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Esther Lin April 10, 2023

The Role of Sex Differences and the Insular Cortex in Post-Traumatic Stress Disorder and Asthma

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Abstract

The Role of Sex Differences and the Insular Cortex in Post-Traumatic Stress Disorder and Asthma

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Post-traumatic stress disorder (PTSD) is a trauma induced psychiatric condition that affects 12 million adults in the United States during a given year. A potential association exists between PTSD and asthma as growing evidence suggests that inflammation plays a role in the pathophysiology of both PTSD and asthma. There is a higher prevalence of PTSD in individuals with asthma compared to other psychiatric conditions like depression and anxiety disorders. Though the definite pathophysiology linking PTSD and asthma risk remains largely unknown, numerous studies suggest that people who were exposed to airway-related trauma were equally likely to develop asthma later in life as those exposed to non-airway related. Further, both PTSD and asthma are shown to be more prevalent in females compared to males. Neurobiologically, the insula has been found to be associated with PTSD symptoms and to be differentially activated by asthma-relevant cues, making it a strong region of interest to study in relation to asthma and PTSD. This present study investigates (1) the relationship between asthma and PTSD in an urban Atlanta population at high risk for trauma and PTSD, (2) how gender modulates the relationship of asthma and PTSD in this population, and (3) how the relationship between asthma and PTSD relate to insula activity in women. In this study, n=588 participants were approached by study staff in the emergency room and outpatient clinics of Grady Memorial Hospital. Participant information was collected through a 2-hour long interview screen assessing asthma presence and PTSD severity through administration of the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) measure. A separate cohort of female participants (n=71) underwent MRI scans during a fearful faces task that measured fear responses. Their responses to the fearful and neutral stimuli were recorded and their insula response were analyzed. Within this population, PCL-5 scores were significantly higher in those with asthma vs. without, while male participants had significantly higher PCL-5 scores than females. There was no significant interaction between sex and asthma on PCL-5 scores. Further, there was no significant interaction between asthma and insula reactivity on PTSD symptom severity. These findings provide continued evidence that sex and asthma separately play a role in PTSD severity, but do not support that the two variables interact to impact PTSD severity or that asthma and insula reactivity interact to predict PTSD severity. Further studies that collect more detailed information regarding asthma, that have more balanced samples, and that analyze subsections of the insula are necessary.

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Introduction

Post-traumatic stress disorder (PTSD) is a trauma induced psychiatric condition that affects 12 million adults in the United States during a given year. Psychiatric disorders like PTSD can cause lasting dysfunction in daily life not only from the trauma-induced mental distress, but also from physical diseases associated with it. Studies have reported physiological changes and disease development in humans following exposure to traumatic events including inflammatory diseases such as asthma (Allgire et al., 2021; Alonso et al., 2014; Chung et al., 2012; Hung et al., 2019). Both PTSD and asthma are more prevalent in women (Christiansen et al., 2014; Kessler et al., 1995; Shansky, 2015) but it is not clear whether this clear sex disparity exists in the co-morbid existence of PTSD and asthma. Physical diseases and psychiatric disorders can affect women and men differently, so understanding the overlap between PTSD, asthma, and sex differences can contribute to the development of personalized treatments that improves health outcomes for both sexes. This association between PTSD, asthma, and sex differences can also be explored through potential overlapping biomarkers like the insular cortex. The purpose of this present study was to investigate (1) whether there is a relationship between asthma and PTSD in an urban Atlanta population at high risk for trauma and PTSD, (2) whether gender modulates the relationship of asthma and PTSD in this population, and (3) how the relationship between asthma and PTSD relate to neuroimaging-based indicators of threat processing in women. Understanding how gender differences and brain neuroanatomical structures underlie the development of debilitating mental and physical illnesses can lead to personalized, novel treatment approaches for affected individuals.

Increasing evidence supports an association between stress and asthma. The stress response to traumatic events can impact both mental and physical health. As previously stated,

studies have reported disease development in humans following exposure to traumatic events (Alonso et al., 2014; Chung et al., 2012; Hung et al., 2019), including inflammatory diseases seen by an increase in levels of proinflammatory mediators (Allgire et al., 2021). Asthma is a chronic pulmonary inflammatory disease with symptoms characterized by transient periods of impaired breathing, wheezing, and coughing (Dharmage et al., 2019). According to the CDC, an estimated 25 million people in the U.S. are diagnosed with asthma and approximately 4,000 Americans die annually from asthma (Centers for Disease Control and Prevention [CDC], 2020). Asthma onset is influenced by genetic and environmental factors, but it can also be vulnerable to both chronic and acute stress. Specifically, psychosocial stress and mood and anxiety disorders appear to increase expression of asthma symptoms (Kewalramani et al., 2008). In fact, a World Mental Health (WMH) survey in 19 countries found an association between PTSD and subsequent asthma in adulthood (Alonso et al., 2014). The chronic stress symptoms of PTSD may further contribute to increased asthma symptoms. PTSD also shares similar physical symptom profiles with asthma, such as hyperventilating in response to traumatic events and reminders (American Psychiatric Association, 2013).

There is also evidence for the converse scenario, in which asthma may exacerbate symptoms of PTSD. There is a higher prevalence of PTSD in individuals with moderate to severe asthma, even above and beyond the rate of other psychiatric conditions like depression and anxiety disorders (Allgire et al., 2021; Chung et al., 2012). A population-based study that assessed individuals nationwide found that patients diagnosed with PTSD had an increased risk of developing asthma compared to patients without PTSD (Hung et al., 2019). Though the definite pathophysiology between PTSD and asthma risk remains largely unknown, numerous studies suggest that people who were exposed to airway-related trauma (i.e. World Trade Center

rescue and recovery workers) were equally likely to develop asthma later in life as those exposed to non-airway related trauma (i.e. sexual violence survivors, hurricane survivors) (Arcaya et al., 2014; Brackbill et al., 2009; de la Hoz et al., 2016; Santaularia et al., 2014). These robust findings on comorbid PTSD and asthma presentation further suggest the possibility of underlying mechanisms and factors contributing to a shared pathophysiology between the two.

Biological sex can be a moderating factor of disease vulnerability and overlap which can have many relevant implications in clinical practice to improve patient health outcomes. In looking closer at prevalence rates, PTSD rates and asthma rates are higher for women than men. Studies have consistently reported higher PTSD rates for women despite limited differences in lifetime prevalence of traumatic events (Breslau et al., 1997). Female veterans also report greater PTSD severity than male veterans (Kang et al., 2005) and the U.S. Department of Veterans Affairs report 19% of female veterans to be diagnosed with PTSD compared to the 10% for males (U.S. Department of Veterans Affairs, 2022). Following motor vehicle accidents, a study found more women to develop PTSD and acute stress disorder (Bryant & Harvey, 2003) and among parents, mothers are almost twice as often diagnosed with PTSD than fathers (Christiansen et al., 2014). This trend also extends to adolescent females who report higher PTSD rates than males (Brosky & Lally, 2004; Cuffe et al., 1998). Prior literature has attributed this sex disparity to differences in neuroendocrine and stress response systems, the severity and type of trauma experienced along with the age of exposure, and differences in coping strategies and socialization (Bangasser & Valentino, 2014; Fonkoue et al., 2020; Kang et al., 2005; Olff, 2017; Ramikie & Ressler, 2018).

This clear sex disparity also exists in asthma as women are more susceptible to asthma than men. While there is a shift in asthma prevalence with age, epidemiological studies have

reported a higher preponderance of asthma in women (65% relevance) after age 13 or the onset of puberty (Chowdhury et al., 2021). Studies analyzing emergency department visits with adult patients presenting asthma symptoms found twice as many female than male patients and a higher risk for women to be admitted into the hospital due to asthma (Prescott et al., 1997; Singh et al., 1999). Further, a nationwide analysis in Italy on patients with severe asthma found almost 2/3 of severe asthmatics to be female (Senna et al., 2020). Like PTSD, studies have suggested the role of sex hormones in explaining the sex difference. Past studies have cited the shift in asthma prevalence with age and sex to coincide with sex hormones that modulate the pathways associated with asthma pathogenesis such as airway inflammation (Fuseini & Newcomb, 2017). Hormone risk factors appear to increase both PTSD and asthma pathophysiology in females, suggesting the presence of other shared risk factors that may be worthwhile to investigate such as brain structures.

The association between asthma and PTSD can also be explored through neuroanatomical features. As mentioned earlier, individuals with asthma prior to PTSD developed more aggravated asthma symptoms after the development of PTSD suggesting possible overlapping mediators and shared mechanisms (Allgire et al., 2021). Recent findings from prospective studies of PTSD and asthma implicate the insular cortex as a potential overlapping mediator between somatic diseases and psychiatric disorders. The insula is a primary neural substrate critically involved in processing emotions, interoceptive information, and somatic sensations (Fonzo et al., 2010; Park et al., 2022; Uddin et al., 2017). Relative to other brain regions, the insula demonstrates distinguishable activation levels in individuals with PTSD or asthma. For example, researchers have found the degree of differential insula activation to predict changes in airway inflammation. Specifically, individuals with greater insula responses

to asthma stimuli had greater inflammatory signals in their lung and greater severity of the disease (Rosenkranz et al., 2012). Though the link between asthma and the insula remains an emerging research topic, studies of inflammation and the insula have theorized that inflammation may induce increased insula sensitivity to interoceptive signals (Karshikoff et al., 2017).

Prior research posits various brain regions to be involved in PTSD including the insular cortex. Insula hyperactivity has been found in PTSD patients including those suffering from interpersonal trauma, intimate partner violence, and combat (Bruce et al., 2013; Duval et al., 2020; Fonzo et al., 2010). Specifically, increased activity in the anterior insula region has been found in patients with PTSD and women exposed to domestic violence (Bruce et al., 2013; Simmons et al., 2008). Anterior insula response to threat cues has also been suggested to be associated with PTSD symptoms of hyperarousal and re-experiencing (Stevens et al., 2018; Yehuda et al., 2015). Researchers have theorized the insula's involvement to be partially due to its ability to mediate the dynamic interface between externally oriented attention and internal self-reflective functioning, further highlighting the interoceptive function unique to the insula (Ulrich et al., 2022). Altogether, this evidence presents the insula as an emerging and promising area of interest to study in relation to the comorbidity of asthma and PTSD.

In the present study, we investigated the relationship between asthma and PTSD symptom severity in the context of sex differences using a large sample of African American women and men in a highly trauma-exposed, low socioeconomic status urban hospital setting. Using functional magnetic resonance imaging (fMRI), we also investigated asthma and PTSD association in relation to insula reactivity to social threat cues in a separate cohort of African American women. Based upon prior findings regarding sex differences in asthma and PTSD (Chowdhury et al., 2021; Fuseini & Newcomb, 2017; Prescott et al., 1997; Senna et al., 2020;

Singh et al., 1999), we hypothesized that people with asthma would have higher PTSD severity than people without asthma, and women with asthma would have greater PTSD severity than men with asthma. Secondly, building upon previous research positing the insula's involvement in PTSD and asthma (Fonzo et al., 2010; Park et al., 2022; Rosenkranz et al., 2012; Uddin et al., 2017), we hypothesized that women with asthma and higher PTSD severity would have greater insula reactivity to social threat cues than women without asthma and PTSD.

Methods

Participants

Participants between the ages of 18 and 65 were recruited from a larger ongoing study of risk factors for PTSD in the Grady Trauma Project. Participants were randomly approached in the outpatient clinics and the emergency room of Grady Memorial Hospital, a public inner-city hospital that serves a primarily low-income, African American population in Atlanta, Georgia. High rates of trauma and posttraumatic symptoms have been previously observed within this patient population. Participants were excluded if they met any of the following exclusion criteria based on self-report: history of psychotic or neurological disorder, psychosis or current psychotropic medication, metal clips or implants, history of head injury or loss of consciousness exceeding five minutes. As well, participants who tested positive for pregnancy or illegal drug use based on urine tests 24 hours before the MRI scan were excluded. Participants were English-speaking and provided written informed consent prior to the study, and compensation was provided. The Institutional Review Boards of Emory University and Grady Memorial Hospital approved all study procedures.

From the initial dataset consisting of *N* = 5,000 individuals, a subset of n = 588 reported on asthma presence, as this question was added to the study in later years. *N* = 290 participants (*N* = 242 females and *N* = 48 males) met criteria for PTSD diagnosis, and *N* = 169 participants (or *N* = 162 females and *N* = 7 males) reported having asthma. Demographic information is listed in **Table 1.**

The fMRI analysis included *N* = 71 women. The mean age of the women was 39 years (*SD* = 11.8); demographics and clinical information is shown in **Table 2**. *N* = 29 women met criteria for PTSD diagnosis and *N* = 11 women reported having asthma. In the MRI study, asthma was reported in a physical health and medical history assessment conducted by a practicing physician.

Measures

Following recruitment, trained interviewers collected detailed demographic and health information and administered an extensive array of psychological measures during a two-hour in-person screen at the Grady Trauma Project office. The study included demographic information on age, sex, race, ethnicity, education, and household monthly income. Since asthma is a primary variable of interest, asthma presence was assessed by the question “Have you ever been diagnosed with asthma?” with answer choices as either “yes” or “no”. For the neuroimaging analysis, asthma diagnosis was ascertained from participant medical history.

Various psychological assessments were administered during the initial participant screen. The focus of the present study are data from the following:

a. PTSD Checklist for DSM-5. The PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013) was used to assess the 20 DSM-5 symptoms of PTSD. The PCL-5 has a variety of purposes

including monitoring symptom change during and after treatment, screening individuals for PTSD, and making a provisional PTSD diagnosis (U.S. Department of Veterans Affairs, 2022). For the purposes of this study, the PCL-5 was used to screen individuals for PTSD. Specifically, the PCL-5 provided quantitative data on the participant's PTSD severity. The PCL-5 is a 20-item self-report measure corresponding to the DSM-5 symptom criteria for PTSD. A sample item includes: "In the past month, how much were you bothered by repeated, disturbing, and unwanted memories of the stressful experience" or "In the past month, how much were you bothered by avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?". The self-report rating scale is based on a 5-point Likert scale (0 = "Not at all", 1 = "A little bit", 2 = "Moderately", 3 = "Quite a bit", and 4 = "Extremely"). A total symptom severity score (0-80) can be obtained by summing the scores for each of the 20 items. A PCL-5 cutoff score between 31-33 is indicative of probable PTSD across samples. The PCL-5 was the primary tool in assessing one of our primary variables of interest, PTSD severity, in participants.

b. PTSD Symptom Scale. The PSS was the primary measure to assess PTSD severity in the neuroimaging subset of participants. The PTSD Symptom Scale (PSS; Foa & Tolin, 2000) was used to assess the frequency and severity of 17 DSM-IV-TR symptoms of PTSD. The PSS is a 17-item self-report measure that asks participants to rate the frequency of symptoms experienced over the past two weeks, from 0 ("Not at all/only once") to 3 ("Almost always/5 or more times per week"). Symptoms are divided into three clusters corresponding to DSM-IV-TR criteria: re-experiencing (i.e. flashbacks/trauma-related nightmares), avoidance (i.e. avoiding certain people, places, situations related to the event), and hyperarousal (i.e. jumpiness, easily startled). A final question asks participants to report the length of their symptoms, from 0 ("less than a month") to

3 (“greater than 1 year”). The total score is calculated by averaging individual items and multiplying the average by 17, yielding a maximum score of 51.

c. Beck Depression Inventory. The Beck Depression Inventory (BDI; Beck et al., 1996) is a widely used and well-validated 21-item self-report inventory that measures the severity and symptoms of depression. Participants are asked to rate each item the extent to which they feel the statements describe how they have been feeling during the past two weeks on a 4-point scale, from 0 (“I get as much pleasure as I ever did from the things I enjoy”) to 3 (“I can’t get any pleasure from the things I used to enjoy”). The scores are totaled and depression symptom severity is considered minimal (scores 0 to 9), mild (10 to 18), moderate (19 to 29), or severe (30 to 63).

d. Anxiety Sensitivity Index. The Anxiety Sensitivity Index (ASI; Reiss et al., 1986) is a 16-item scale used to measure fear of anxiety-related sensations that individuals could have, particularly those common in panic disorder. A higher score on the ASI serves as a powerful and unique predictor of people with a high risk of anxiety disorders such as panic disorders and phobias or as an indicator of post-traumatic stress. The ASI asks participants to rate each item on a 5-point scale, from 0 (“very little”) to 4 (“very much”). An individual’s score is the sum of the scores on the 16 items.

e. Childhood Trauma Questionnaire. The Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998) is a self-report inventory that measures five categories of traumatic experiences in childhood: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse, that occurred between birth until the age of 17 years. This 28-item screen asks participants to rank the extent to which they believe the statements to be true about their experiences as a child and teenager, from 1 (“never true”) to 5 (“always true”). The measure yields a total score

for childhood trauma as well as subscores for each of the five categories of maltreatment, with higher scores indicative of more abuse. In a prior study with this sample, Cronbach's *a* was 0.83 for physical abuse, 0.86 for emotional abuse, and 0.95 for sexual abuse (Mandavia et al., 2016).

f. Traumatic Events Inventory. The Traumatic Events Inventory (TEI; Schwartz et al., 2005) is a 14-item screen for assessing lifetime trauma history in individuals. The TEI asks about any traumatic or stressful events that the participants may have experienced, witnessed, or been confronted with in their lifetime, as well as the age of first exposure and frequency of exposure. Trauma types queried include natural disasters, serious accidents or injuries, military combat, being confronted with the murder of a close friend or family member, being attacked with and without a weapon, witnessing violence between parents or caregivers as a child, being beaten or physically punished, verbally abused, or sexually abused as a child, and being raped or sexually assaulted as an adult. An open-ended question also asks about any other events that may have been traumatic or particularly stressful for the participant. The total number of trauma types experienced or witnessed during participants' childhood and adulthood was used to further identify any relation between traumatic events and asthma.

Brain Imaging Procedures

A cohort of female participants (n = 71) completed an fMRI scan while viewing the fearful faces task. The fMRI study procedures have been published previously and followed Stevens et al. (2013). Eight fearful and eight neutral (4 male and 4 female) faces were selected from a stimulus set of Ekman and Friesen (1976). Stimuli were projected onto a 24-inch screen at a resolution of 1280 x 1024 using EPrime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Participants viewed 30 blocks of static fearful and neutral face stimuli of Caucasian race (15 fearful and 15 neutral blocks that were randomly intermixed). Each block

consisted of eight faces presented in a random order. Each individual face stimuli were presented for 500 ms, followed by a 500ms presentation of a fixation cross. A 10,000 ms rest period was presented after every 10th block during which participants were instructed to "relax and look at the screen". Face stimuli were presented at a size of 4.3 x 6.7' on a black background, and the fixation cross and instructions were presented in white 18-point Courier New font on a black background.

Brain Imaging Acquisition and Analysis

Brain imaging data were acquired on a Siemens 3.0T Magnetom Trio TIM MRI Scanner using a 12-channel coil. Functional images were acquired using the Z-SAGA pulse sequence to minimize signal loss caused by susceptibility artifacts. Preprocessing was conducted in SPM8 software and followed methods in Kilaru et al. (2016). Correction for slice timing and spatial realignment were applied to images in SPM8. Images were then normalized with unified segmentation and smoothed with a 9 mm Gaussian kernel. Insular cortex responses were extracted from a bilateral region of interest (ROI) created using the Automated Anatomical Labeling Atlas 3 (AAL3) (Rolls et al., 2020). In follow-up analyses, an anterior insula ROI was created using a 10mm sphere based on coordinates defined from a prior PTSD neuroimaging study (Laird et al., 2011; Leroy et al., 2022).

Statistical Analyses

All statistical analyses were run in R version 4.2.1 and R Studio version 2022.07.2. The dplyr package in R was utilized for data organization. Statistical significance was set at $\alpha = 0.05$ (2-tailed) for all analyses.

In order to assess the association between asthma and PTSD severity, an independent sample, two-tailed t-test was used. This tested group differences in PTSD severity in those with vs. without asthma. We also assessed for an association between sex and PTSD severity by testing for group differences in PTSD severity in females vs. males.

A two-way ANOVA was performed to assess the hypotheses on whether sex (female or male) modulates the relation between asthma and PTSD in this population. Sex (female or male) and asthma presence (yes or no asthma) were the two categorical variables of interest, and PTSD severity (measured by PCL-5 scale) was the quantitative variable. Follow-up ANCOVA analyses including the TEI and CTQ were additionally conducted.

To investigate how the association between asthma and PTSD relates to anterior insula activity in women, regression models were used to test for asthma*insula interaction effects on PTSD symptoms collected at the time of scan, as measured by the PSS. Age was included as a covariate. Follow-up analyses to test for asthma*insula interaction effects on BDI and ASI were also conducted. After examining interaction effects for whole insula, we then repeated regression models with asthma*anterior insula interaction effects.

Exploratory whole-brain, multiple regression analyses were conducted with asthma and PSS scores as separate covariates and as an interaction effect (asthma*PSS). The resulting maps were tested for significance using cluster-defining threshold of $p < .005$, with cluster-level family-wise error correction set to $p < .05$. This produced an extent threshold of $k= 141$ for PSS score correlations.

Results

Sample Characteristics

Table 1 lists the clinical and demographic characteristics of our general population. Within the asthma group, a higher percentage of female participants reported having asthma (n = 162 or 31.83%) than male participants (n = 7 or 4.14%). More participants in the asthma group also reported taking asthma medication (n = 104 or 61.90%) than not taking medication (64 or 38.10%). The asthma group had a greater PTSD severity score (PCL-5 total *M* = 34.18, *SD* = 20.95) than the no asthma group (PCL-5 total *M* = 30.04, *SD* = 20.63). Participants with asthma also endorsed higher levels of childhood maltreatment (CTQ total *M* = 53.35, *SD* = 21.05) and reported more traumatic events in their lifetime (TEI total *M* = 6.20, *SD* = 3.36) than participants without asthma.

Educational achievement was somewhat similar between both groups with the highest percentage completing some college or technical school, constituting 28.40% of participants with and without asthma. Overall, majority of the participants were single or never married in both groups, making up 57.99% of participants with asthma and 60.04% of participants without asthma. Furthermore, participants in the no asthma group reported a history of more times being arrested (*M* = 4.14, *SD* = 7.24) and more times being in jail (*M* = 4.17, *SD* = 7.57) than participants with asthma. All subsequent comparisons of the asthma and no asthma groups were controlled for covariates such as age.

Table 2 shows the clinical and demographic features of our neuroimaging participants. Of the 71 females included in the neuroimaging portion, most were not diagnosed with asthma (n = 60). The asthma group reported greater PTSD severity (PSS total *M* = 16.09, *SD* = 14.01) than the no asthma group (PSS total *M* = 12.61, *SD* = 11.53). Both groups reported similar levels of traumatic events experienced in their lifetime (TEI total *M* = 4, *SD* = 2). The asthma group reported greater anxiety sensitivity scores (ASI total *M* = 34.60, *SD* = 12.93) than the no asthma

group (ASI total *M* = 24.17, *SD* = 14.61). The no asthma group reported higher depression symptoms (BDI total *M* = 13.98, *SD* = 12.86) than the asthma group (BDI total *M* = 11.55, *SD* = 8.68).

Differences in PTSD severity among individuals with asthma vs. without asthma

First, we examined whether individuals with asthma have higher PTSD symptom severity. As shown in **Fig. 1a**, individuals with asthma (*M* = 34.18, *SD* = 20.95) had significantly higher PCL-5 scores than those without asthma (*M* = 30.04, *SD* = 20.63), t(306) = -2.18, *p* = 0.03. Men had significantly higher PCL-5 scores than women t(102)=2.75, *p* = 0.007 (**Fig. 1b**). Men also had significantly greater number of arrests t(76) = 3.08, *p* = 0.003 and significantly greater number of times being in jail t(75) = 2.70, *p* = 0.009 than women.

To examine if there was an interaction effect between asthma and sex on PTSD severity, a two-way ANOVA was performed. This revealed that there was not a significant interaction effect between asthma and sex on PCL-5 scores F(1, 584) = 2.73, *p* = 0.10 (**Fig. 2**). In follow-up ANCOVA models including the CTQ and TEI separately, the interaction was still not significant, *p* > .05.

Differences in PTSD severity among women with vs. without asthma

Among the neuroimaging cohort, we examined whether women with asthma have higher PTSD severity. As shown in **Fig. 3a**, individuals with asthma (*M* = 16.09, *SD* = 14.01) did not have significantly higher PSS scores than those without asthma (*M* = 12.61, *SD* = 11.53), t(12.61) = -0.78, *p* = 0.45. Women with asthma also did not have significantly higher BDI scores than women without asthma t(19.15)=0.78, *p* = 0.44 (**Fig. 3b**). However, women with asthma (*M*

= 34.60, *SD* = 12.93) did have significantly higher ASI scores than women without asthma (*M* = 24.17, *SD* = 14.61), t(13.63)=-2.30, *p* = 0.04 (**Fig. 3c**).

Whole insula reactivity to fearful faces among women with PTSD and asthma

Regression models were used to examine the interaction effect between asthma*insula reactivity on PSS scores (**Tables 3 and 4**). When controlling for age, there was no significant interaction effect between asthma and left insula reactivity (β = 35.87, ΔR^2 = 0.03, t= 1.04, *p* = 0.30) or right insula reactivity (β = 15.18, ΔR^2 = 0.05, t= 0.47, *p* = 0.64) (**Fig. 4**).

Whole insula reactivity to fearful faces among women with asthma and anxiety or depression

Regression models were used to examine the interaction effect between asthma*insula reactivity on BDI Scores (**Tables 5 and 6**). When controlling for age, there was a significant interaction effect between asthma and left insula reactivity (β = 83.05, ΔR^2 = 0.14, t= 2.48, *p* = 0.02) but no significant interaction between asthma and right insula reactivity (β = 55.69, ΔR^2 = 0.13, t= 1.75, *p* = 0.09). Follow-up analyses showed a significant positive correlation between the left insula and BDI scores in the no asthma group (r(58) = 0.32, *p* = 0.01) while the asthma group showed no significant correlation (r(9) = -0.58, *p* = 0.06) (**Fig. 5**). Regression models were also used to examine the interaction effect between asthma*insula reactivity on ASI Scores (**Tables 7 and 8**). When controlling for age, there was no significant interaction effect between asthma and left insula reactivity (β = 65.53, ΔR^2 = 0.07, t= 1.56, *p* = 0.13) or right insula reactivity β = 20.15, ΔR^2 = 0.04, t= 0.50, *p* = 0.62).

Whole brain reactivity to fearful faces among women with PTSD and asthma

Exploratory whole-brain analysis revealed a significant positive correlation between PSS scores and reactivity to fearful vs. neutral faces in the right superior frontal gyrus (z = 4.05, x,y,z = 22, 68, 10, k = 141) and right precuneus (z = 3.65 , x,y,z = 6, -52, 70, k =141) (**Fig. 6**). There were no significant effects of asthma on the response to fearful<neutral faces on any brain region. Furthermore, an exploratory whole-brain analysis of the interaction between asthma and PSS scores showed no significant results.

Anterior insula reactivity to fearful faces among women with asthma and PTSD

Regression models were used to examine the interaction effect between asthma*anterior insula reactivity on PSS scores (**Tables 9 and 10**). When controlling for age, there was no significant interaction effect between asthma and left anterior insula reactivity ($\beta = 36.23$, $\Delta R^2 = 0.04$, $t= 1.43$, $p = 0.16$) or right anterior insula reactivity ($\beta = 2.36$, $\Delta R^2 = 0.05$, $t= 0.07$, $p = 0.95$).

Anterior insula reactivity to fearful faces among women with asthma and depression or anxiety

Regression models were used to examine the interaction effect between asthma*anterior insula reactivity on BDI Scores (**Tables 11 and 12**). When controlling for age, there was a significant interaction effect between asthma and left anterior insula reactivity ($\beta = 61.52$, $\Delta R^2 = 0.11$, $t= 2.43$, $p = 0.02$) but no significant interaction between asthma and right insula reactivity ($\beta = 36.93$, $\Delta R^2 = 0.10$, $t= 1.02$, $p = 0.31$). Follow-up analyses revealed a significant negative correlation between the left anterior insula and BDI scores ($r(9) = -0.63$, $p = 0.04$) in the asthma group while the no asthma group did not show a significant correlation ($r(58) = 0.21$, $p = 0.11$) (**Fig. 7**). Regression models were used to examine the interaction effect between asthma*anterior

insula reactivity on ASI Scores (**Tables 13 and 14**). When controlling for age, there was a significant interaction effect between asthma and left anterior insula reactivity ($\beta = 73.13$, $\Delta R^2 = 0.11$, $t = 2.37$, $p = 0.02$) but no significant interaction between asthma and right insula reactivity ($\beta = -2.07$, $\Delta R^2 = 0.08$, $t = -0.05$, $p = 0.97$). Follow-up analyses revealed that both asthma ($r(8) = -0.53$, $p = 0.11$) and no asthma group ($r(52) = 0.23$, $p = 0.10$) did not show a significant correlation between the left anterior insula and ASI scores (**Fig. 7**).

Discussion

The current study aimed to investigate 1) the role and potential influence of sex differences in the link between asthma and PTSD and 2) whether the insular cortex could be utilized as an overlapping biomarker to examine this association between asthma and PTSD in an urban population at high risk for trauma and PTSD. This was the first study to investigate the role of sex differences in connecting asthma, PTSD, and insula reactivity. Our hypothesis on asthma presence and PTSD severity was supported as individuals with asthma had significantly higher PTSD symptoms compared to individuals without asthma, a finding that is consistent with past literature. Overall, we did not find support for our hypotheses regarding sex differences and asthma and PTSD in this population. Instead, PTSD severity was significantly higher in male compared to female participants, inconsistent with prior findings, and sex did not significantly modulate the relationship between asthma diagnosis and PTSD. Furthermore, we did not find support for our hypotheses relating insula reactivity to asthma and PTSD in women – insula responses to threat cues were not associated with asthma or PTSD.

Our work presents robust evidence for an association between asthma and PTSD. Individuals with asthma are more likely to have greater PTSD severity than those without asthma. This finding is consistent with prior literature examining associations between asthma

and PTSD. A twin-study found PTSD symptoms to be associated with elevated presence of asthma in adult males who previously served in the military (Goodwin et al., 2007). Another study done on the general population in Europe suggested an association of trauma exposure and PTSD with airflow limitation and an obstructed respiratory system (Spitzer et al., 2011). Our findings extend this association between asthma and PTSD to an urban, minority population in Atlanta, GA. When considering sex and PTSD severity, our findings showed males having higher PTSD severity than females, which was inconsistent with previous studies (Breslau et al., 1997; Olff, 2017). Possible explanations for this finding could include our sample having significantly more women than men, leading to a greater range in PTSD severity scores among women. The men in this study also reported a significantly higher incarceration rate and have been involved in significantly more arrests than women, which may contribute to a greater trauma load and increased PTSD severity.

In looking closer at how sex interacts with asthma and PTSD, our hypothesis that women with asthma would have greater PTSD severity than men with asthma was not supported, as our findings indicated that sex did not interact with asthma to affect PTSD symptoms in this sample. As previously mentioned, this study is the first to investigate sex differences pertaining to asthma and PTSD comorbidity. However, prior studies looking at sex differences in asthma and PTSD separately consistently report females having higher prevalence rates for PTSD and for asthma. Women are twice as likely to develop PTSD following trauma (Haskell et al., 2010; Shansky, 2015) with proposed mechanisms pointing towards differences in sex hormones, epigenetic interactions, and the timing and type of trauma exposure (Ney et al., 2019; Olff, 2017; Ramikie & Ressler, 2018). Asthma is also more prevalent in women espescially after puberty (Chowdhury et al., 2021; Ekpruke & Silveyra, 2022; Rogliani et al., 2022). Explanations for this

sex disparity has been attributed to the influences of hormonal interplay after puberty as well as differences in respiratory systems, inflammation biomarkers, and the physical environment and occupational life between men and women (Chowdhury et al., 2021; Ekpruke & Silveyra, 2022).

Several factors may explain the discrepancy between the current findings and those of previous studies.

Most notably, our sample included a disproportionate number of males to females making it difficult to capture a difference in sex interactions. Despite our non-significant results, it is of interest that the means of PCL-5 scores between males and females are reversed (PCL-5 scores for males with no asthma trended higher than males with asthma, while PCL-5 scores for females with asthma trended higher than females without asthma). This finding could be further explored in future studies with a greater number of male participants. As posited by the explanations above, examining sex differences in PTSD and in asthma can be complicated due to the multifaceted interactions between neurobiology, genetics, and the environment involved in both disorders, and need consideration in future study design examining the relationship between sex, asthma, and PTSD. Our finding that sex differences do not modulate PTSD and asthma interaction further highlight the complex nature and relation underlying inflammatory diseases and trauma disorders.

Our results regarding the relation between insula reactivity to threat, PTSD, and asthma in women were also not in line with prior studies. Our hypothesis was not supported as we did not find this relationship when examining whole insula reactivity to fearful faces in women with asthma and PTSD. This study is the first to examine whole insula reactivity in relation to comorbid PTSD and asthma. The insula was of particular interest to us due to its differing reactivity levels in individuals with PTSD or asthma. Previous neuroimaging studies have found

increased insular reactivity in patients with PTSD and women exposed to domestic violence (Bruce et al., 2013; Simmons et al., 2008). Insula activation levels were even suggested to be associated with hyperarousal and re-experiencing symptoms (Stevens et al., 2018; Yehuda et al., 2015). However, these findings were discovered when looking at different subsections of the insula, particularly the anterior portion. It could be of particular interest to explore the anterior insula specifically in future studies. Asthma studies also suggest that the anterior insula is of particular importance, with it being implicated in asthma pathology. One neuroimaging study that compared general cues with asthma-relevant cues found differing activity between the mid, anterior, and posterior regions of the insula to be associated with changes in airway inflammation during stress (Rosenkranz et al., 2012). The inconsistency in our results could thus be partially attributed to differences in function among the areas of the insula. As with our first sample, this analysis also suffered from differences in sample size between groups. Our sample only included 11 female participants with asthma vs. 60 without asthma. This limited sample size for neuroimaging analyses makes it challenging to observe a difference as it decreases the statistical power of our analyses and makes it difficult to accurately test for the impact of asthma on insula reactivity. Future investigations with larger sample sizes looking at particular insular regions could better capture potential effects.

Additionally, the fearful faces task utilized may have impacted results. Our accompanying fMRI task involved participants viewing fearful Caucasian faces as this task has been well validated in prior literature in PTSD case-control studies (Brewin et al., 2000; Shin et al., 2005). Previous neuroimaging tasks used to investigate insula responses with PTSD also involved emotional facial expressions such as the emotional face matching task and the emotional interference task, while the asthma study used a variation of the Stroop task (Bruce et

al., 2013; Fonzo et al., 2010; Rosenkranz et al., 2012). However, future studies should examine insula responses to African American faces and to possibly include facial expressions or visual stimuli that have some overlap with the distressing physical features of asthma and panic attacks. Perhaps the incorporation of stimuli that are related to the features of PTSD and asthma may allow us to examine more direct engagements between these disorders and brain regions.

In looking closer at the insula's involvement with psychiatric disorders, we found the left insula to be associated with depression symptoms and the left anterior insula to be associated with both depression and anxiety symptoms. The insula's involvement in depression and anxiety pathology is consistent with prior literature. Insula functional connectivity is shown to be altered in those with major depressive disorder (MDD). Studies have found reduced connectivity between the anterior insula and the middle front gyrus and higher frontal regions in MDD patients (Iwabuchi et al., 2014; Kandilarova et al., 2018). The insula has also been associated with MDD symptoms as one study found left anterior insula activity to be correlated with depression severity in MDD patients suffering from somato-vegetative symptoms (Wiebking et al., 2010) and another discovered increased activity in the left insula in MDD patients and suggested this activity to correspond with MDD symptoms such as increased introspective self-focus and rumination (Pastrnak et al., 2021). Similarly, greater insula reactivity is also implicated in individuals with anxiety. Anxiety prone subjects have greater insula reactivity during tasks involving emotional faces or aversive stimuli, and higher scores on anxiety measures were associated with greater anterior insula activation (Simmons et al., 2008; Stein et al., 2007). Individuals with generalized social anxiety disorder (gSAD) also had greater insula reactivity to negative stimuli and the extent of insula activation correlated with their trait anxiety scores (Shah et al., 2009). Specific to the anterior insula, gSAD participants had anterior insula hyper-

reactivity when viewing fearful faces and reduced connectivity between the anterior insula and prefrontal regions involved in cognitive control and emotion regulation (Klumpp et al., 2012). These findings, in addition to our current findings, demonstrate the insula and anterior insula as target regions to further investigate neurobiology factors underlying psychiatric disorders as the insula is a multimodal integration region involved in evaluating emotional salience of external and internal stimuli (Pastrnak et al., 2021).

Exploratory whole brain findings found right superior frontal cortex and right precuneus reactivity to fearful faces to be associated with PTSD and provided further support for the association between asthma and PTSD among an urban, minority population. The superior frontal cortex is thought to be involved with higher cognitive functioning, particularly with the working memory and one study demonstrated abnormal frontal cortex activity in brain processes associated with the working memory in PTSD patients (du Boisgueheneuc et al., 2006; Weber et al., 2005). Structurally, there appears to be a reduction in gray matter volume in the frontal cortex regions (Begemann et al., 2023; Chen et al., 2012; O'Doherty et al., 2017) and an increase in cortical thickness in the superior frontal cortex for PTSD subjects (Clausen et al., 2020; L. Li et al., 2022). Furthermore, the superior frontal cortex has also been associated with inflammation as earlier studies found a positive correlation between inflammatory factors and functional changes in the superior frontal cortex while another found stronger airway inflammation and decreased asthma control to be associated with reduced activation to negative stimuli in the superior frontal cortex (Ritz et al., 2019; Xia et al., 2014). Like the superior frontal cortex, the precuneus is also involved in memory, specifically autobiographical memory and in self-referential processing (Cavanna & Trimble, 2006; Kelley et al., 2002). Limited studies have looked at the right precuneus exclusively, but studies analyzing whole precuneus have found

reduced precuneus activation in PTSD patients and associated precuneus activity with trauma memory generalization and flashbacks (Geuze et al., 2008; Hayes et al., 2011; Whalley et al., 2013). One study also found increased sensitivity of the precuneus to memory formation in an emotional context (Whalley et al., 2009). Furthermore, alterations in the precuneus are also observed in asthmatic patients. Resting-state neuroimaging studies found patients with asthma exhibiting regional abnormalities in the right precuneus (S. Li et al., 2020; Zhang et al., 2017). Other studies have also reported reduced gray matter volume in bilateral precuneus and reduced activity in the precuneus in individuals with asthma (Ritz et al., 2019; Wang et al., 2014). This evidence in addition to our findings altogether suggests the right frontal superior cortex and right precuneus as fascinating, strong regions of interests for further exploration in associating asthma and PTSD.

This study has a number of strengths. To date, it is the first study to examine sex differences and the insular cortex in asthma and PTSD comorbidity. Prior research has established the co-occurrence of psychiatric disorders with inflammatory diseases, but limited knowledge is presented on the underpinnings and mechanisms behind this. Our work investigating sex differences and neuroanatomy with PTSD and asthma allowed for a deeper exploration into this disentanglement between somatic diseases and mental disorders. Secondly, urban minority women remain the most understudied population in research literature but are the most affected by psychiatric disorders and chronic lung diseases. This study examines the association between asthma and PTSD within a large, minority urban population allowing for more powerful effect sizes and direct, valuable investigations in populations most at risk.

Several limitations of the current study must be acknowledged when evaluating the results, in addition to what has been mentioned. Our participants were primarily African

American due to the prevalence of PTSD among this population (Roberts et al., 2011) and the makeup of the urban hospital we obtained our data from (Gillespie et al., 2009), but this could limit the generalizability of our findings. Future studies could benefit from including an equal proportion of both sexes, and to include men and women of various races and ethnicities. Furthermore, we did not have information on the severity and timing of asthma. Asthma is a variable condition classified by intermittent, persistent-mild, persistent-moderate, and persistent-severe (Colice, 2004). We were unable to see whether participants with asthma had experienced trauma before or after their diagnosis, and whether frequency of asthma attacks influences PTSD severity scores. We also did not have information on the specifics of participant trauma history such as the timing of their traumatic events to be compared with asthma. To assess PTSD severity, this study used the PCL-5 for the general sample and the PSS for DSM-IV-TR for the neuroimaging sample. Both scales measure PTSD symptoms, but the PCL-5 has been found to have a higher Cronbach alpha than the PSS (Wortmann et al., 2016). It could be advantageous for future studies to use one standardized measure to assess PTSD and to possibly incorporate clinician-administered interviews to screen for other potential psychiatric comorbidities. Lastly, the design of this study and complex nature of PTSD and asthma makes it difficult to establish a directionality between asthma and PTSD. Rather, our study provides a look on the general relationship of asthma and PTSD in the context of sex and brain structures. Future studies may more accurately capture the relationship between sex, asthma, and PTSD by incorporating a longitudinal study design examining asthma and PTSD rates over time, more complete measures of asthma and PTSD, more even numbers of males and females, and participants with vs. without asthma.

In sum, our findings did not provide support for an interaction between sex and asthma and PTSD. The whole insula also did not appear to exhibit differing activation levels to threat in relation to PTSD and asthma. Asthma and PTSD remain an emerging and relevant area of research investigation that involves brain and body communication. Further understanding their comorbidity through neurobiological mechanisms and population differences is of significant importance in developing specialized, personalized treatments for individuals most at risk.

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Table 1. Clinical and demographic features of general sample.

Demographics	**Asthma**	**No Asthma**
	(*n* = 169)	**(*n* = 419)**
Sex (%)		
Female	162 (95.86%)	347 (82.82%)
Male	7 (4.14%)	72 (17.18%)
Age, mean (SD)	41.94 (13.59)	41.53 (13.56)
PCL-5, mean (SD)	34.18 (20.95)	30.04 (20.63)
CTQ, mean (SD)	53.35 (21.05)	49.02 (20.60)
TEI, mean (SD)	6.20 (3.36)	5.54 (3.27)
Asthma Medication (%)		
Yes	104 (61.90%)	N/A
No	64 (38.10%)	N/A
Number of times in jail, mean (SD)	2.89 (2.82)	4.17 (7.57)
Number of arrests, mean (SD)	2.94 (2.81)	4.14 (7.24)
Race (%)		
African American/Black	152 (89.94%)	370 (88.52%)
Hispanic/Latino	0 (0.00%)	6 (1.44%)
Asian	0 (0.00%)	2 (0.48%)
Caucasian/White	8 (4.73%)	25 (5.98%)
Mixed	4 (2.37%)	13 (3.11%)
Other	5 (2.96%)	2 (0.48%)
Education (%)		
Some high school	31 (18.34%)	53 (12.65%)
High school degree	36 (21.30%)	109 (26.01%)
GED	6 (3.55%)	14 (3.34%)
Some college or technical school	48 (28.40%)	119 (28.40%)
Technical school graduate	15 (8.88%)	24 (5.73%)
College graduate	22 (13.02%)	73 (17.42%)
Graduate school	11 (6.51%)	27 (6.44%)
Relationship Status (%)		
Single/Never married	98 (57.99%)	251 (60.04%)
Married	21 (12.43%)	54 (12.92%)
Divorced	25 (14.79%)	59 (14.11%)
Separated	9 (5.33%)	17 (4.07%)
Widowed	11 (6.51%)	13 (3.11%)
Domestic partner	5 (2.96%)	24 (5.74%)

*PTSD-Checklist DSM-5 (PCL-5) Range: 0-80, Childhood Trauma Questionnaire (CTQ) Range: 5-125. Traumatic Events Inventory (TEI)

Table 2. Clinical and demographic features of fMRI sample.

Demographics	**Asthma**	**No Asthma**
	(*n* = 11)	**(*n* = 60)**
Age, mean (SD)	44.73 (11.31)	38.12 (11.65)
PSS, mean (SD)	16.09 (14.01)	12.61 (11.53)
TEI, mean (SD)	4.36 (2.31)	4.66 (2.17)
ASI, mean (SD)	34.60 (12.93)	24.17 (14.61)
BDI, mean (SD)	11.55 (8.68)	13.98 (12.86)
Education (%)		
Some high school	1 (9.09%)	12 (20.00%)
High school degree	4 (36.36%)	14 (23.33%)
GED	1 (9.09%)	3 (5.00%)
Some college or technical school	3 (27.27%)	17 (28.33%)
Technical school graduate	0 (0%)	8 (13.33%)
College graduate	2 (18.18%)	3 (5.00%)
Graduate school	0 (0%)	3 (5.00%)

*PTSD Symptom Scale (PSS) Range: 0-40, Traumatic Events Inventory (TEI), Anxiety Sensitivity Index (ASI) Range: 0-64, Beck Depression Inventory (BDI) Range: 0-63

Table 3. Regression results using PSS and left insula as the criterion.

	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	23.48	9.07	2.59	0.01
Age	-0.07	0.12	-0.58	0.57
Asthma	-4.07	4.19	-0.97	0.33
Left Insula	-61.08	66.69	-0.92	0.36
Asthma*Left Insula	35.87	34.40	1.04	0.30

Table 4. Regression results using PSS and right insula as the criterion.

Predictor	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	22.04	8.79	2.51	0.01
Age	-0.09	0.12	-0.74	0.46
Asthma	-2.98	3.97	-0.75	0.46
Right Insula	-13.14	61.96	-0.21	0.83
Asthma*Right Insula	15.18	32.23	0.47	0.64

Table 5. Regression results using BDI and left insula as the criterion.

Predictor	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	23.16	8.81	2.63	0.01
Age	-0.13	0.12	-1.10	0.28
Asthma	-2.33	4.07	-0.57	0.57
Left Insula	-141.04	64.79	-2.18	0.03
Asthma*Left Insula	83.05	33.43	2.48	0.02

Table 6. Regression results using BDI and right insula as the criterion.

Predictor	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	20.87	8.69	2.40	0.02
Age	-0.17	0.12	-1.39	0.17
Asthma	-0.45	3.93	-0.12	0.91
Right Insula	-82.87	61.25	-1.35	0.18
Asthma*Right Insula	55.69	31.86	1.75	0.09

Table 7. Regression results using ASI and left insula as the criterion.

Predictor	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	21.78	11.35	1.92	0.06
Age	0.18	0.16	1.07	0.29
Asthma	-1.45	5.36	-0.27	0.79
Left Insula	-114.43	81.57	-1.40	0.17
Asthma*Left Insula	65.53	42.10	1.56	0.13

Table 8. Regression results using ASI and right insula as the criterion.

Predictor	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	18.61	11.33	1.64	0.11
Age	0.16	0.17	0.94	0.35
Asthma	0.54	5.26	0.10	0.92
Right Insula	-25.86	77.79	-0.33	0.74
Asthma*Right Insula	20.15	40.52	0.50	0.62

Table 9. Regression results using PSS and left anterior insula as the criterion

	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	22.65	8.75	2.59	0.01
Age	-0.07	0.12	-0.54	0.59
Asthma	-3.70	3.98	-0.93	0.36
Left Anterior Insula	-68.70	47.96	-1.43	0.16
Asthma*Left Anterior Insula	36.23	25.37	1.43	0.16

Table 10. Regression results using PSS and right anterior insula as the criterion

Predictor	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	20.97	9.11	2.30	0.02
Age	-0.08	0.12	-0.67	0.51
Asthma	-2.58	4.04	-0.64	0.53
Right Anterior Insula	12.94	69.13	0.19	0.85
Asthma*Right Anterior Insula	2.36	36.24	0.07	0.95

Table 11. Regression results using BDI and left anterior insula as the criterion

	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	20.24	8.73	2.32	0.02
Age	-0.13	0.12	-1.05	0.30
Asthma	-0.87	3.97	-0.22	0.83
Left Anterior Insula	-106.96	47.84	-2.24	0.03
Asthma*Left Anterior Insula	61.52	25.30	2.43	0.02

Table 12. Regression results using BDI and right anterior insula as the criterion

Predictor	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	20.16	9.13	2.21	0.03
Age	-0.17	0.12	-1.39	0.17
Asthma	0.03	4.05	0.01	0.99
Right Anterior Insula	-43.64	69.31	-0.63	0.53
Asthma*Right Anterior Insula	36.93	36.33	1.02	0.31

Table 13. Regression results using ASI and left anterior insula as the criterion

	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	20.54	10.78	1.91	0.06
Age	0.19	0.16	1.21	0.23
Asthma	-1.20	5.06	-0.24	0.81
Left Anterior Insula	-126.94	58.40	-2.17	0.03
Asthma*Left Anterior Insula	73.13	30.87	2.37	0.02

Table 14. Regression results using ASI and right anterior insula as the criterion

Predictor	Estimate	Standard Error	T value	Pr (>|t|)
(Intercept)	16.34	11.65	1.40	0.17
Age	0.15	0.17	0.90	0.37
Asthma	1.78	5.33	0.33	0.74
Right Anterior Insula	31.96	88.66	0.36	0.72
Asthma*Right Anterior Insula	-2.07	46.34	-0.05	0.97

Figures

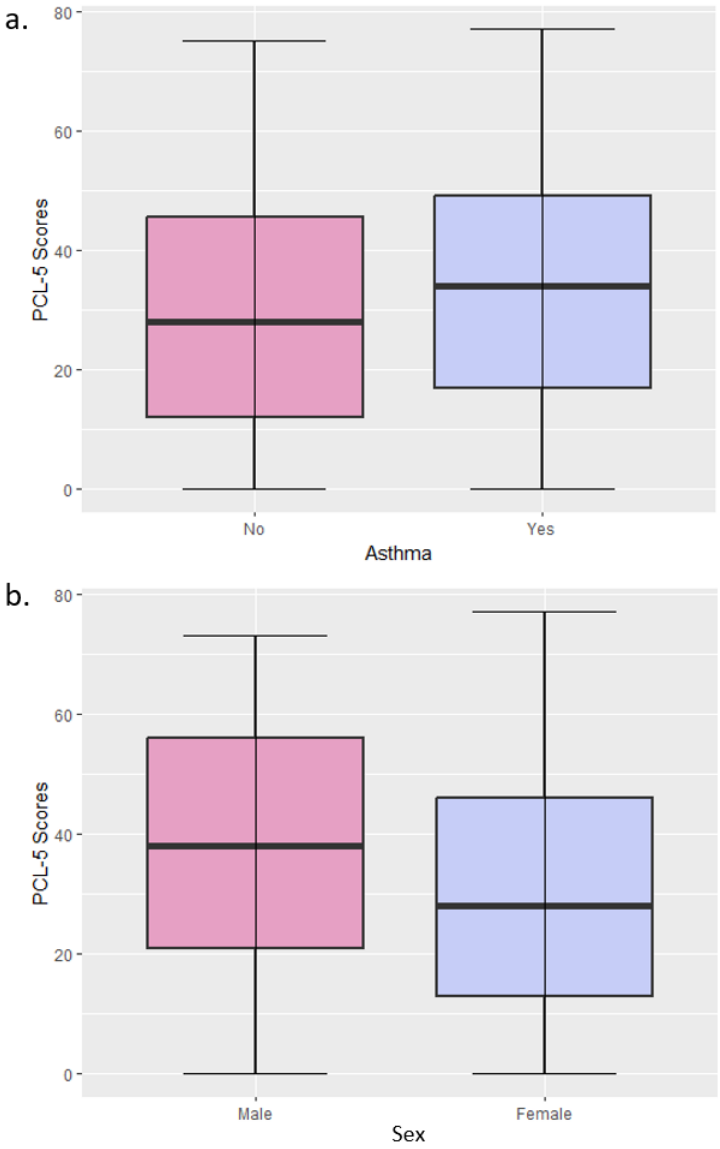

Figure 1. Differences in PTSD severity among individuals with asthma vs. without asthma. (a) Differences in PCL-5 scores among people with vs. without asthma. Results indicated a significant difference (p<.05) in PCL-5 scores between individuals with vs. without asthma, with the asthma group having significantly higher PCL-5 scores (M=34.18). (b) Differences in PCL-5 scores among men vs. women. Results revealed that men had significantly higher PCL-5 scores than women (p<.05).

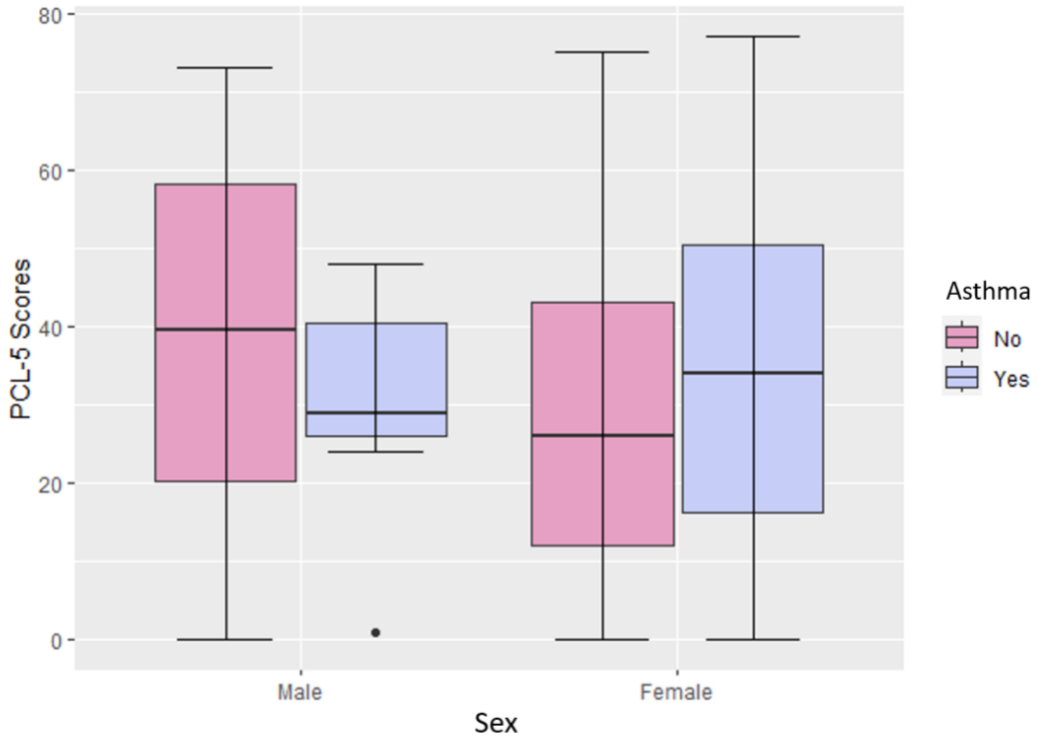

Figure 2. PTSD severity scores among males and females and asthma presence. A two-way ANOVA revealed no significant interaction effect between asthma and sex on PCL-5 scores.

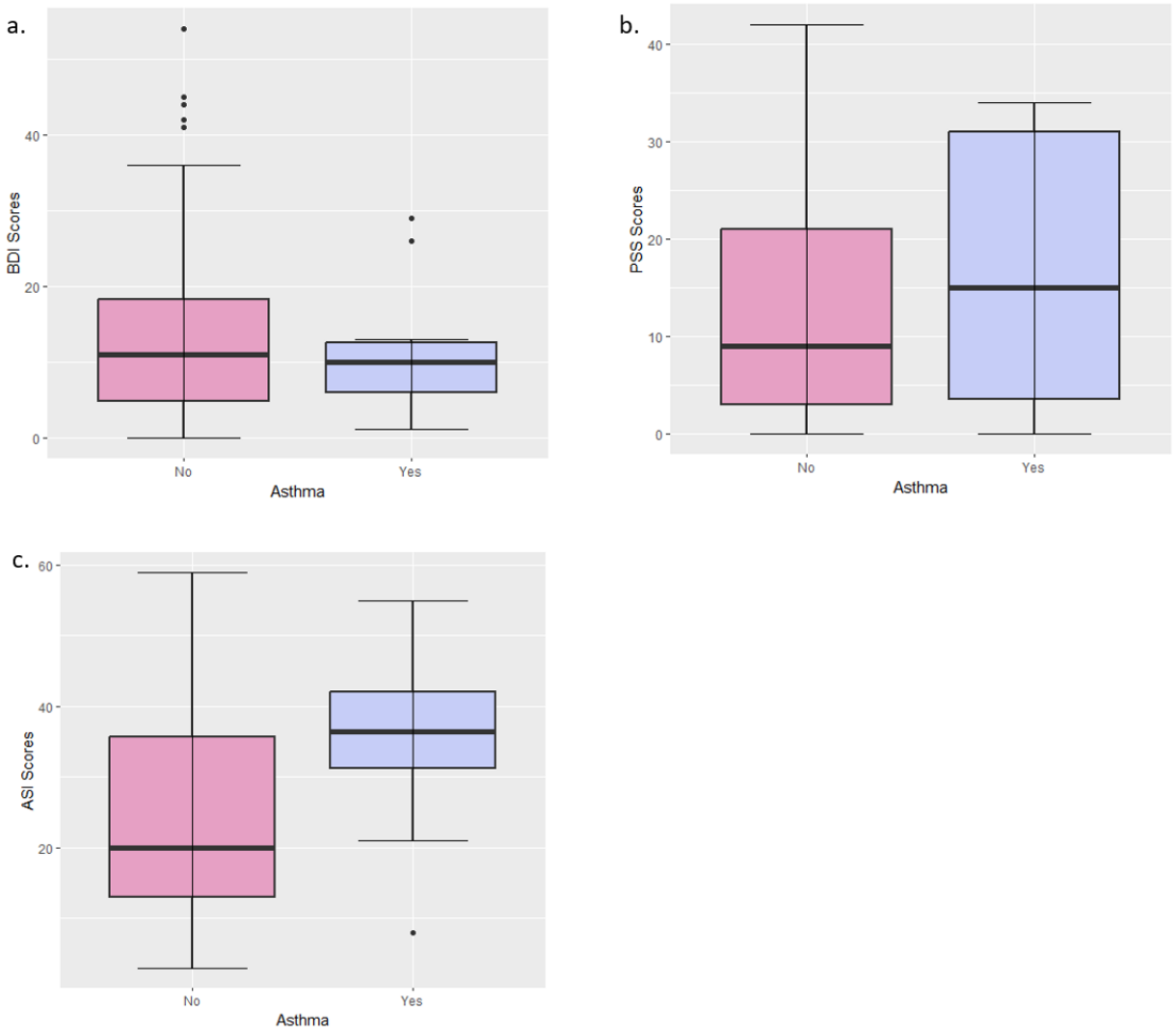

Figure 3. (a) Differences in PSS scores among women with vs. without asthma. (b) Differences in BDI scores among women with vs. without asthma. (c) Differences in ASI scores among women with vs. without asthma. Results indicate a significant difference (p<.05) in ASI scores between women with vs. without asthma, as women with asthma have significantly higher ASI scores (M=34.60).

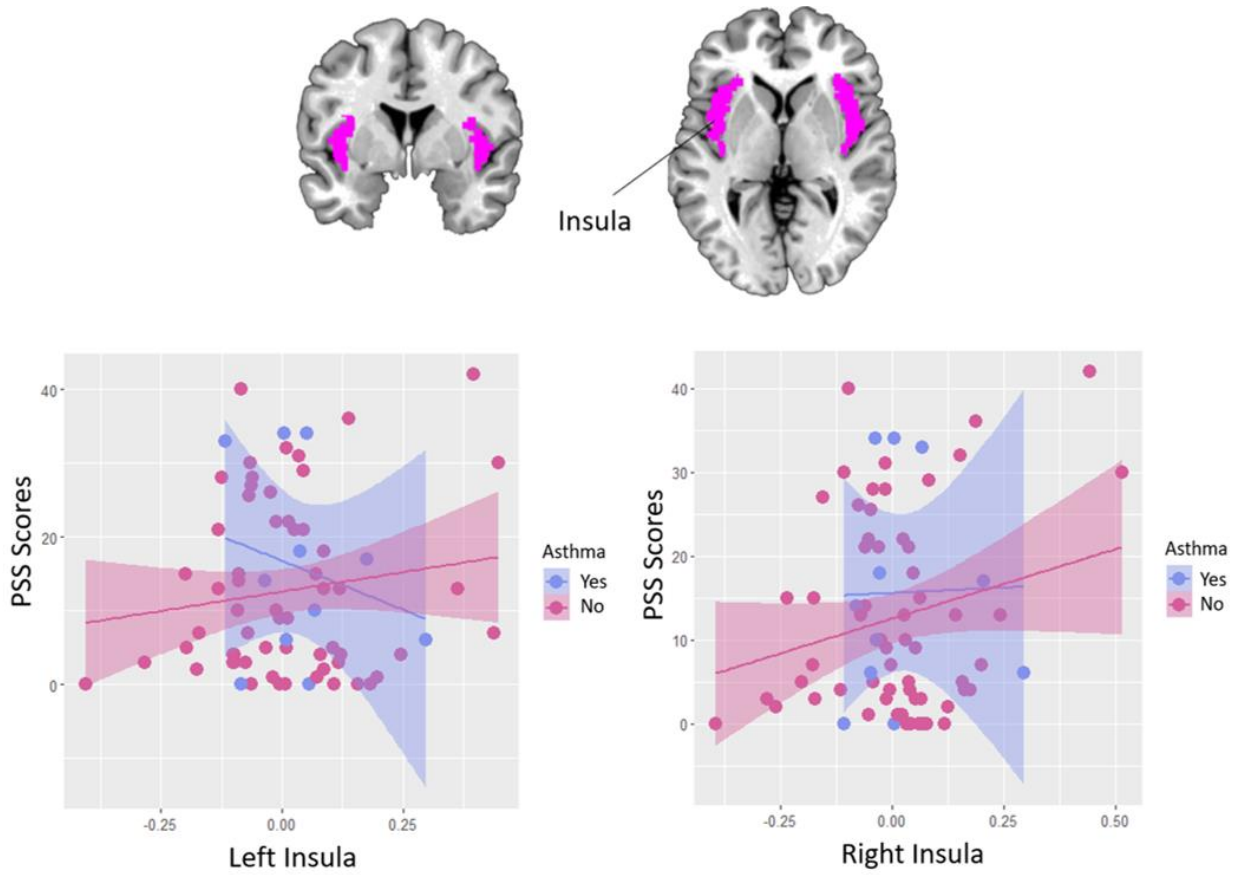

Figure 4. Region of interest and asthma-by-insula interaction effects predicting subsequent PTSD symptoms. Figure 4 depicts the whole insula region of interest (ROI). There was not a significant interaction effect between left insula and right insula and asthma for PSS scores.

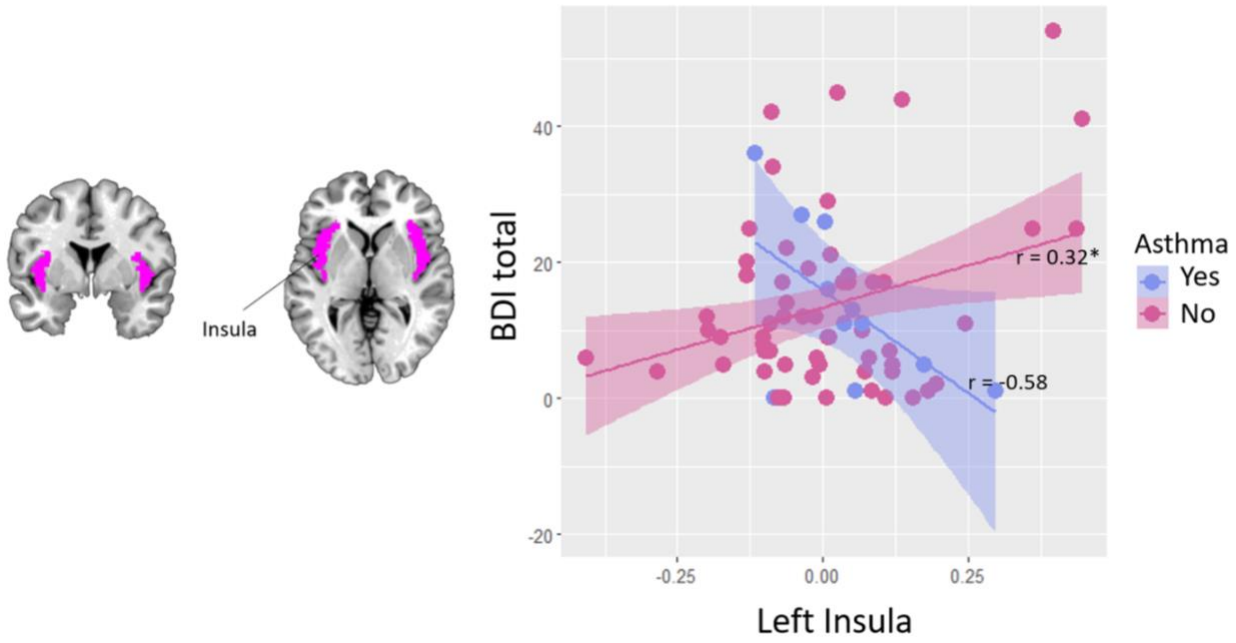

Figure 5. Region of interest and asthma-by-insula interaction effects predicting subsequent depression symptoms. Figure 5 depicts the whole insula region of interest (ROI). There was a significant interaction effect between left insula and asthma for BDI scores. The no asthma group showed a significant positive correlation between the left insula and BDI scores ($r(58) = 0.32$, $p = 0.01$) while the asthma group showed no significant correlation ($r(9) = -0.58$, $p = 0.06$).

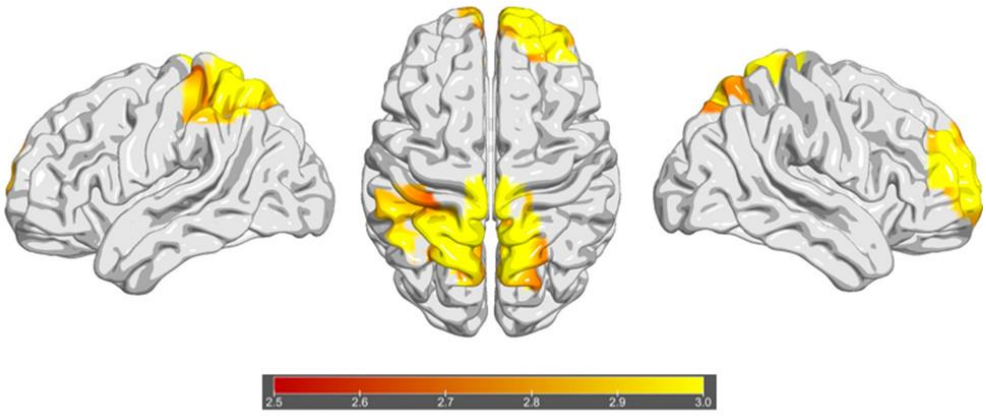

Figure 6. Whole-brain clusters in response to fearful faces among individuals with different PTSD symptoms. There was significant positive correlation between PSS scores and reactivity to fearful vs. neutral faces in the right frontal superior cortex and right precuneus.

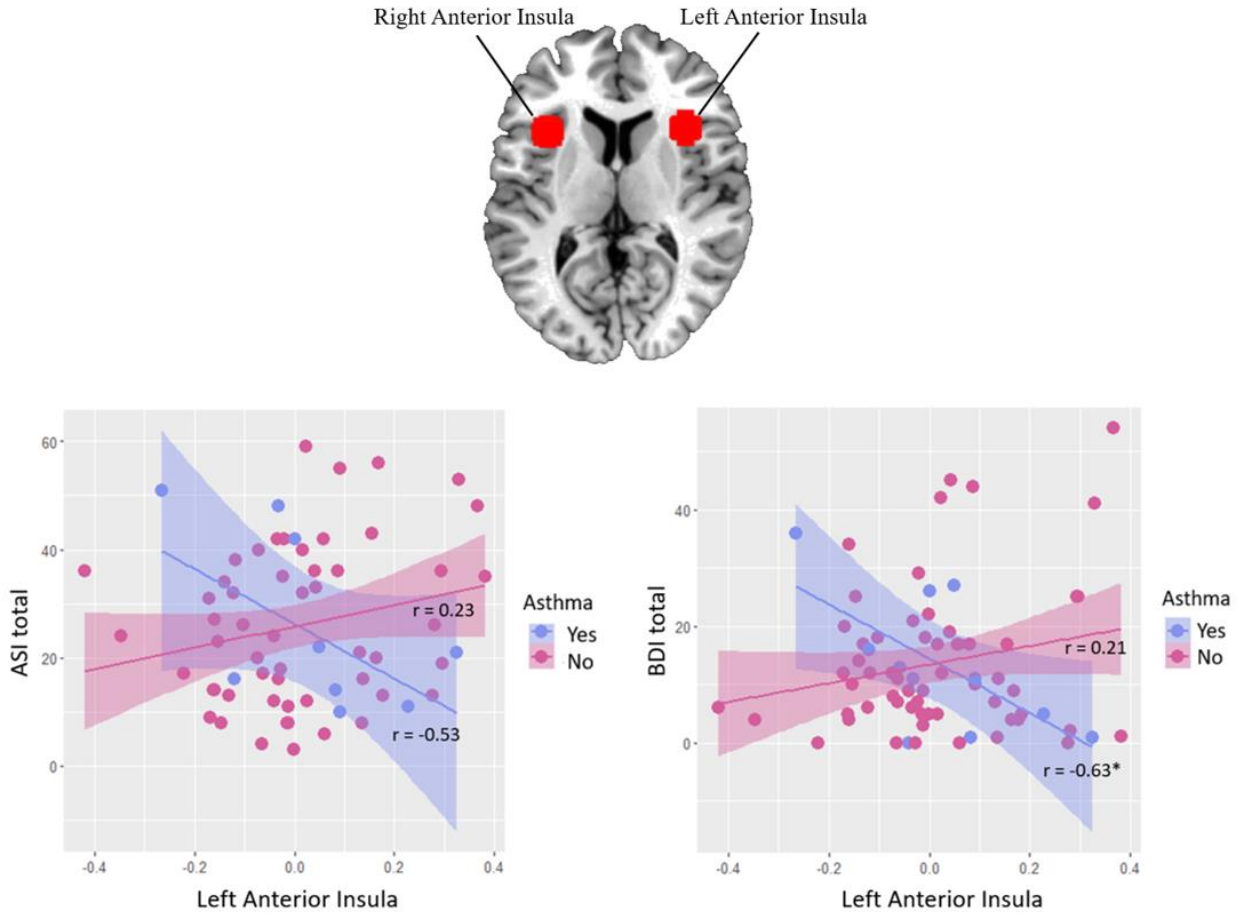

Figure 7. Region of interest and asthma-by-left anterior insula interaction effects predicting subsequent depression and anxiety symptoms. Figure 7 depicts the right and left anterior insula region of interest (ROI). There was a significant interaction effect between left anterior insula and ASI scores and between left anterior insula and BDI scores. Both asthma (r(8) = -0.53, p = 0.11) and no asthma group (r(52) = 0.23, p = 0.10) did not show a significant correlation between the left anterior insula and ASI scores. The asthma group showed a significant negative correlation between the left anterior insula and BDI scores (r(9) = -0.63, p = 0.04) while the no asthma group did not show a significant correlation (r(58) = 0.21, p = 0.11).