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Association between posttraumatic stress disorder severity and amygdala habituation to fearful stimuli

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Abstract

Background: Amygdala hyperreactivity to threat has been proposed to be a causal contributor to posttraumatic stress disorder (PTSD). However, emerging literature in healthy samples shows higher test-retest reliability for amygdala habituation (the change over time in response to repeated stimuli) than for its reactivity to threat. Amygdala habituation has received relatively little attention in relationship to PTSD, despite the key role of this region in the etiology of the disorder. Thus, we investigated habituation to repeated fearful face stimuli and PTSD, in a large sample of trauma exposed African American women.

Methods: African American women (N = 100) were recruited from a nonprofit hospital serving a largely low-income population with a high risk of trauma exposure. Participants underwent functional magnetic resonance imaging, passively viewing fearful and neutral face stimuli, and reported their history of trauma exposure and current PTSD symptoms. We examined associations between PTSD symptom severity and amygdala reactivity (fearful > neutral) and habituation (early > late) to fearful faces. Secondary analyses tested whether amygdala habituation to fearful faces mediated the association between childhood trauma and PTSD.

Results: PTSD symptom severity and PTSD status (based on self-report measure) were both positively associated with amygdala habituation to repeated fearful face stimuli. Whole-brain analysis showed that this association extended to the bilateral hippocampus and left fusiform gyrus. The association held when controlling for trauma history and depressive symptoms. Amygdala habituation to fearful faces partially mediated the association between childhood trauma severity and PTSD symptom severity.

Conclusion: Individuals with greater PTSD symptom severity showed greater amygdala habituation to social threat cues (fearful faces), and greater habituation may partly explain the association between childhood trauma exposure and current PTSD symptoms. Further

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CONFLICT OF INTERESTS
Dr. Ressler reports personal fees from Alkermes, Inc, grants from Nobilis, Inc, personal fees from Resilience Therapeutics, outside the submitted work. Dr. van Rooij has a patent 62/775,982 pending. Remaining authors declare that there are no conflict of interests.
examination of the dynamics of the amygdala response to threat cues may lead to new insights in
the understanding and treatment of stress-related disorders.

Keywords
amygdala; fear; fMRI; habituation; trauma

1 | INTRODUCTION
The estimated lifetime prevalence of posttraumatic stress disorder (PTSD) among adult
Americans is 6.8% according to a replication of the National Comorbidity Survey (Kessler
et al., 2005). Furthermore, women are twice as likely to be diagnosed with PTSD as men
(Breslau, Chilcoat, Kessler, & Davis, 1999; Tolin & Foa, 2006). Efforts to understand the
underlying neurobiological contributors to PTSD have focused largely on the function of the
amygdala (Shin & Liberzon, 2010), a brain region that is central to recognizing and
coordinating responses to emotionally salient stimuli, including emotional facial expressions
(Adolphs, 2002, 2003; Calder, Lawrence, & Young, 2001; Davis & Whalen, 2001; Ledoux,
2000). Individuals with PTSD show amygdala hyperreactivity to negative emotional stimuli,
relative to control groups (Fonzo et al., 2010; S. L. Rauch et al., 2000; Shin et al., 2005;
Stevens et al., 2013), and this hyperreactivity has been proposed as a causal contributor to
the disorder (Admon et al., 2009). However, reactivity has been shown to be a less stable
biomarker of amygdala function than dynamic amygdala responses to repeated stimuli,
which show high levels of test-retest reliability (Gee et al., 2015; Plichta et al., 2014). Given
the key role of the amygdala in theories of PTSD neurobiology and the potential value of a
highly stable biomarker of amygdala function, further investigation of amygdala habituation
in PTSD is warranted. Here, we examined amygdala habituation to repeated threat stimuli
using functional magnetic resonance imaging (fMRI) in trauma-exposed women with
varying severity of PTSD symptoms and PTSD symptom clusters.

In a healthy brain, the amygdala response to threatening stimuli or other negative emotional
stimuli is initially high, and decreases rapidly to repeated presentations of the stimuli
(habituation; Fischer et al., 2003; Phelps et al., 2001; Wright et al., 2001). Amygdala
habitation during visual processing of fearful faces compared with neutral faces has been
shown in both the left and right amygdala (Breiter et al., 1996) and no specific hypothesis
regarding laterality of amygdala habituation exists. Habituation is a typical response that
relies heavily on well-established learning circuits at the cellular level involving depression
of synaptic transmission (V. F. Castellucci & Kandel, 1974; V. Castellucci, Pinsker,
Kupfermann, & Kandel, 1970). Notably, habituation has been implicated as a key
mechanism for many desensitization-based psychotherapies, including prolonged exposure
therapy (Foa, 2011; Sripada & Rauch, 2015), and is relevant to PTSD due to the aberrant
responses to threat cues that are likely repeated in the environment. PTSD is therefore
hypothesized to be specifically associated with habituation of negative stimuli.

In PTSD, surprisingly few studies have investigated how the amygdala response changes
over repeated presentations of negative stimuli. Existing findings point to a positive
association between symptom severity and amygdala habituation to threat. An early study

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with a small sample size showed an increase in the amygdala response to repeated threat stimuli over time (sensitization) in healthy controls, whereas there was no such increase in individuals with PTSD (Protopopescu et al., 2005). Similarly, in a study of adolescents, those with PTSD showed greater amygdala habituation than a group with depression or anxiety (van den Bulk et al., 2016). Additional research is needed to determine whether the findings are related to trauma exposure, as previous research used nontrauma-exposed control groups, understand the relationship within sub-clusters of PTSD symptoms, and understand the mechanism through bilateral amygdala in the relationship between childhood trauma and adulthood PTSD symptom severity.

Here, we sought to examine associations between bilateral amygdala habituation and PTSD in a well-powered sample, and to account for the effects of trauma history, depressive and trait anxiety symptoms. We investigated associations between PTSD symptom severity, PTSD diagnosis, and PTSD symptom clusters with dynamic amygdala responses to fearful stimuli in a large civilian sample with a history of multiple traumas. We also tested for potential mediation by bilateral amygdala habituation to fearful stimuli between childhood trauma severity and adulthood PTSD symptom severity. We hypothesized that greater PTSD symptom severity and PTSD diagnosis would be associated with greater amygdala habituation to repeated fearful face stimuli, even after controlling for trauma load and depressive and trait anxiety symptoms, and that bilateral amygdala habituation would mediate the relationship between childhood trauma and adulthood PTSD.

2 | MATERIALS AND METHODS

2.1 | Participants

One hundred and African American women between the ages 18 and 62 were recruited from an ongoing larger study of risk factors of PTSD. Participants were randomly approached in the outpatient clinics of Grady Memorial Hospital, a nonprofit hospital that provides care to the socioeconomically disadvantaged populations in metropolitan Atlanta, Georgia. The hospital patient population is more than 85% African American, and thus we included only those who self-reported as African American to increase data homogeneity. Additionally, this group is underrepresented in psychiatric imaging research studies despite high rates of trauma and PTSD symptoms being previously observed in this population (Binder et al., 2008). Men were not included in the current study due to significant sex differences in neural processing of emotional stimuli (Stevens & Hamann, 2012).

All participants were screened and met the following inclusion criteria: no neurological disorder, psychosis, current psychotropic medication, or metal clips or implants. All participants had normal or corrected-to-normal vision. Exclusion criteria included the following: history of bipolar disorder, schizophrenia, other psychotic disorder, pregnancy, or illegal drug use (cocaine, marijuana, opiates, amphetamines, and methamphetamines). Urine tests, conducted 24 hr before the MRI scan, were used to detect and exclude women who were pregnant or tested positive for illegal drug use.

After fMRI data collection, 18 participants were excluded: 15 for falx calcification, 2 for absolute head motion > 3 mm, and 1 for problems with stimulus presentation, resulting in a...
final sample of $N = 100$ (additional clinical and demographic characteristics in Table 1). Participants provided written informed consent for all parts of the study, and the Institutional Review Boards of Emory University and Grady Memorial Hospital approved the study procedures.

2.2 Measures

Participant demographics collected and used in the analyses included age, average household monthly income, and highest education attained. Interviews were conducted by trained interviewers in the general medical clinics of Grady Hospital. Clinical measures were collected by interviewer-assisted self-report measures, and assessments of current symptoms were administered within 24 hr of the MRI scan.

PTSD symptoms over the prior 2 weeks were assessed with the 17-item modified PTSD Symptom Scale (MPSS) for DSM-IV-TR, a psychometrically reliable scale with a range from 0 to 51 (Coffey, Dansky, Falsetti, Saladin, & Brady, 1998; Falsetti, Resnick, Resick, & Kilpatrick, 1993; Foa & Tolin, 2000; Foa, Riggs, Dancu, & Rothbaum, 1993). The total score was used as a measure of PTSD symptom severity (Binder et al., 2008; Schwartz, Bradley, Sexton, Sherry, & Ressler, 2005). For the purposes of correlational analyses examining different symptom subtypes, we elected to break symptom clusters into four types: re-experiencing, avoidance, numbing, and hyperarousal, consistent with changes implemented in the DSM-5 (American Psychiatric Association, 2013). Symptom severity was used as the primary psychiatric outcome of interest, but in secondary analyses we classified PTSD status as (a) PTSD+, individuals who met DSM-IV criteria for PTSD based on the MPSS, and (b) PTSD−, trauma-exposed controls who did not meet DSM-IV criteria for PTSD.

The Beck Depression Inventory (BDI) is a psychometrically validated and widely used self-report inventory of current depressive symptoms (Beck, Steer, & Brown, 1996). 21 items assess the presence and severity of depressive symptoms over the past 2 weeks rated on a scale of 0 (not at all/never) to 3 (extremely/every day). A total BDI score was calculated by summing all individual items. An additional cutoff score of ≥14 was used to distinguish high versus low levels of depressive symptoms, as proposed by the original authors of the instrument (Beck et al., 1996).

The State-Trait Anxiety Inventory (STAI) is a 21-item questionnaire that was used as an objective measures of anxiety state and trait (Spielberger, Gorsuch, & Lushene, 1970), and has been validated for different patients and populations (Guillén-Riquelme & Buela-Casal, 2014). Anxiety trait is a more stable aspect associated with the individual propensity to deal with more or less anxiety throughout life.

The Trauma Exposure Inventory (TEI) is a 14-item screen for lifetime history of traumatic events (Schwartz et al., 2005). The total number of different types of events experienced in adulthood was used as an index of adult trauma load.

The Childhood Trauma Questionnaire (CTQ) is a 28-item self-reported inventory assessing five types of maltreatment (sexual abuse, physical abuse, emotional abuse, emotional...
neglect, and physical neglect; Bernstein, Ahluvalia, Pogge, & Handelsman, 1997; Bernstein et al., 1994). Total score and subscale scores for each of the three type of child abuse was used to assess the childhood trauma history (Bernstein et al., 2003). Childhood trauma history, including sexual, emotional, and physical abuse, was categorized into minimal, moderate, and severe levels, as established by Bernstein and Fink (Bernstein & Fink, 1998; Bernstein et al., 1994), and was used for mediation analyses.

2.3 | Brain imaging acquisition

The fMRI study procedures have been published previously and followed Stevens et al. (2013). Briefly, participants passively viewed 30 blocks of static fearful and neutral face stimuli of Caucasian race (15 fearful and 15 neutral blocks, and randomly intermixed). Blocks consisted of eight trials. Each face stimulus was presented for 500 ms, followed by a 500 ms presentation of a fixation cross. After every 10th block, a 10,000 ms rest period with the instruction “relax and look at the screen” was presented. Brain imaging data were acquired on a Siemens 3.0T Magnetom Trio TIM MRI scanner (Siemens, Malvern, PA) using a 12-channel coil. Functional images were acquired using the Z-SAGA pulse sequence (Heberlein & Hu, 2004) to minimize signal loss caused by susceptibility artifacts.

Preprocessing was conducted in SPM8 software (IBM Corp. Armonk, NY) and followed methods detailed in Kilaru et al. (2016). In SPM8, correction for slice timing and spatial realignment was applied to the images. Then the images were normalized with unified segmentation, and smoothed with a 9 mm Gaussian kernel. The six realignment parameters were included in the subject-level design matrix as covariates to correct for head motion. Amygdala responses were extracted from a bilateral region of interest (ROI) created using the probability mask from the SPM Anatomy Toolbox, at a threshold of 50% (Eickhoff et al., 2005). To examine regions outside the ROIs, whole-brain analyses were conducted with SPM’s cluster-based thresholding and an initial cluster-forming threshold of p < .005.

2.4 | Statistical analyses

The main effects of task included a comparison of fearful and neutral face stimuli to measure amygdala reactivity, and a comparison of early and late blocks of stimuli to measure amygdala habituation. Early blocks were composed of the first five fearful or neutral face blocks and these were compared with the late blocks, consisting of the last five fearful or neutral blocks. The full timecourses of the BOLD response within the amygdala ROI were extracted for all participants, and examined visually to confirm that this segmentation into sets of five blocks was appropriate. Example timecourses are shown in Figure 1. To assess task-related amygdala activation, a 2 × 2 within-subjects analysis of variance (emotion: fear vs. neutral; time: early vs. late blocks) modeled task-related responses, irrespective of PTSD symptoms.

Next, β-weight contrast values were extracted and four different contrasts were created to estimate associations between PTSD symptom severity and task-related amygdala activation: (a) amygdala reactivity comparing fearful > neutral face stimuli, (b) amygdala habituation to fear to compare early > late blocks of fearful face stimuli, (c) amygdala habituation to neutral comparing early > late blocks of neutral face stimuli, and (d)
amygdala habituation to fear minus neutral face stimuli. Associations with PTSD symptom severity were analyzed using hierarchical multiple regressions. Sensitivity analyses were performed using hierarchical multiple regression to adjust for depressive symptoms (BDI score), trait anxiety symptoms (STAI score), number of childhood (CTQ score), and adulthood traumas experienced (TEI score). To examine potential differential associations with PTSD symptom clusters, we first conducted intercluster correlations between hyperarousal, avoidance, numbing, and intrusive symptoms, and then separately analyzed the associations between these symptoms with bilateral amygdala habituation to fearful face stimuli. Next, hierarchical multiple regressions were conducted to estimate the association between PTSD status and amygdala habituation, again separately for fear and neutral face stimuli.

Finally, mediation analysis was used to examine whether bilateral amygdala habituation to fearful faces mediates the relationship between childhood trauma severity (unexposed, mild, or severe) and PTSD total symptom severity. The mediation test was conducted according to Baron and Kenny (Baron & Kenny, 1986).

3 | RESULTS

3.1 | Sample characteristics

Table 1 shows demographic and clinical characteristics for the final sample for analysis, which included African American women (ages 18–62, M= 37.9, SD= 11.3). All participants were exposed to at least one Criterion A trauma (range = 1–13). Many participants experienced childhood abuse (M = 42.9, SD = 18.2; where 25 represents no abuse, range = 0–125), and usually a number of different types of traumatic events in adulthood (M = 4.5, SD = 2.3). Of these women, 60% had <$1000 monthly household income, and the highest degree of education for 47% of these women was a GED or an education below 12th grade. There was a wide range of symptom severity for PTSD (M = 14.0, SD = 12.0, range = 42.0) and depression (M = 13.4, SD = 11.6, range = 54.0). Based on the self-report measures, 39% were classified as PTSD + (according to DSM-5 criteria), 39% were classified as depression + (BDI ≥ 14), and 26% of the total sample were PTSD+ and depression+. Motion levels were very low across all participants; the maximum absolute motion during the MRI scan was M = 0.714 mm for x/y/z, and M = 0.847 degrees for yaw/roll/pitch. There was no correlation between any of the motion parameters and PTSD symptoms.

3.2 | Task-related amygdala activation: Reactivity and habituation

The Emotion (fear vs. neutral) × Time (early vs. late blocks) interaction was not significant (p = .78), however, main effects for both emotion and time were observed. Amygdala activation was significantly greater for fearful than neutral faces, F(1,99) = 4.41, p = .04 demonstrating increased amygdala reactivity to fearful faces across the whole group. Second, amygdala activation was significantly smaller during early versus late blocks F(1,99) = 6.43, p = .01, indicating negative amygdala habituation or sensitization across the whole group (Figure 2a). However, there was a wide range in individual habituation scores (early–late blocks) for the fearful face blocks as illustrated in Figure 2b.
3.3 | Association with PTSD symptom severity
As shown in Table 1, PTSD symptom severity was not associated with amygdala reactivity. However, symptom severity was positively associated with amygdala habituation to fearful faces. Sensitivity analyses controlling for childhood and adult trauma exposure, depression symptom severity, and trait anxiety, showed an independent association with PTSD symptoms (Table 2 and Figure 2c), such that more severe PTSD symptoms predicted greater habituation to fearful faces. To test relationships of amygdala habituation with specific symptoms, we separately examined the hyperarousal, avoidance, numbing, and intrusive symptom clusters. The clusters were significantly correlated with one another (range of \( r = .64-.73; \ p < .001 \)), and all showed similar positive associations with habituation to fearful faces (Table 1). Total PTSD symptom severity was not associated with amygdala habituation to neutral faces, but significantly correlated with amygdala habituation to fearful minus neutral faces (Table 1).

Similarly, in a comparison of PTSD+ (\( n = 39 \)) and PTSD− (\( n = 61 \)), PTSD+ was associated with greater amygdala habituation to fearful faces \([F(98,1) = 8.7, \ p = .004; \ PTSD+ : M(SD) = 0.1(0.7); \ PTSD− : M(SD) = -0.3(0.7)\]). After sensitivity analysis controlling for trauma history, depressive symptoms and trait anxiety symptoms, the group difference was reduced but remained statistically significant \([F(94,5) = 3.5, \ p = .006]\). For habituation to neutral faces, there was no association with PTSD status, \( p = .74 \). For bilateral amygdala reactivity, there was no association with PTSD status, \( p = .34 \).

Whole-brain analyses of the habituation contrasts (early > late) for fearful and neutral face stimuli showed that the pattern of results for the amygdala ROI extended to nearby medial temporal lobe and ventral visual regions, as shown in Figure 3. There was a positive correlation between PTSD symptom severity and habituation to fearful faces in a cluster peaking in the right parahippocampal gyrus and overlapping the right amygdala and hippocampus, and in a similar cluster peaking in the left fusiform and overlapping the left amygdala and hippocampus. There were no negative correlations between PTSD symptom severity and habituation to fearful faces, and no significant associations with habituation to neutral faces.

3.4 | Amygdala habituation to fearful faces as a potential mediator of the childhood trauma—PTSD association
Given the relatively high rate of childhood trauma exposure in this sample, and the known association between childhood trauma and adult PTSD, a mediation analysis was used to test the hypothesis that amygdala habituation to fearful face stimuli mediated the association between childhood trauma severity and PTSD symptom severity (Figure 4). The number of childhood trauma exposures and PTSD symptom severity both showed significant linear associations with amygdala habituation to fearful faces. The association between childhood trauma severity and PTSD symptom severity without the proposed mediator was \( \beta = .26 (\ p = .01) \). A reduction in the regression coefficient was found when amygdala habituation was included in the model simultaneously (\( \beta = .17, \ p = .09 \)), which indicated partial mediation.
The current study found that greater PTSD symptom severity was associated with heightened amygdala habituation to repeated fearful stimuli in a large sample of civilian women. We found that this association remained significant after controlling for trauma load and depressive and trait anxiety symptoms. Furthermore, amygdala habituation to fearful faces partially mediated the relationship between childhood trauma exposure and PTSD symptom severity.

In a quantitative meta-analysis of positron emission tomography (PET) and fMRI studies of PTSD published before 2011, the bilateral amygdala was hyperresponsive to negative, nontrauma related stimuli among PTSD patients (Hayes, Hayes, & Mikedis, 2012). Increased amygdala activity has also been observed in response to trauma-related stimuli in PTSD patients (Liberzon et al., 1999; S. L. Rauch et al., 1996, 2000; Shin et al., 1997). However, several studies have found null findings (Bremner, Narayan et al., 1999; Bremner, Staib et al., 1999; Bremner et al., 2003; Britton, Phan, Taylor, Fig, & Liberzon, 2005; Lanius et al., 2001; Shin et al., 1999), or reduced amygdala activation in PTSD patients versus control participants (Luan Phan, Britton, Taylor, Fig & Liberzon, 2006). One recent study has shown that amygdala reactivity can be altered bi-directionally in the same subjects depending on the stimulus type and the degree of PTSD symptoms (Brashers-Krug & Jorge, 2015). Thus, reactivity may not be the most reliable measure of response to stimuli to understand the dynamic response of the bilateral amygdala.

Recent findings indicate that amygdala habituation to emotional stimuli may be a more reliable fMRI indicator of amygdala function than the mean amplitude, after assessing within-subject reliability and retest-reliability (Gee et al., 2015; Plichta et al., 2014). In the current study, PTSD symptom severity was not associated with bilateral amygdala reactivity whereas PTSD symptom severity was positively associated with bilateral amygdala habituation to fearful stimuli (and fearful minus neutral stimuli). Our findings were consistent with the single previous study of amygdala habituation in adult PTSD, which tested habituation in response to emotional words among 9 participants with sexual/physical assault PTSD, and 14 healthy controls (Protopopescu et al., 2005). Similar to our study, they found greater habituation to emotional stimuli in PTSD than healthy control subjects. Work in adolescents showed greater amygdala habituation to emotional stimuli for a childhood sexual abuse (CSA)-related PTSD group (n = 19) compared with the healthy controls (n = 26) and a DSM-IV depressive and/or anxiety disorder group (n = 25) (van den Bulk et al., 2016). Because this pattern was not found among the healthy controls nor the depressive/anxiety group, it is likely that childhood abuse history and related stress responses have a specific effect on amygdala habituation above and beyond any impact of depressive or anxiety symptoms. Our findings among a large civilian sample of adult women with PTSD support this hypothesis as an association between PTSD symptoms and status with amygdala habituation was demonstrated even after controlling for trauma load, depressive symptoms and trait anxiety. Together these studies suggest that amygdala dynamics to fearful stimuli are related to PTSD symptoms irrespective of depressive and trait anxiety symptoms.
Even though PTSD symptoms were related to amygdala habituation while correcting for depressive symptoms, it is noteworthy that depressive symptoms alone also significantly correlated with amygdala habituation. We postulate that reduced habituation reflects a physiological adaptation after exposure to childhood trauma or chronic stress as demonstrated in the PTSD− group. This group does not show the expected initial high amygdala response to fearful faces followed by a rapid habituation as observed in the PTSD+ group. This pattern could suggest that the PTSD− group used an attentional coping strategy associated with resilience after (childhood) trauma exposure. On the other hand, repeated exposure to threatening stimuli may desensitize the amygdala resulting in increased amygdala habituation as observed in the highly traumatized women with PTSD in the current sample. Habituation may therefore reflect mechanisms different from typical PTSD biomarkers of hyperarousal, which are more related to acute trauma. Importantly, amygdala habituation indeed mediated the relation between childhood trauma and PTSD symptoms, supporting this interpretation.

It is unlikely that greater amygdala habituation to fearful stimuli is a good indicator of general population-level stress vulnerability before trauma. We have previously tested whether amygdala habituation in the peri-traumatic period predicted future PTSD recovery trajectories, using the same fMRI paradigm and analyses used in the current study (Stevens et al., 2017). Participants were scanned approximately 1 month after a trauma resulting in an emergency department visit, and PTSD symptoms were measured at intervals throughout the year following trauma exposure. This study found that amygdala reactivity, but not amygdala habituation, predicted greater future PTSD symptoms (Stevens et al., 2017).

There are several potential interpretations of the different results from the prior longitudinal study and the current cross-sectional study. First, in the emergency department study (Stevens et al., 2017), fMRI was conducted in the weeks following a traumatic event, a time during which the brain is likely to be “in flux” even when there was no physical trauma. During this peritraumatic period, amygdala dynamics may reflect something different than in a cross-sectional chronic PTSD sample.

Secondly, only a quarter (26%) of the sample in the emergency department study reported significant childhood abuse, whereas more than half (52%) of the current study sample reported childhood abuse. A greater proportion of participants in the current sample may have experienced abuse at a critical age (Khan et al., 2015), potentially impacting amygdala development during a sensitive period (Dunn, Nishimi, Powers, & Bradley, 2017; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014; Tottenham et al., 2010). This explanation is consistent with the above-described hypothesis that amygdala habituation is an important marker of childhood or chronic stress, extending our understanding of the mechanistic pathway between early life stress and adulthood psychiatric outcomes.

This interpretation is further supported by previous psychophysiological research identifying a pattern of autonomic hyporeactivity in some participants with PTSD, but not others. Several studies found that individuals with multiple trauma exposures were more likely to show blunted autonomic reactivity, whereas those with single or acute trauma exposure showed autonomic hyperreactivity to negative stimuli (D’Andrea, Pole, DePierro, Freed, &
Wallace, 2013; McTeague et al., 2010). It has been hypothesized that, for individuals with multiple traumatic experiences beginning in childhood, it may be adaptive not to engage sympathetic responses to conserve resources and to balance allostatic load (Danese & McEwen, 2012). Such blunted physiological responses have often been interpreted as reflecting emotional disengagement or numbing.

Neuroimaging treatment studies in PTSD, especially for therapies involving an exposure-based component, have shown that increased amygdala reactivity to emotional stimuli predicted PTSD treatment nonresponse (Fonzo et al., 2017; Van Rooij, Kennis, Vink, & Geuze, 2016). At the same time, other studies of exposure treatment responsiveness among PTSD patients show that emotional disengagement may hinder treatment. An absence of cortisol level increases at pre- and mid-treatment, a potential biomarker of low emotional engagement, was found in treatment nonresponders (Norrholm et al., 2016; Rauch et al., 2015). Amygdala habituation is relevant to such exposure-based therapies because these treatments rely on individuals to actively engage with their trauma memories and allow for extinction of emotional responses to the memories over repeated imaginal exposures. Emotional disengagement may interfere with the required processes needed for normal exposure-driven extinction. Thus, heightened amygdala habituation to fearful stimuli—a potential measure of emotional disengagement—may be a potential biomarker of treatment nonresponse PTSD, and future studies are needed to test this hypothesis.

In addition to the ROI analyses, whole brain analyses also showed a positive correlation between PTSD symptoms and bilateral amygdala habituation, underscoring the strength of the finding. A positive correlation between PTSD symptoms and habituation was also observed in the right parahippocampal gyrus/hippocampus and the left fusiform gyrus. The hippocampus has often been implicated in PTSD and is involved in memory and context processes (Liberzon & Abelson, 2016). The left fusiform gyrus is an area involved in facial recognition (Albonico & Barton, 2017; Wang et al., 2017). The positive correlation between habituation in these regions and PTSD symptoms points to the possibility that amygdala-mediated excitation of feedback projections to the ventral visual stream (Amaral, Behniea, & Kelly, 2003) and associative memory regions (McGaugh, 2002) also habituate in individuals with PTSD.

Several important limitations exist in this study. First, due to its cross-sectional nature and use of retrospective self-reports, we cannot make assertions about causality or time of onset of bilateral amygdala habituation in relation to PTSD symptoms. Future longitudinal work in a sample with similarly high levels of childhood trauma is needed to determine whether differential amygdala dynamics consequently contributed to the severity of PTSD symptoms or vice versa. Second, although the CTQ and MPSS measurements have been both well-validated (Bernstein et al., 2003; Falsetti et al., 1993), they are self-report measures of childhood trauma and PTSD symptoms and are thus subject to a variety of biases, including recall bias. Again, prospective longitudinal studies following children during development would allow for greater inferential power. Further, the faces included in the fMRI task are from the Ekman stimulus set, while validated, are all Caucasian, and there may be the potential impact of outgroup effects, especially considering our sample of all African American women. Additional studies investigating amygdala habituation among trauma-
exposed women and men of different racial and ethnic groups would allow for transportability (Greenland & Robins, 1988) of these findings to a wider population.

5 | CONCLUSIONS

Our findings expand the literature on differential amygdala habituation in PTSD patients in a large civilian sample of African American women. Findings from this study demonstrate a positive association between PTSD symptoms and amygdala habituation to fearful faces, particularly among individuals with a history of childhood abuse. Heightened amygdala habituation may be a neurobiological marker of an altered pattern of threat reactivity in those with childhood or chronic trauma exposure, which differs from the typical pattern of hyperreactivity often observed in PTSD. As such, rapid amygdala habituation may reduce engagement in prolonged exposure therapy and increase the risk for treatment resistance in PTSD.

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FIGURE 1.

Example of full-time series over the Faces task, for the bilateral amygdala ROI. The predicted time courses for the fearful (black line) and neutral (gray line) face blocks are plotted across each volume of the run. The time series for the BOLD signal within bilateral amygdala ROI (blue line), is plotted using a simple mean to collapse across all voxels within the mask, and standardized within-subject. (a) Shows the amygdala time series for an example participant who met criteria for current PTSD (PSS total = 40). (b) Shows an example participant who did not meet criteria for current PTSD, and did not endorse any symptoms (PSS total = 0). The blue boxes indicate the early and late blocks for fearful stimuli, both consisting of five blocks of fearful face stimuli. The Fs and Ns above the figure indicate fearful (F) or neutral (N) blocks.
Amygdala responses to the fearful and neutral face stimuli. (a) Amygdala responses by emotion condition, for the early and late phases of the task. Error bars indicate ±1 SE. (b) Change over time (Early: first five blocks > Late: last five blocks) in the amygdala response to fearful face stimuli. Each bar shows habituation for a single participant, ordered in ascending sequence to illustrate the wide range of individual variation. Negative values (sensitization) indicate an increase in the amygdala response over time. Positive values (habituation) indicate a decrease in the amygdala response over time. (c) Total posttraumatic stress disorder (PTSD) symptom severity was positively associated with bilateral amygdala habituation to fearful face stimuli. The bilateral amygdala ROI is overlaid on a representative single-subject brain in Montreal Neurological Institute (MNI) space. (d) Individuals who met DSM-IV-TR criteria for probable PTSD based on self-report of (a,b,c, and d) cluster criteria showed significantly greater amygdala habituation than trauma-exposed controls.
FIGURE 3.
Whole-brain correlation between habituation to fearful face stimuli (first five blocks > last five blocks) and PTSD symptom severity, $p < .05$, FWE-corrected. A positive association was observed in two large clusters, overlapping the hippocampus, amygdala, and parahippocampal gyrus in the right hemisphere ($34, -28, -14; Z = 4.11; k = 227$), and overlapping the hippocampus, amygdala, parahippocampal gyrus, and fusiform gyrus in the left hemisphere ($-34, -28, -18; Z = 4.16, k = 248$). No region showed a negative correlation with posttraumatic stress disorder symptom severity. Clusters are overlaid on a representative single-subject brain in Montreal Neurological Institute space.
FIGURE 4.
Mediation model showing the standardized linear regression coefficients ($\beta$) for the mediated pathways in which bilateral amygdala habituation to fearful faces mediated the relationship between childhood trauma severity (CTQ total number of types of abuse experienced at the moderate/severe level) and PTSD symptom severity. CTQ, Childhood Trauma Questionnaire; PTSD, posttraumatic stress disorder.
### TABLE 1

Sociodemographic factors, trauma history, and clinical symptoms with Pearson correlation to bilateral amygdala habituation to fearful, neutral, and fearful-neutral faces and bilateral reactivity to fearful faces (n = 100)

<table>
<thead>
<tr>
<th>Sociodemographic factors</th>
<th>Overall (mean ± SD or %)</th>
<th>Bilateral amygdala habituation to fearful face stimuli r (p-value)</th>
<th>Bilateral amygdala habituation to neutral face stimuli r (p-value)</th>
<th>Bilateral amygdala habituation fearful minus neutral face stimuli r (p-value)</th>
<th>Bilateral amygdala reactivity r (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.9 ± 13.9</td>
<td>0.07 (.48)</td>
<td>0.07 (.50)</td>
<td>−0.00 (.99)</td>
<td>−0.07 (.48)</td>
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<tr>
<td>Household monthly income (%)</td>
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<tr>
<td>$0–999</td>
<td>60.0</td>
<td>0.02 (.83)</td>
<td>0.06 (.53)</td>
<td>−0.04 (.70)</td>
<td>−0.10 (.31)</td>
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<tr>
<td>$1000–1,999</td>
<td>25.0</td>
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<tr>
<td>$2000 or more</td>
<td>15.0</td>
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<tr>
<td>Education attainment (%)</td>
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<tr>
<td>Less than high school graduate</td>
<td>14.0</td>
<td>0.17 (.10)</td>
<td>0.49 (.63)</td>
<td>0.10 (0.34)</td>
<td>−0.09 (.38)</td>
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<tr>
<td>High school graduate or GED</td>
<td>33.0</td>
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<td></td>
<td></td>
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<tr>
<td>More than high school</td>
<td>53.0</td>
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<tr>
<td>Trauma history</td>
<td></td>
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<tr>
<td>Childhood trauma (CTQ total)</td>
<td>42.9 ± 18.2</td>
<td>0.26 (.01)</td>
<td>−0.05 (.62)</td>
<td>0.26 (.01)</td>
<td>0.18 (.08)</td>
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<tr>
<td>No. of adulthood traumas (TEI total)</td>
<td>4.5 ± 2.3</td>
<td>0.26 (.01)</td>
<td>−0.15 (.13)</td>
<td>0.36 (.00)</td>
<td>−0.08 (0.43)</td>
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<tr>
<td>Clinical symptoms</td>
<td></td>
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<tr>
<td>Depressive symptoms</td>
<td>13.4 ± 11.6</td>
<td>0.25 (.01)</td>
<td>−0.08 (.45)</td>
<td>0.29 (.00)</td>
<td>0.17 (.08)</td>
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<tr>
<td>Met criteria (%)</td>
<td>39.0</td>
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<tr>
<td>PTSD symptoms</td>
<td>14.0 ± 12.0</td>
<td>0.33 (.00)</td>
<td>0.01 (.95)</td>
<td>0.28 (.00)</td>
<td>0.10 (.30)</td>
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<tr>
<td>Met criteria (%)</td>
<td>39.0</td>
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<td>Comorbid PTSD and MDD (%)</td>
<td>26.0</td>
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<td>PTSD symptom clusters a</td>
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<td>Intrusive</td>
<td>3.3 (3.5)</td>
<td>0.31 (.01)</td>
<td>0.04 (.99)</td>
<td>0.23 (.09)</td>
<td>0.07 (.95)</td>
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<tr>
<td>Hyperarousal</td>
<td>5.3 (4.3)</td>
<td>0.28 (.02)</td>
<td>−0.07 (.99)</td>
<td>0.30 (.01)</td>
<td>0.12 (.63)</td>
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<tr>
<td>Numbing</td>
<td>2.7 (3.3)</td>
<td>0.28 (.02)</td>
<td>0.05 (.99)</td>
<td>0.19 (.22)</td>
<td>0.12 (.63)</td>
</tr>
<tr>
<td>Avoidance</td>
<td>2.7 (2.5)</td>
<td>0.29 (.01)</td>
<td>−0.02 (.99)</td>
<td>0.27 (.03)</td>
<td>0.03 (.99)</td>
</tr>
</tbody>
</table>

Abbreviations: CTQ, Childhood Trauma Questionnaire; GED, general educational development; PTSD, posttraumatic stress disorder; SD, standard deviation; TEI, trauma exposure inventory; MDD, major depressive disorder.
The p values for associations with symptom clusters are corrected for family-wise error rate.
**TABLE 2**

Results of hierarchical multiple regression model examining PTSD symptom severity on bilateral amygdala dynamics to fearful faces

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>t (p value)</th>
<th>F (p value)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model (n = 100)</td>
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<td>3.84 (.003)</td>
<td>.17</td>
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<tr>
<td>Step 1</td>
<td></td>
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<tr>
<td>Childhood trauma</td>
<td>.15</td>
<td>1.36 (.18)</td>
<td></td>
<td></td>
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<tr>
<td>Adulthood trauma</td>
<td>.14</td>
<td>1.31 (.19)</td>
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<tr>
<td>Depressive symptoms</td>
<td>.12</td>
<td>0.75 (.46)</td>
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<tr>
<td>Trait anxiety</td>
<td>−.20</td>
<td>−1.38 (.17)</td>
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<td>Step 2</td>
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<tr>
<td>PTSD symptoms</td>
<td>.28</td>
<td>2.12 (0.04)</td>
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</tr>
</tbody>
</table>

Note: β represents the standardized β coefficient and R² values reported are the adjusted values.

Abbreviation: PTSD, posttraumatic stress disorder.