Research Article

AMYGDALA RESPONSE TO NEGATIVE STIMULI PREDICTS PTSD SYMPTOM ONSET FOLLOWING A TERRORIST ATTACK

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Objective: ***Individuals with posttraumatic stress disorder (PTSD) exhibit heightened amygdala reactivity and atypical activation patterns in the medial prefrontal cortex (mPFC) in response to negative emotional information. It is unknown whether these aspects of neural function are risk factors for PTSD or consequences of either trauma exposure or onset of the disorder. We had a unique opportunity to investigate this issue following the terrorist attacks at the 2013 Boston Marathon and the ensuing manhunt and shelter in place order. We examined associations of neural function measured prior to the attack with PTSD symptom onset related to these events.*** **Methods:** ***A sample of 15 adolescents (mean age = 16.5 years) who previously participated in a neuroimaging study completed a survey assessing posttraumatic symptoms related to the terrorist attack. We examined blood oxygen level dependent (BOLD) response to viewing and actively down-regulating emotional responses to negative stimuli in regions previously associated with PTSD, including the amygdala, hippocampus, and mPFC, as prospective predictors of posttraumatic symptom onset.*** **Results:** ***Increased BOLD signal to negative emotional stimuli in the left amygdala was strongly associated with posttraumatic symptoms following the attack. Reduced bilateral hippocampal activation during effortful attempts to down-regulate emotional responses to negative stimuli was also associated with greater posttraumatic symptoms. Associations of amygdala reactivity with posttraumatic symptoms were robust to controls for pre-existing depression, anxiety, and PTSD symptoms and prior exposure to violence.*** **Conclusions:** ***Amygdala reactivity to negative emotional information might represent a neurobiological marker of vulnerability to traumatic stress and, potentially, a risk factor for PTSD. Depression and Anxiety 00:1–9, 2014.***

Key words: ***amygdala; hippocampus; trauma; terrorism; posttraumatic stress disorder; stress***

Most people will experience a traumatic event at some point in their lives. Population-based data indicate that at least two-thirds of U.S. adults and youths will be exposed to a lifetime traumatic event.[1–4] Although trauma exposure is pervasive, only a minority of individuals develop

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posttraumatic stress disorder (PTSD).[1–4] The conditional risk of PTSD is less than 50% even for severe events.[5,6] Despite extensive efforts to identify risk factors that confer vulnerability to PTSD following trauma exposure, meta-analyses suggest that psychosocial and environmental risk factors explain only about 20% of the variance in risk for PTSD among trauma-exposed individuals.[7,8]

Recent work has attempted to identify neurobiological markers associated with PTSD vulnerability, such as autonomic nervous system and hypothalamic–pituitary–adrenal axis activity in acutely traumatized individuals. However, these markers have not reliably predicted PTSD across studies.[9–11] In contrast, reduced hippocampal volume has been consistently observed among individuals with PTSD.[12] Small hippocampal volume has been observed among veterans with PTSD and their monozygotic twins discordant for trauma exposure, suggesting that reduced hippocampal volume could be a vulnerability marker for PTSD.[13] Additionally, numerous studies have observed differences in neural function among individuals with PTSD, including heightened amygdala activation, reduced activity in the ventromedial prefrontal cortex (vmPFC), and rostral anterior cingulate cortex (rACC) in response to emotional or threatening cues, and elevated activity in the dorsal ACC (dACC) during fear conditioning, extinction learning recall, and response selection.[14–19] The extent to which these disruptions in neural function represent vulnerability markers for the disorder or consequences of trauma exposure or PTSD onset is unknown. However, atypical medial PFC (mPFC) function has been identified as a potential familial risk factor for PTSD, indicating that some of these differences might increase vulnerability to PTSD.[20,21]

Identifying neurobiological vulnerability markers for PTSD *prior* to trauma exposure is challenging, in part because most traumatic events do not occur at random. A variety of individual-level characteristics predict trauma exposure, including sociodemographic factors, prior trauma, and psychopathology.[2,4,22–24] As such, it is difficult to disentangle, even in longitudinal studies, whether neurobiological indicators are markers of vulnerability to trauma-related psychopathology or simply predict differential risk of trauma exposure. One strategy for overcoming these challenges is to study traumatic events that are unrelated to preexisting characteristics, such as natural disasters and terrorist attacks. However, neurobiological markers are not generally available in trauma-exposed individuals prior to these kinds of unpredictable and low-probability traumatic events. The only existing evidence regarding premorbid neural function and vulnerability to psychopathology following traumatic stressors comes from an innovative study in which neuroimaging data were collected on a sample of new recruits to the Israeli Defense Forces. Amygdala reactivity prior to combat exposure during anticipation of outcomes following a risky choice and presentation of military-themed content predicted severity of PTSD symptoms following deployment.[25,26] However, these findings could reflect (a) a marker of PTSD risk; (b) a predictor of greater combat exposure, which has been linked to individual-level characteristics in military samples[27,28]; or (c) the effects of prior psychopathology or trauma exposure, factors strongly linked to PTSD[4,22,29] that were not examined in these studies.

In the current study, we examined whether aspects of neural function predicted onset of posttraumatic symptoms in adolescents following the terrorist attack at the 2013 Boston Marathon. The attack killed three spectators and injured hundreds of bystanders. Four days after the attack, a manhunt for the perpetrators resulted in an unprecedented shelter in place order that required residents of Boston and surrounding communities to remain indoors. The public transportation system, educational institutions, local government offices, and most businesses were closed. Although direct exposure to the attack was limited to spectators at the finish line of the marathon, hundreds of thousands of Boston residents watched the manhunt unfold live on television, while the shelter in place order was in effect (about 12 hr). This kind of indirect exposure to terrorist attacks and their sequelae has been shown to precipitate PTSD symptoms in children and adults living in proximity to the attack.[30–33] Here, we examine if neural function assessed in the year prior to the terrorist attack predicts posttraumatic symptom onset following the attack. These data provide a unique opportunity to examine preexisting neural markers of risk for posttraumatic symptoms following a terrorist attack, and the only study, to our knowledge, to examine such predictors of response to an unpredictable traumatic event.

MATERIALS AND METHODS

SAMPLE

Following the Boston Marathon terrorist attack, we sent an online survey to adolescents who participated in studies in our lab in the 2 years prior to the event. Requests for parental permission to recontact their children and adolescent surveys for those who provided consent were sent beginning 1 month following the attack and were open for a 2-week period. Data for the current report were drawn specifically from an ongoing fMRI study. Forty adolescents completed fMRI scans prior to the terrorist attack (time since scan = 2.0–59.6 weeks). We obtained parental permission and received completed surveys from 15 of these participants (37.5% of the original sample). Participation in the survey was unrelated to preexisting internalizing symptoms or child maltreatment, but adolescents with high community violence exposure were less likely to respond ($t = 4.0$, $P < .001$). Participants ranged in age from 14.1 to 19.1 years at the time of scan ($M = 16.49$ years) and from 14.8 to 19.9 years at the time of the survey ($M = 17.25$ years). All participants reported exposure to media coverage of the bombings on the day of the marathon and the shelter in place order (with the exception of two participants who skipped the latter survey item). See Table 1 for sample sociodemographic and preattack characteristics and degree of exposure to the shelter in place order.

TABLE 1. Distribution of sociodemographic factors, exposure to media coverage and the shelter in place order, prior trauma exposure, and preexisting psychopathology

	%	(*n*)
Female	66.7	10
Race/ethnicity		
White	46.7	7
Black	26.7	4
Latino	13.3	2
Other/biracial	13.3	2
Exposure to media coverage[a]	100.0	13
Exposure to shelter in place[a]	76.9	10
	M	(*SD*)
Prior maltreatment (CTQ)	23.53	(10.64)
Prior community violence (SAVE)	44.93	(7.91)
Preexisting depressive symptoms (CDI)	3.08	(1.83)
Preexisting anxiety symptoms (MASC)	25.58	(17.05)
Preexisting PTSD symptoms (YSR)	55.29	(7.35)

[a]Two participants skipped the survey questions about exposure to the shelter in place order and media coverage during that day. Proportions are reported based on the sample of participants who responded to these questions.

fMRI TASK

Participants engaged in a well-established event-related task designed to assess neural markers of emotional reactivity and emotion regulation[34] that has previously been used in dozens of investigations,[35] including with children and adolescents.[36] Task design and construction of contrasts for analysis were based on the substantial prior literature on this task. Specifically, participants viewed neutral and negative images drawn from the International Affective Picture System (IAPS).[37] Prior to each image, participants were shown an instructional cue to either "look" or "decrease." During *look* trials, participants were instructed to allow their emotions to unfold naturally, and to not engage in active strategies to modify their emotional response. During *decrease* trials, participants engaged in specific cognitive reappraisal strategies to try to reduce their emotional response.

All participants completed a training session prior to the MRI where they received detailed instructions about how to respond to each cue, observed examples completed out loud by a research assistant, and practiced with sample images not included in the task. On decrease trials, participants were instructed to think about the image in a way that made it psychologically more distant (e.g., imagine the scene as far away, that the situation did not involve them, that the people in the image were actors, etc.). These strategies have been used in previous studies with this task.[34,36]

Stimuli were presented in four runs lasting 9 min each. The average valence and arousal of images and the number of faces within each image were equivalent for look and decrease trials. The stimuli were matched on valence and arousal during *look* and *decrease* trials. The instructional cue appeared for 2 s, the emotional stimulus appeared for 6–10 s, the rating screen appeared for 4 s, and the intertrial interval (ITI) lasted from 1 to 6.5 s. Because the stimulus and ITI were jittered, each part of the task was modeled independently.

IMAGE ACQUISITION

Scanning was performed on a 3T Siemens Trio scanner at the Harvard Center for Brain Science using a 32-channel head coil. Anatomical scans (T1-weighted multiecho MPRAGE volumes) were acquired for coregistration with fMRI (TR = 2,530 ms, TE = 1,640–7,040 ms, flip angle = 7°, FOV = 220 $mm^{[2]}$, 176 slices, in-plane voxel size = 1 $mm^{[3]}$). To reduce motion-related artifacts a navigator echo was used prior to scan acquisition, which compares slices to this echo online and permits up to 20% of slices be reacquired.

Blood oxygen level dependent (BOLD) signal during functional runs was acquired using a gradient-echo T2*-weighted EPI sequence. Thirty-two 3-mm-thick slices were acquired parallel to the AC-PC line (TR = 2,000 ms, TE = 30 ms, flip angle = 90°, bandwidth = 2,300, echo spacing = 0.5, FOV = 256 × 256, matrix size = 64 × 64). Prior to each scan, four images were acquired and discarded to allow longitudinal magnetization to reach equilibrium. An online prospective motion correction algorithm (PACE) was used to reduce the effect of motion artifacts.

IMAGE PROCESSING

T1-weighted scans were processed using FreeSurfer version 5.0.[38–42] Automatic image segmentation was used to identify subcortical gray matter structures. Gray/white matter and gray matter/cerebrospinal fluid (CSF) boundaries were constructed using spatial intensity gradients across tissue classes. Following reconstruction, the cortex was parcellated based on the structure of gyri and sulci.[40,43] The results were inspected and manually edited to optimize accurate placement of gray/white and gray/CSF borders based on shifts in the image intensity gradient.[38,41] FreeSurfer morphometric procedures have demonstrated good test–retest reliability across scanner manufacturers and field strengths,[44,45] been validated against manual measurement[46,47] and histological analysis,[48] and used in children.[49–51]

Preprocessing and statistical analysis of fMRI data was performed in Nipype (http://nipy.sourceforge.net/nipype/), a platform that implements analysis tools from multiple software packages using the Python programming language.[52] fMRI preprocessing included spatial realignment, slice-time correction, and spatial smoothing (6 mm full-width half-maximum (FWHM)), implemented in FSL.[53] Data were inspected for artifacts using custom artifact detection software (ART).[54] Volumes with motion >3 mm or >3 SD change in signal intensity were excluded from analysis, and six rigid-body motion regressors were included in person-level models. Person- and group-level models were estimated in FSL. A component-based anatomical noise correction method[55] was used to reduce noise associated with physiological fluctuations, including cardiac pulsations and respiratory-induced modulations of the magnetic field. Following estimation of the person-level models, the resulting contrast images were normalized into standard anatomical space, and anatomical coregistration of the functional data with each participant's T1-weighted image was performed. Normalization was implemented in Advanced Normalization Tools (ANTs) software.[56] These registration and normalization procedures are superior to standard techniques found in other software packages, particularly for children.[57]

POSTTRAUMATIC SYMPTOMS

Posttraumatic symptoms *specifically related to the attack* were assessed using a brief version of the Impact of Events Scale-Revised (IES-R),[58] which has sound psychometric properties and discriminates between individuals with and without PTSD.[59,60] The IES-6 is an abbreviated form of the IES-R, and is a widely used screener for PTSD symptoms. Respondents rated the frequency of hyperarousal (e.g., "I had trouble concentrating"), intrusive thoughts (e.g., "I thought about it when I didn't want to"), and avoidance (e.g., "I tried not to think about it") experienced since the bombings, on a 5-point Likert scale ranging from 0 (almost never) to 4 (almost always). Previous studies have shown

that the IES-6 explains most of the variance of the IES-R,[61] and the measure demonstrated good internal consistency in our sample (α = .89).

PRE-ATTACK SURVEY MEASURES

As part of the study that took place prior to the terrorist attack, we collected information on internalizing symptoms, child maltreatment, and community violence exposure. Depressive symptoms were assessed with the Children's Depression Inventory (CDI),[62] anxiety symptoms were assessed with the Multidimensional Anxiety Scale for Children (MASC),[63,64], and PTSD symptoms were assessed with the Youth Self-Report Form.[65] Child maltreatment was assessed with the Childhood Trauma Questionnaire (CTQ),[66] a 28-item scale that assesses the frequency of maltreatment exposure during childhood and adolescence.[66,67] We summed items from the physical, sexual, and emotional abuse subscales. Community violence exposure was assessed using the Screen for Adolescent Violence Exposure (SAVE),[68] a 32-item measure assessing violence exposure in school, home, and neighborhood contexts. We standardized the CTQ and SAVE scores and summed them to create an index of prior violence exposure.

STATISTICAL ANALYSIS

fMRI Analysis. To identify task-related activity, regressors were created for each phase of the task: instructional cue, stimulus, and rating periods separately for look and decrease trials for neutral and negative stimuli. Using FSL, a general linear model (GLM) was constructed to estimate the association between variation in BOLD signal and task demands across time for each subject, prior to normalization. Using this GLM, individual-level estimates of BOLD activity were identified and submitted to group-level random effects models that contrasted activity across conditions. Here, we focus on neural activity to the emotional stimulus. We report (a) emotional reactivity to negative stimuli (look negative > look neutral trials); and (b) emotion regulation (decrease > look trials for negative stimuli), which are the standard contrasts used in studies of this task (see [35] for a meta-analysis). In the whole brain analysis we corrected for multiple comparisons using cluster-level correction in FSL, which estimates cluster-level significance using Gaussian random field theory; our primary threshold was $P < .001$, as recommended.[69]

We examined task-related activity in five regions of interest (ROIs), selected based on prior evidence for atypical patterns of neural activity to emotional stimuli in individuals with PTSD.[70] ROIs were included if there was significant task-related activation in those regions in the whole-brain analysis. Potential ROIs were the amygdala, hippocampus, dACC, rACC, and vmPFC. We constructed structural ROIs in each participant's native space using in FreeSurfer (Fig. 1). We extracted the average estimate of neural activity within the entire ROI for each participant. For ROIs that met our a priori and task-active criteria, we examined associations with PTSD symptoms following the terrorist attack. Gender, age, and time since scan were included as covariates in all analysis. Finally, we conducted sensitivity analysis to determine whether our results were explained by preexisting internalizing symptoms (depression, anxiety, or PTSD) or exposure to violence by reestimating our final models after controlling for these factors.

RESULTS

NEURAL ACTIVITY AND POSTTRAUMATIC SYMPTOMS

Emotional Reactivity. In whole-brain cluster-level corrected analysis, the amygdala and vmPFC exhibited significantly greater activation during viewing of negative emotional stimuli relative to neutral stimuli. ROI analyses revealed that left amygdala activation, $\beta = .72$, $P = .013$, to negative emotional stimuli was positively associated with posttraumatic symptoms related to the terrorist attack (Fig. 2). No association was observed with right amygdala activation, $\beta = .11$, $P = .78$, or vmPFC activation in either hemisphere, $\beta = .21$–$.41$, $P = .46$–$.15$.

Emotion Regulation. In whole-brain analysis, the hippocampus and vmPFC were recruited during regulation trials relative to trials involving simple viewing of negative stimuli. ROI analyses revealed that hippocampal activation during emotion regulation was negatively related to posttraumatic symptoms, such that lower hippocampal activation in both the right, $\beta = -.78$, $P = .046$, and left hemisphere, $\beta = -.67$, $P = .030$, was associated with higher symptoms (Fig. 3).

SENSITIVITY ANALYSIS

After controlling for preexisting symptoms, the association between amygdala reactivity and posttraumatic symptoms remained significant in the left amygdala, $\beta = .98$, $P = .007$, and became marginally significant in the right amygdala, $\beta = 1.05$, $P = .070$. Hippocampal activation during emotion regulation remained marginally associated with posttraumatic symptoms in the left, $\beta = -.69$, $P = .077$, but not right, $\beta = -.71$, $P = .20$, hemisphere.

Activation in the left amygdala, $\beta = .70$, $P = .019$, during emotional reactivity trials also remained a significant predictor of posttraumatic symptoms after controlling for prior violence exposure. Neural activity during emotion regulation trials remained significantly associated with posttraumatic symptoms in the left hippocampus, $\beta = -.69$, $P = .025$, and marginally in the right hippocampus, $\beta = -.77$, $P = .053$, after controlling for prior violence.

When both internalizing symptoms and prior violence exposure were controlled, amygdala activation was a significant predictor of posttraumatic symptoms in both the left, $\beta = .97$, $P = .009$, and right, $\beta = 1.27$, $P = .027$, hemisphere. Hippocampal activation was no longer associated with posttraumatic symptoms, $\beta = -.66$–$.67$, $P = .14$–$.30$.

DISCUSSION

Trauma exposure is pervasive, yet only a minority of individuals develops PTSD following a traumatic event. Identifying factors associated with PTSD risk is important not only for informing models of disorder etiology but also for improving efforts to target early interventions at trauma-exposed individuals most likely to develop PTSD. Here, we provide novel evidence that amygdala reactivity to negative emotional stimuli, measured prior to a terrorist attack, is associated with

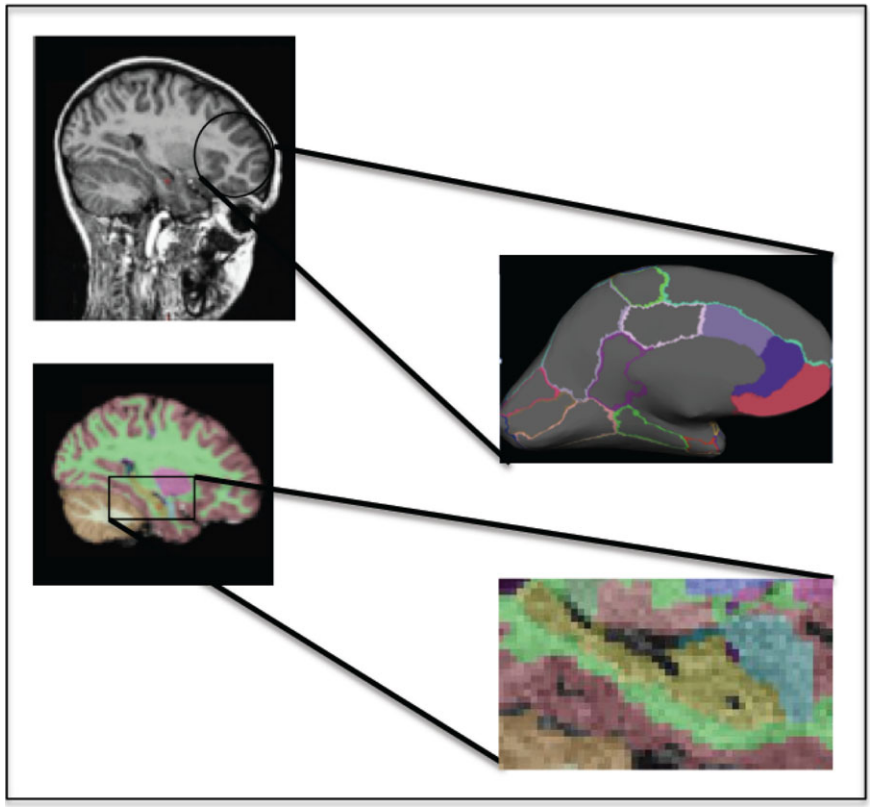
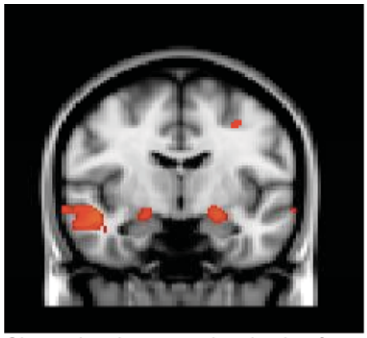


Figure 1. Three regions within medial prefrontal cortex (mPFC) were examined. These included dorsal anterior cingulate cortex (light purple; caudal_acc), rostral anterior cingulate cortex (dark purple; rostral_acc), and ventromedial prefrontal cortex (pink; medial orbitofrontal and frontal pole). All regions of interest are defined anatomically based on the individual's own anatomy using FreeSurfer and shown on the expanded cortical surface for viewing purposes; cortical regions were defined using the 2005 segmentation atlas. Within the subcortex two regions were identified: the amygdala (blue) and hippocampus (yellow). All regions shown here are from individual representative subject's aparc (cortex) and aseg (subcortex) segmentation. Activation during contrasts of interest was extracted from within the entire structure for each ROI.

subsequent onset of posttraumatic symptoms. These findings suggest that amygdala reactivity to negative emotional information might represent a useful marker of PTSD risk.

Heightened amygdala activity in response to threatening or negative emotional stimuli has been observed consistently in individuals with PTSD.[15,17,18,70] However, these studies have been unable to disentangle whether amygdala reactivity is a risk factor for PTSD or a consequence of trauma exposure or PTSD. Our findings suggest that heightened amygdala activity is associated with vulnerability to trauma-related psychopathology. Predeployment amygdala recruitment predicts PTSD symptoms following combat exposure.[25,26] We extend this previous work in several ways. First, we measured posttraumatic symptoms in response to a terrorist attack—an event for which exposure is unpredictable and independent of individual-level characteristics. In military samples, combat exposure is likely to be predicted by genetics and personality characteristics[27,28]; even where service is mandatory, personality factors might shape degree of trauma exposure during combat, meaning that associations between predeployment measures of neural function and PTSD symptoms could reflect associations between neural function and degree of combat exposure. Second, our findings were robust to controls for preexisting internalizing symptoms and prior violence exposure, factors not accounted for in previous military studies. Third, our sample was composed of adolescents, indicating that individual differences in amygdala reactivity are associated with posttraumatic symptoms during the developmental period of highest risk for trauma exposure.[2] Finally, the task we used to assess amygdala response was designed to assess emotional reactivity and regulation in an ecologically valid manner, using realistic stimuli that have parallels to emotional situations encountered in daily life. Together with previous evidence from military samples,[25,26] our findings suggest that amygdala reactivity represents a vulnerability marker for PTSD.

Reduced hippocampal activation during active efforts to reduce negative emotional reactions through cognitive reappraisal predicted higher posttraumatic symptoms related to the attack, although our sensitivity



Cluster-level corrected activation for look negative > look neutral contrast. Amygdala activation in the left but not right hemisphere was significantly associated with PTSD symptoms.

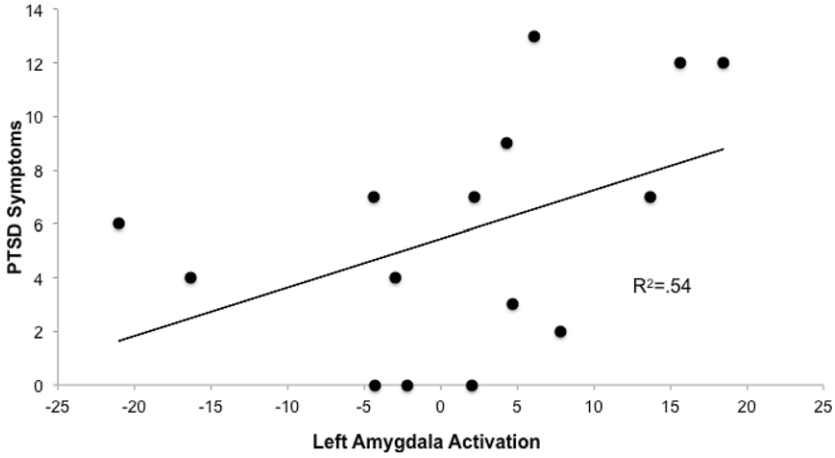
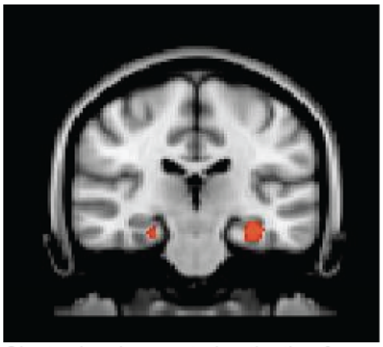


Figure 2. Left amygdala activation for the contrast of look negative > look neutral. Model controls for age, gender, time since scan, and symptoms of depression and anxiety prior to the attack; R^2 represents contribution of amygdala activity over and above these covariates.

analysis suggests that this finding was explained by preexisting internalizing symptoms. Theoretical models of neural function in PTSD argue that disruptions in hippocampal function are a central feature of the disorder.[71,72] Deficits in contextual discrimination and in generalization of extinction learning to novel contexts might contribute to poor contextualization of fear cues and deficits in identifying safety cues in PTSD.[71,72] However, the precise nature of hippocampal deficits in PTSD remains to be elucidated. Previous studies have examined hippocampal function largely within the context of long-term memory tasks, with some reporting reduced activation during encoding and retrieval,[73] and others documenting elevated activation.[74] Our findings suggest that hippocampal response to emotional stimuli might be important to consider in future neuroimaging studies of PTSD.

We found no evidence for an association between mPFC activation during emotional reactivity or regulation trials and posttraumatic symptoms. A variety of deficits in functioning of mPFC regions have been observed in PTSD, including reduced vmPFC activation and elevated dACC activation during fear extinction recall,[14–19] some of which appear to be familial risk factors for PTSD.[20,21] This finding should be interpreted with caution given the small size of our sample and the fact that our task was not designed to assess mPFC function. In addition, because we utilized structural ROIs,



Cluster-level corrected activation for decrease > look negative contrast. Hippocampal activation in both hemispheres was significantly associated with PTSD symptoms.

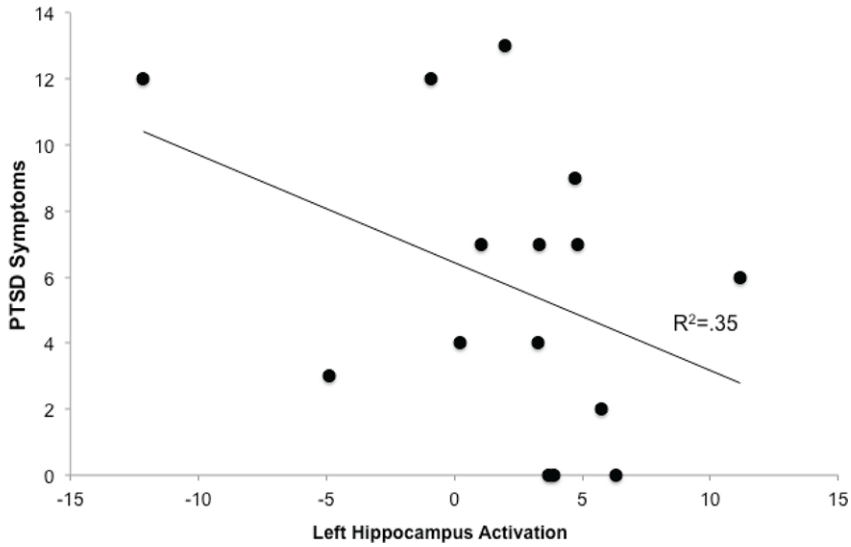


Figure 3. Left hippocampal activation for the contrast of decrease > look negative. Model controls for age, gender, time since scan, and symptoms of depression and anxiety prior to the attack; R^2 represents contribution of hippocampal activity over and above these covariates.

the lack of association could reflect the relatively larger size of cortical than subcortical ROIs.

Study findings should be interpreted in light of several key limitations. Most notably, the number of participants in the study was small. This limitation is particularly important to consider in interpreting null findings. Second, the response rate to the survey was low. This was due largely to parental nonresponse to our e-mail requesting permission to contact their children, and was likely influenced by the short time (2 weeks) in which we actively collected survey responses. Our analysis of selection bias with regard to survey completion suggests that preexisting internalizing symptoms and child maltreatment did not influence the likelihood of responding, but that adolescents with high exposure to community violence were less likely to participate. Third, we were unable to collect follow-up neuroimaging data, which would have allowed us to determine whether exposure to the attacks was associated with changes in neural function. Finally, we assessed posttraumatic symptoms in relation to an event of low severity with regard to objective life threat that no longer qualifies as a Criterion A traumatic event in DSM-5.[75] However, considerable variation in posttraumatic symptoms associated with the event was observed, consistent with prior evidence indicating that terrorist attacks can trigger PTSD symptoms even in individuals who were not directly exposed.[30–33] Moreover, the unique nature of the terrorist attacks at the Boston Marathon and the ensuing manhunt likely resulted in appraisals of perceived threat for youths who were not present at the bombings but were required to stay indoors during the shelter in place order.[76] Nonetheless, future research is needed to replicate the patterns observed here in response to other types of traumatic events.

CONCLUSION

Heightened amygdala reactivity to negative emotional information is associated with future onset of posttraumatic symptoms following a terrorist attack, independent of prior internalizing symptoms—including symptoms of PTSD—and violence exposure. These findings suggest that elevated amygdala reactivity to negative emotional information could represent a neurobiological marker of vulnerability to traumatic stress and, potentially, a risk factor for PTSD.

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