tomography, in healthy women (Lane et al., 2009).

In the following study we also tested the effects of combined meditation and aerobic exercise on interoceptive accuracy and interoceptive sensiblity. Interoceptive accuracy was assessed behaviorally and interoceptive sensibility was measured via self-report. Interoception is the mental awareness of the body's physiological state and is intergral to theories of how emotions are sensed and felt in the body, and interpreted by the brain (e.g., Barrett & Simmons, 2015; Craig, 2009). It was hypothesized that interoceptive accuracy and sensibility would improve after training with meditation and aerobic exercise in women with HIV. But interoceptive measures did not change after training, though interoceptive self-regulation was enhanced after training, and these changes approached significance (p = 0.06; Figure 7C). The negative findings might be explained in part by the fact that many women were scoring at ceiling on the self-regulation subscale (as indicated by a score of 5), and thus there was not much room to improve on this measure after training. Elsewhere we have reported that the combination of meditation and aerobic exercise significantly decreased trauma-related and ruminative thoughts, as well as perceived stress and depressive symptoms in women with HIV (Millon and Shors, under review). Given the substantial changes in various outcomes related to mental health, it is somewhat surprising that interoceptive sensibility did not also increase; however, prior to training, mental health outcomes were not related to either interoceptive accuracy or sensibility in our sample of women with HIV (Millon and Shors, under review). Thus, the measures of interoception used in this study might capture regulatory dimensions of body awareness that did not substantially overlap with measures of mental health. Overall, we hesitate to extrapolate too much from these negative findings. But quite likely, a potential explanation for the lack of groups findings might be related to individual differences in treatment response. The combination of meditation and aerobic exercise was potentially effective for those women who had low scores of interoceptive self-regulation prior to the intervention, but not for those women who reported high self-regulation prior to any training.

Very few studies have tested the relationship between HRV and interoception. Those that have report no relationship between HRV and interoceptive accuracy, as assessed by the heartbeat tracking task; however, participants' confidence in their task performance significantly related to low- and high-frequency HRV (Owens et al., 2018). These findings are interesting to consider as others have reported experienced meditators are not necessarily more accurate at tracking their heartbeats compared to novice meditators, but they *report* that they are more accurate at doing so (Khalsa et al., 2008). In light of these data, it might be the case that targeting a person's confidence in their ability to track and sense their bodily signals might be sufficient to enhance overall mental health, regardless of whether or not the person actually is better at tracking heartbeats or improves with training. These caveats might be important to consider when providing behavioral health treatments, such as the meditation and aerobic exercise intervention employed here, that seek to collectively target mental and physical health and the connection between the two.

Table 1. A correlation matrix of five measures of mental health.

	RRS	BDI	PSS	PTCI	BAI
RRS	1.00				
BDI	0.79***	1.00			
PSS	0.69**	0.62***	1.00		
PTCI	0.77***	0.52**	0.44**	1.00	
BAI	0.61***	0.63***	0.43***	0.31	1.00

***p < 0.01, ***p < 0.001*

Table 2. Factor loadings and variance explained by a primary shared factor ("Mental Health") extracted from five self-report psychological measures using an exploratory factor analysis (*n* = 35).

Ruminative Responses Scale (RRS)	0.94
Beck Depression Inventory (BDI)	0.87
Perceived Stress Scale (PSS)	0.75
Posttraumatic Cognitions Inventory (PTCI)	0.75
Beck Anxiety Inventory (BAI)	0.73
Eigenvalue	3.30
Proportion of common variance	66%

Table 3. Means and standard errors for MAIA scales (*n* = 37).

Subscale (# of items)	**Mean (Standard Error)**	**Range**
Noticing (4)	3.40 (.19)	.25-5.00
Not-Distracting (6)	2.68 (.23)	0-5.00
Not-Worrying (5)	2.62 (.17)	.40-4.80
Attention Regulation (7)	2.97 (.20)	0-5.00
Emotional Awareness (5)	3.61 (.20)	0-5.00
Self-Regulation (4)	3.24 (.24)	0-5.00
Body-Listening (3)	3.07 (.23)	0-5.00
Trusting (3)	3.28 (.25)	0-5.00
Total (37)	**24.86 (1.14)**	**8-37**

Table 4. Group means (and standard deviations) for percent endorsed for each stimulus and response type as well as recognition memory and pattern separation scores. Data collected from training (n = 19) and no-training (n = 7) groups at initial and follow-up testing six weeks apart.

	Targets (Old)			**Lures (Similar)**			**Foils (New)**			**Recog. Mem.**	**Patt. Sep.**
	Old	*Similar*	*New*	*Old*	*Similar*	*New*	*Old*	*Similar*	*New*		
Training											
Initial Testing	81%	13%	6%	54%	32%	14%	10%	20%	69%	71%	12%
	(12%)	(9%)	(5%)	(21%)	(22%)	(9%)	(15%)	(14%)	(18%)	(21%)	(24%)
Follow-up	73%	19%	8%	52%	38%	10%	14%	23%	63%	59%	15%
	(19%)	(13%)	(8%)	(17%)	(19%)	(6%)	(20%)	(13%)	(24%)	(31%)	(23%)
No Training											
Initial Testing	57%	25%	18%	45%	34%	22%	20%	25%	55%	36%	9%
	(28%)	(24%)	(14%)	(18%)	(28%)	(15%)	(17%)	(22%)	(23%)	(35%)	(11%)
Follow-up	40%	28%	32%	30%	33%	36%	15%	30%	56%	25%	3%
	(35%)	(25%)	(31%)	(27%)	(24%)	(25%)	(13%)	(19%)	(22%)	(42%)	(16%)

Table 5. HRV. Heart rate variability measures (log-transformed) prior to and after combined meditation and aerobic exercise training (n = 15).

	Pre-Training			*Post-Training*				
	Mean	**SD**	**SEM**	**Mean**	**SD**	**SEM**	***p***	**Cohen's *d***
SDNN	3.14	0.67	0.17	3.18	0.65	0.17	> 0.05	0.09
RMSSD	3.16	0.79	0.20	3.19	0.78	0.20	> 0.05	0.06
VLF Power (ms^2)	3.33	1.23	0.32	3.07	0.90	0.23	> 0.05	0.21
LF Power (ms^2)	5.21	1.19	0.31	5.31	1.17	0.30	> 0.05	0.09
HF power (ms^2)	5.40	1.55	0.40	5.27	1.53	0.40	> 0.05	0.13
LF/HF ratio	-0.20	0.77	0.20	0.05	0.91	0.24	> 0.05	0.23

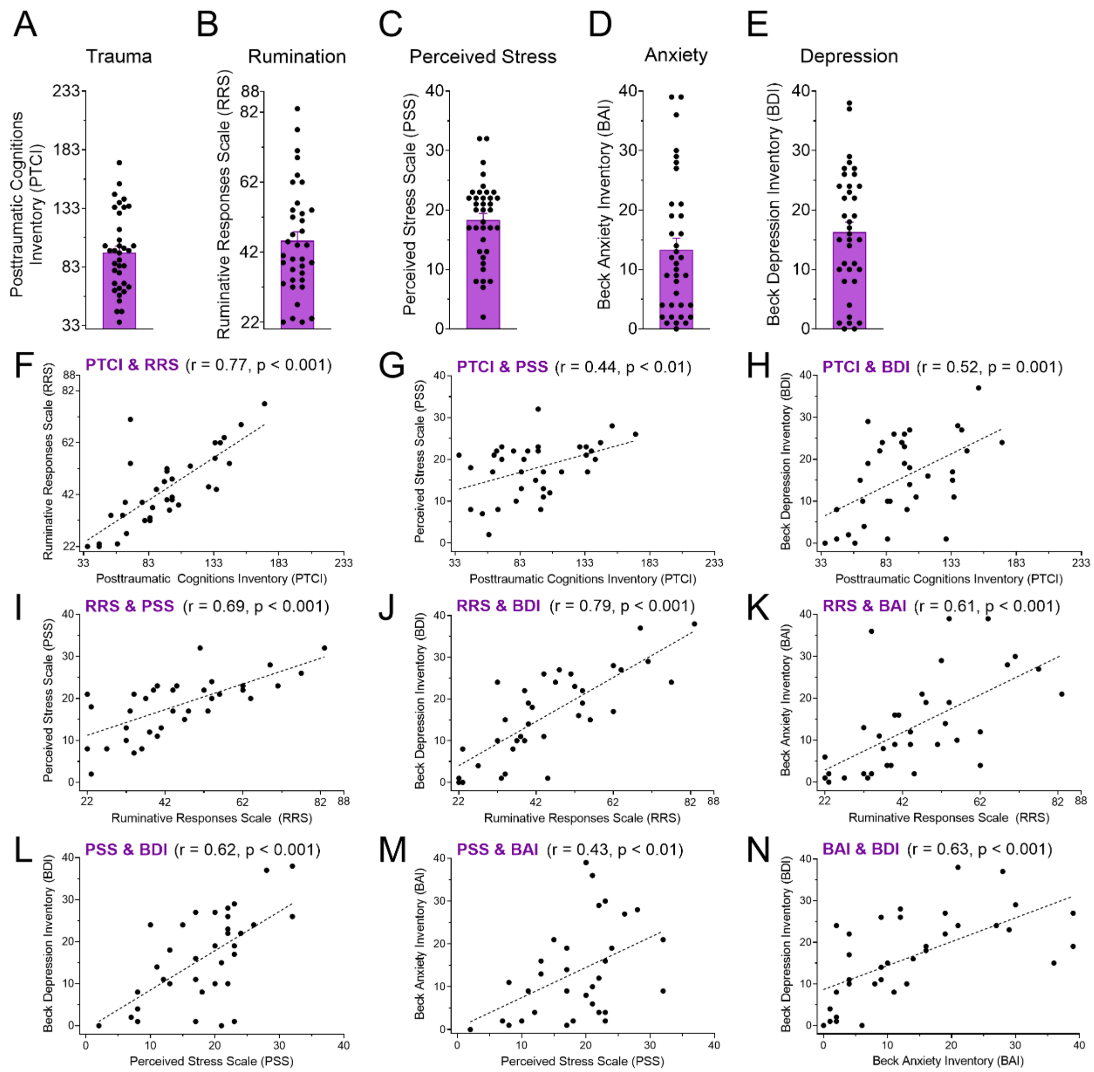

Figure 1. Column scatterplots of (A) posttraumatic cognitions as assessed by the Posttraumatic Cognitions Inventory (*n* = 37), (B) ruminative thoughts as assessed by the Ruminative Responses Scale (*n* = 37), (C) perceived stress as assessed with the Perceived Stress Scale (*n* = 38), (D) depressive symptoms as assessed with the Beck Depression Inventory (*n* = 38), and (E) anxiety symptoms as assessed with the Beck Anxiety Inventory (*n* = 37) in women with HIV. The number of trauma-related thoughts were highly correlated to the number of ruminative thoughts (F), and moderately correlated with reported levels of perceived stress

(G), and depression (H) in women with HIV. The number of ruminative thoughts were highly correlated to reported levels of perceived stress (I), and symptoms of depression (J) and anxiety (K). Reported levels of perceived stress were highly correlated with symptoms of depression (L) and moderately correlated with symptoms of anxiety (M). Finally, symptoms of anxiety and depression (N) were highly correlated in women with HIV.

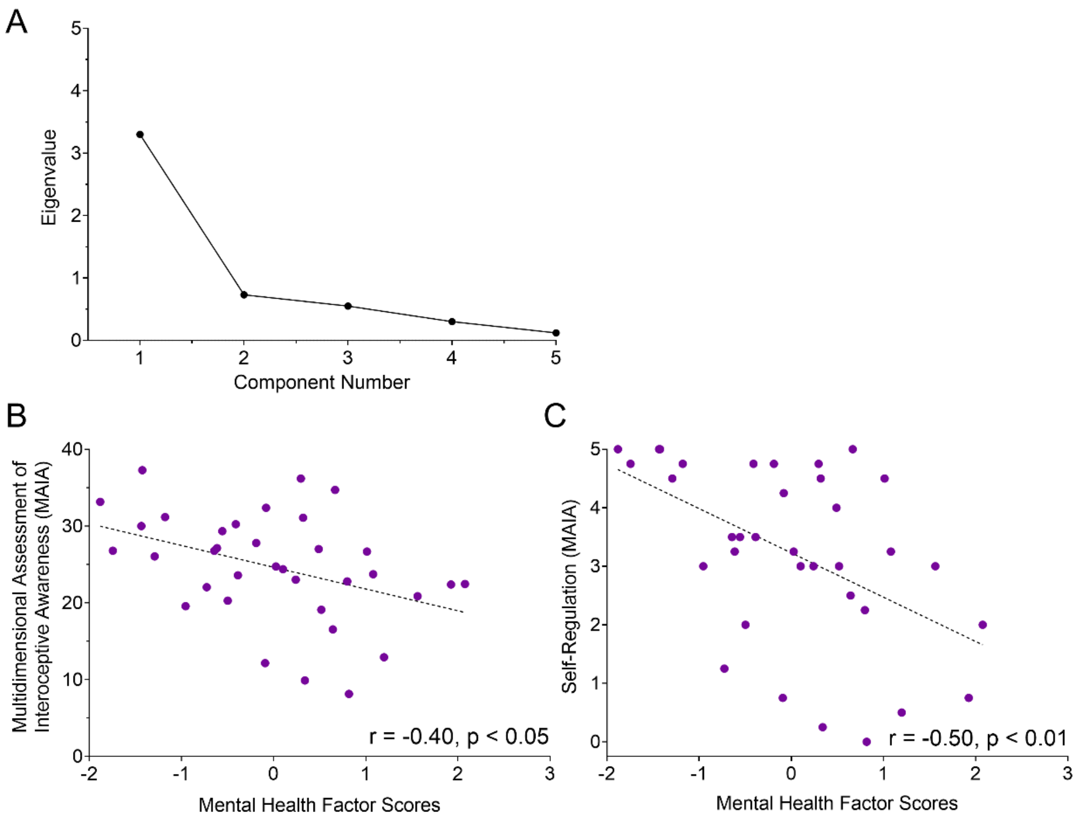

Figure 2. (A) Scree plot of the number of components (represented on the x-axis) and corresponding Eigenvalues per component (y-axis) extracted from the exploratory factor analysis of the five questionnaire measures of PTCI, RRS, PSS, BDI and BAI. Factor scores of mental health inversely correlated with (B) interoceptive sensibility as well as the (C) self-regulation subscale of the Multidimensional Assessment of Interoceptive Awareness (MAIA), such that women with fewer numbers of mental health symptoms (assessed with factor scores) reported higher levels of interoceptive sensibility, r = -0.40, p < 0.05, as well as higher levels of self-regulation when assessed with self-report, r = -0.50, p < 0.01, n = 35.

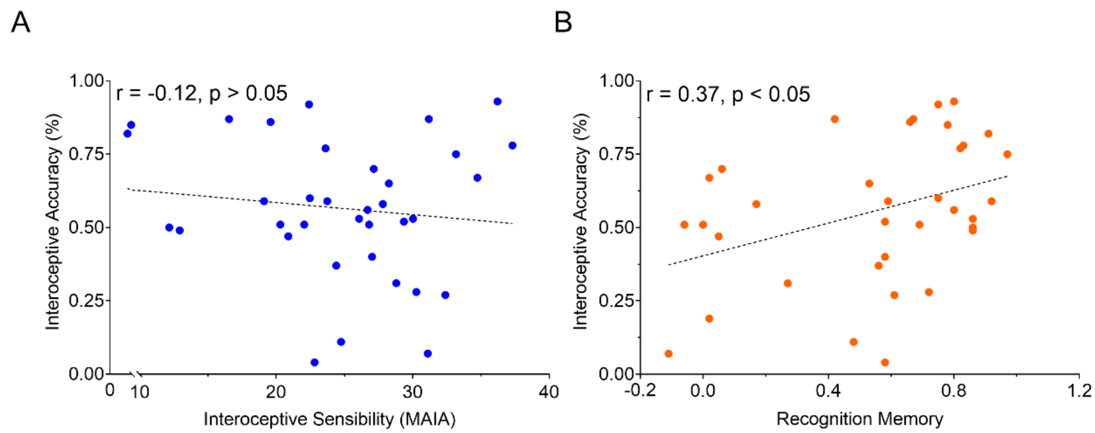

Figure 3. (A) Interoceptive sensibility (MAIA scores) did not relate to interoceptive accuracy (heartbeat tracking scores) in women with HIV, $p > 0.05$. (B) Interoceptive accuracy moderately correlated with recognition memory scores, $r = 0.37$, $p < 0.05$ in women with HIV ($n = 35$).

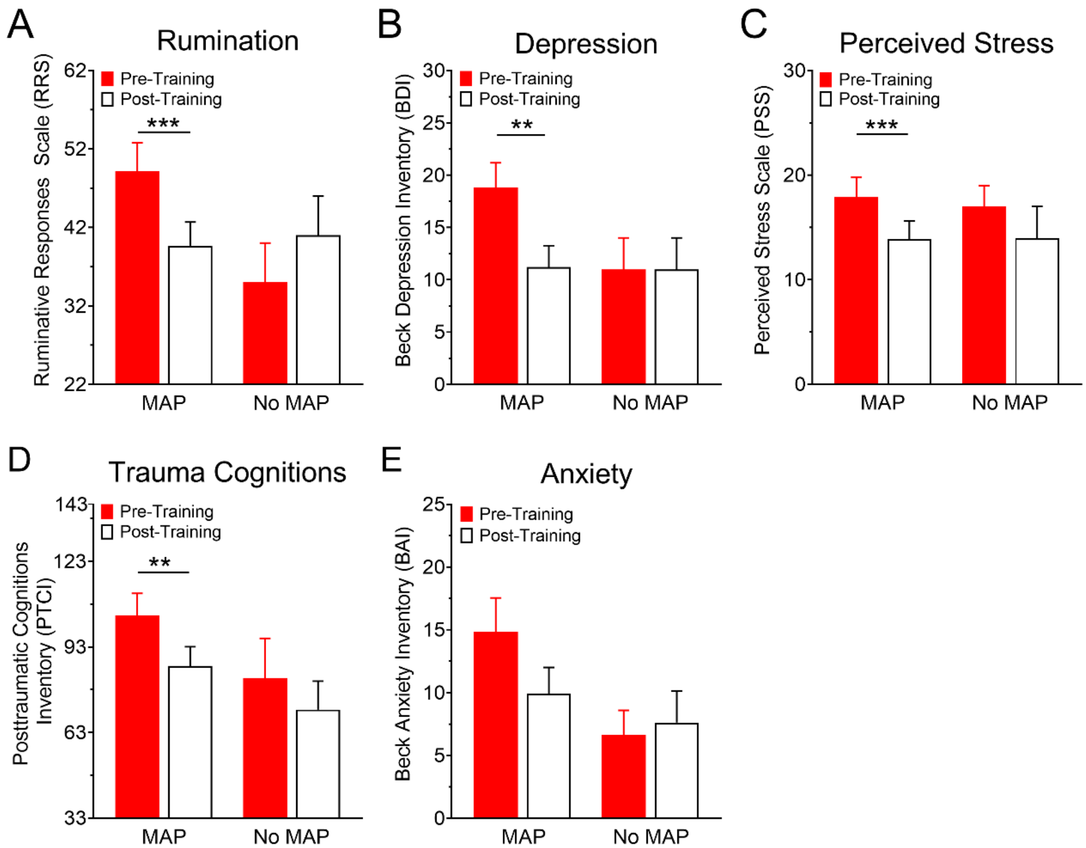

Figure 4. Women with HIV reported significantly fewer (A) numbers of ruminative thoughts, (B) symptoms of depression, (C) perceived stress, and (D) trauma-related cognitions after six weeks of combined meditation and aerobic exercise compared to women who did not train. (E) Decreases in anxiety symptoms trended toward significance after six weeks of training in women with HIV ($p = 0.05$). $^{**}p < 0.01$, $^{***}p < 0.001$.

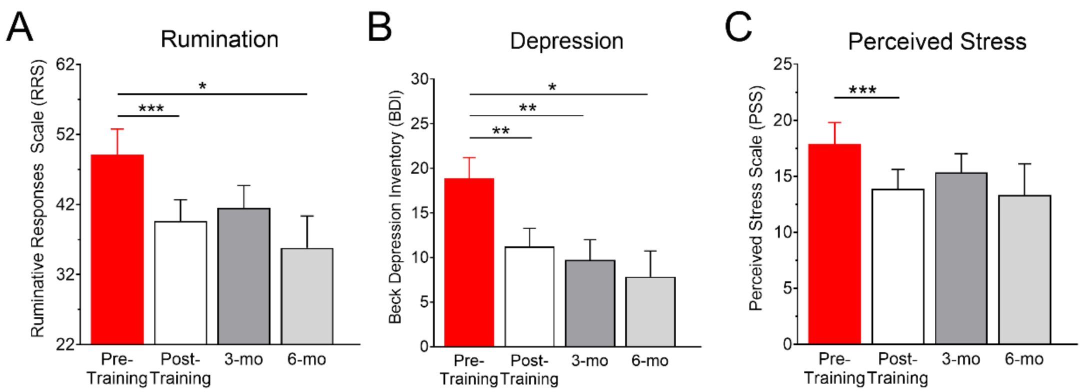

Figure 5. A) Decreases in rumination as assessed with the Ruminative Responses Scale persisted at six months but not at three months. B) Decreases in depressive symptoms as assessed with the Beck Depression Inventory persisted at three months and six months after training. C) Decreases in Perceived Stress as assessed with the Perceived Stress Scale decreased as compared to prior to training but did not reach significance at three months and six months after training. **p* < 0.05, ***p* < 0.01, ****p* < 0.001.

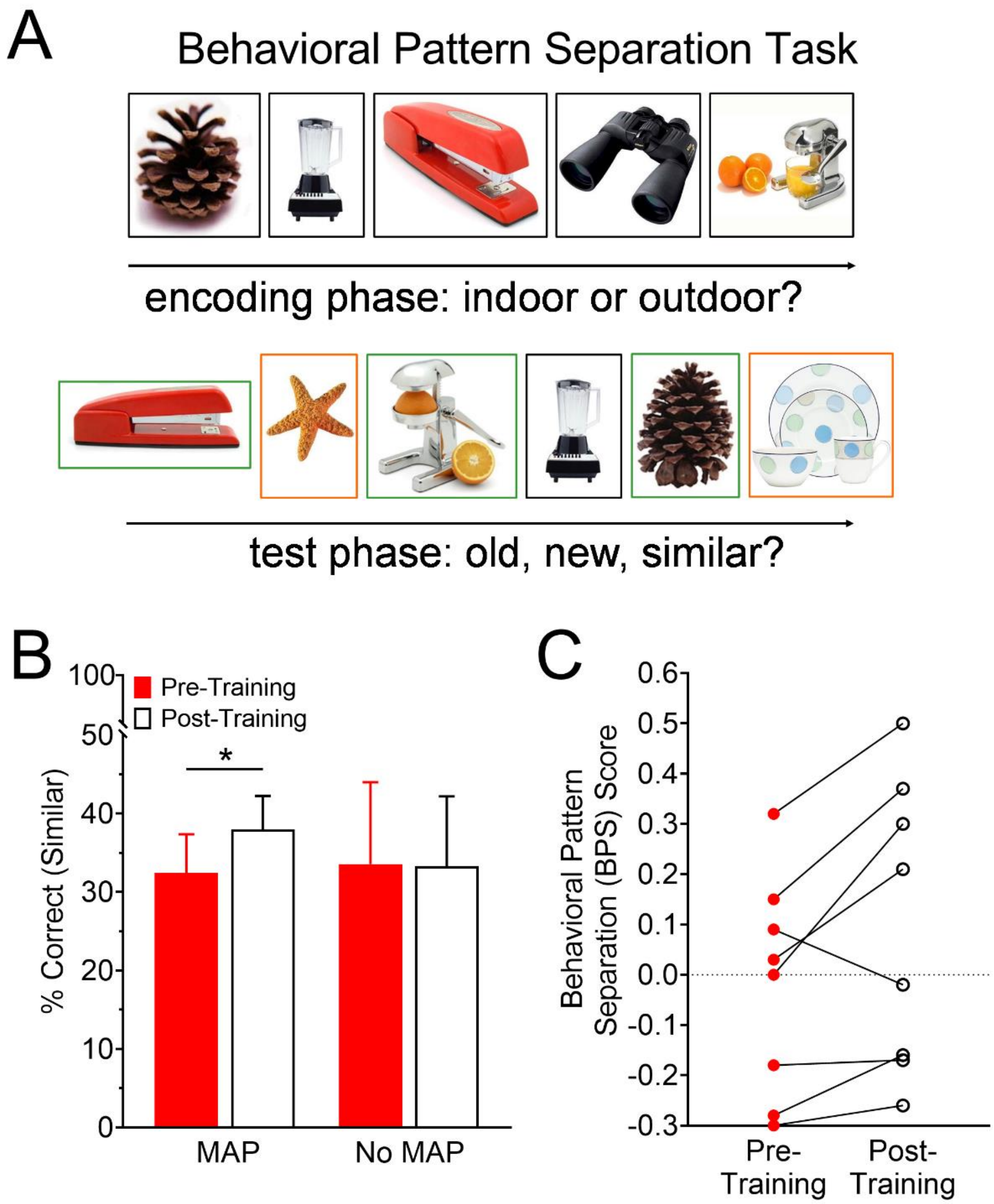

Figure 6. A) Behavioral Pattern Separation Task adapted from Stark and colleagues (2013). Participants initially encoded a series of everyday objects. The encoding phase was immediately followed by a surprise recognition test that had 64 identical images to those from the encoding phase (old), 64 novel objects not previously seen, and 64 objects similar to what participants had seen before in the

encoding phase but not exactly the same. B) Women with HIV who engaged in six weeks of silent meditation and aerobic exercise training ($n = 19$) significantly improved on pattern separation accuracy as assessed by the percentage of correct responses to similar items after training, as compared to women who did not train ($n = 7$). *Asterisk indicates $p < 0.05$. C) Women with HIV who had recognition memory scores of 80% or above prior to training ($n = 8$) were further assessed on pattern separation scores, which were calculated as the percentage of correct responses to similar objects minus the percentage of incorrect similar responses to novel objects. These women significantly improved on pattern separation scores after six weeks of combined meditation and aerobic exercise training, $p < 0.05$.

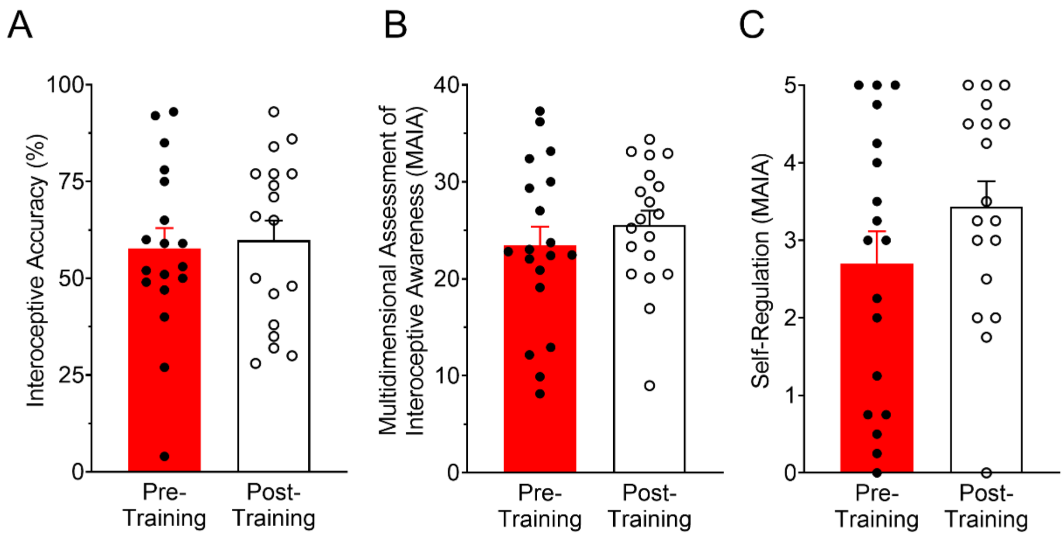

Figure 7. A) Interoceptive accuracy as assessed by the heartbeat tracking task and B) interoceptive sensibility assessed with the Multidimensional Assessment of Interoceptive Awareness did not significantly change after six weeks of combined meditation and aerobic exercise training in women with HIV. C) Self-regulation subscale scores of interoceptive sensibility after six weeks of training compared to prior to training approached significance but did not meet threshold (p = 0.06) in women with HIV.

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