Received: 22 June 2018 | Revised: 20 December 2018 | Accepted: 21 January 2019

DOI: 10.1111/psyp.13349

WILEY PSYCHOPHYSIOLOGY SPR

Transdiagnostic trauma severity in anxiety and mood disorders: Functional brain activity during emotional scene processing

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Funding information
National Institute of Mental Health, Grant/Award Number: MH094386 and MH099078

Abstract

Exposure to traumatic events is not unique to post-traumatic stress disorder (PTSD) and is a significant factor in the development of physical and mental disease across the diagnostic spectrum. Using fMRI, this study assesses functional activation in the amygdala and visual cortex during emotional scene processing in a sample of anxiety and mood disorder patients ($N = 162$). Replicating previous studies with healthy young participants, a strong covariation was found between functional activity in the amygdala and ventral visual cortex, with blood-oxygen-level dependent (BOLD) activity overall significantly enhanced in both regions when viewing emotionally arousing, compared to neutral, scenes. BOLD changes during emotional processing predicted questionnaire reports of experienced trauma and PTSD-like symptoms (e.g., intrusive thoughts, bad dreams, re-experiencing) and associated functional impairment. Patients showing the smallest BOLD changes when viewing emotional (compared to neutral) scenes in the amygdala and ventral visual cortex reported the highest trauma scores, whereas those patients with the largest amygdala emotional reactivity differences reported the lowest trauma scores. Experiencing a life-threatening event (to self or other) that prompts high fear, distress, and functional impairment was associated with reduced functional limbic-visual activity, independent of a PTSD diagnosis. The findings suggest that experienced trauma may be a transdiagnostic vulnerability factor contributing significantly to psychopathology in many patients with anxiety and mood disorders.

KEYWORDS

amygdala, anxiety, fMRI, mood disorders, PTSD, RDoC, trauma, visual cortex

1 | INTRODUCTION

Research with animals has identified dense connectivity between limbic and sensory processing areas, providing evidence that amygdala activation prompts a re-entrant signal to ventral temporal regions, enhancing functional brain activity as organisms confront motivationally relevant stimuli (Amaral, Price, Pitkanen, & Carmichael, 1992; Freese & Amaral, 2006; Shi & Davis, 2001; Spiegler & Mishkin, 1981). Studies with human participants have found similar evidence of enhanced amygdala/inferotemporal coactivation to visual motive cues, measuring blood-oxygen-level dependent (BOLD) activity when participants view emotionally arousing scenes (e.g., Bradley et al., 2015; Frank & Sabatinelli, 2014; Lane, Chua, & Dolan, 1999; Wendt, Weike, Lotze, & Hamm, 2010) or affective facial expressions (Breiter et al.,

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1996; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004).

In a previous study, we assessed BOLD differences in the amgydala and inferotemporal cortex in two groups, one reporting high fear of snakes and a second group reporting low snake fear (Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005). For low fear participants, BOLD changes showed significant covariation between amygdala and inferotemporal cortex, with functional activity in both regions greatest when viewing highly arousing scenes of erotica or mutilated human bodies. Although similar amygdala/inferotemporal covariation was found for fearful participants, BOLD amplitude was uniquely increased in both regions for these high fear participants when viewing pictures of snakes—matching the heightened BOLD activity found for mutilation scenes. A subsequent study using a fast, single slice sampling technique (permitting high frequency sampling of BOLD activity) supported a re-entrant hypothesis that amygdala activation precedes responding in more caudal, visual sensory areas (Sabatinelli, Lang, Bradley, Costa, & Keil, 2009). That is, differences in the amygdala when viewing emotional, compared to neutral, scenes occurred approximately 1 s before these differences were observed in secondary visual cortex.

The present research explores BOLD reactivity in these same amygdalar and visual sensory areas in a large sample of patients with anxiety and mood disorders. Previous studies measuring reflex reactivity (somatic and autonomic) in these patients have reported significant differences in emotional response that are related to diagnosis, comorbidity, and differences in questionnaire-based symptom reports (e.g., Cuthbert et al., 2003; Lang, McTeague, & Bradley, 2016). For example, post-traumatic stress disorder (PTSD) patients presenting with a single traumatic event showed a dramatic increase in psychophysiological measures (skin conductance, startle probe amplitude), relative to controls, when exposed to an aversive, compared to neutral, narrative imagery challenge. PTSD patients who presented with multiple traumatic events, on the other hand, showed a reduced, blunted response (McTeague et al., 2010). Importantly, multiple-trauma PTSD patients also scored higher on questionnaire measures of anxiety, depression, and life dysfunction, had more comorbid disorders, and were judged clinically to have a more severe disorder and poorer treatment prognosis.

In a recent review, Hughes and Shin (2011) consider a number of fMRI studies that compared brain function in PTSD patients and healthy controls. Amygdala activation is a common target in this research, and picture stimuli—scenes or faces, emotionally arousing or neutral—are often the emotional challenge employed. The findings in these studies are mixed, however, with some studies reporting greater BOLD changes in the amygdala for unpleasant scenes (Felmingham et al., 2010; Rauch et al., 2000), whereas others do not find differences in aversive processing, when compared to functional activity for neutral stimuli (Brunetti et al., 2010; Hendler et al., 2003). Interestingly, previous PTSD studies using pictures have primarily emphasized the amydala's connections to frontal regions (e.g., insula, prefrontal cortex) and generally have not explored connections to visual system processing, which is the focus of the current study.

Traumatic events are, of course, not unique to PTSD, and previous research suggests that trauma exposure is frequently involved in other internalizing disorders, for example, in depression (Starr & Moulds, 2006), social anxiety (Wild, Hackmann, & Clark, 2008), and panic disorder (Bandelow et al., 2002). As highlighted in diathesis stress models (e.g., Belsky & Pluess, 2009; McEwen, 2017), exposure to stressful events is a significant factor in the development of physical and mental disease across the diagnostic spectrum. Thus, our research follows the NIMH Research Domain Criteria (RDoC) initiative: "To explore potential dimensional, biological measures of psychopathology, unconstrained by current diagnostic categories" (e.g., Insel & Cuthbert, 2015).

Participants include a broad range of patients diagnosed with anxiety/mood and related internalizing disorders, and functional brain activity is measured in the context of emotional picture viewing, focusing on BOLD activity in the amygdala and ventral visual cortex. Brain indices of emotion and sensory processing are measured as patients and healthy controls view a series of emotionally arousing (unpleasant or pleasant) or neutral pictures, using a rapid serial visual presentation (RSVP) paradigm in which multiple exemplars of the same content (e.g., violence) are presented rapidly, at the rate of 18 scenes in 6 s (333 ms each). Previous studies have confirmed that rapid presentation prompts a similar pattern of BOLD activity in visual cortex as do slower rates (Junghofer et al., 2006) and was utilized here to provide a broader set of affective cues in a briefer time frame than is possible with a single, longer duration picture presentation.

The Posttraumatic Diagnostic Scale (Foa, 1996; Foa, Cashman, Jaycox, & Perry, 1997), which measures trauma frequency, severity, symptomology, and interference in life function, was used to measure trauma exposure. The project's research aims are to determine if functional brain activity (a) in the amygdala and inferotemporal cortex BOLD changes in this patient sample show, overall, the same pattern of covariation and affective modulation that was previously found when young, healthy participants viewed pictures; (b) differs for anxiety/mood disorder patients and healthy controls, varying in amplitude with questionnaire reports of trauma experience; (c) relates to additional psychopathology factors of negative affect (anxiety and depression) and/or anxious arousal; and (d) relates to differences in clinician-determined diagnosis, comorbidity, transdiagnostic severity, and treatment prognosis.

2 | METHOD

2.1 | Participants

The participants were 162 patients evaluated for treatment at the University of Florida Fear and Anxiety Disorders Clinic and 35 healthy controls who did not differ in mean age, gender distribution, or level of education (see Table 1). A structured clinical interview (Anxiety Disorder Interview Schedule IV, Brown, DiNardo, & Barlow, 1994) was conducted to establish DSM-IV (American Psychiatric Association, 1994) primary and comorbid diagnoses, and patients responded to a battery of psychopathology questionnaires 1 month, on average, before the fMRI session. The University of Florida Institutional Review Board (IRB-01) approved the study procedures, and participants provided informed consent before assessment.

2.2 | Rapid serial visual presentation

Each 6-s trial presented 18 pictures at the rate of three per second (i.e., 333 ms each) in a rapid stream (see Figure 1). The 18 pictures presented on each trial were of the same content and depicted either erotica, families, neutral objects, neutral people, contamination, or violence; each 6-s trial was separated by a variable intertrial interval of 9 or 12 s. Each set of 18 scenes was presented three times in a distributed fashion (e.g., all six contents were presented before repeating), which resulted in a total scan time of approximately 5 min. Pictures were selected from the International Affective Picture System[1] (IAPS, Lang, Bradley, & Cuthbert, 2008) and presented in grayscale. Of the 108 scenes (18 pictures × 6 contents), all participants saw the same set of 90 pictures, consisting of 15 pictures for each of the six contents, with an additional 18 scenes (three per content) that were presented to approximately half of the participants, and a different set of 18 presented to the other half, in order to counterbalance whether a scene was new or old in a later acquisition.[2]

Twelve different orders were constructed that varied, across participants, the serial position in which of the six contents were presented across the study, as well as the order of specific scenes within each 6-s stream. Thus, across both repetitions and participants, pictures were presented in different orders.

2.3 | fMRI: data collection, preprocessing, and analysis

Data were collected in a 3T Philips scanner with a 32-channel head coil. The scanning sequence began with acquisition of a 160-slice sagittal scout set using a standard T1-weighted fast-field echo sequence. Functional volumes were 53 3.5-mm coronal slices acquired using a T2*-weighted echo planar imaging sequence with a 3,000 ms TR, 30 ms TE, 90-degree flip angle, 72 × 72 acquisition matrix, and 180 mm FOV (2.5 × 2.5 in-plane voxel resolution). Offline, the functional data were slice-time adjusted, motion corrected, spatially smoothed (5.0 mm FWHM Gaussian kernel), and converted to percent BOLD signal change (for each voxel across the entire time series) using the Analysis of Functional Neuroimages software (AFNI, Cox, 1996).

For each individual, the hemodynamic time series was deconvolved using a 15-s cubic spline response function for each emotional content (6), together with motion (6) and baseline drift (5) parameters. The resulting impulse response function for each picture content was spatially normalized and resampled to a 2.5-mm isotropic voxel size, and values from 6–12 s postpicture onset were averaged (i.e., TR 2, 3, 4) for each voxel, content, and participant. Then, a whole brain analysis across participants was conducted that compared BOLD activity when viewing emotional (i.e., averaging erotica, families, contamination, threat) and neutral scenes (i.e., averaging neutral objects, neutral people) in eight axial slices (20 mm) covering three regions of interest (ROI) including the amygdala, inferotemporal, and occipital cortex. The resulting t values were thresholded at $q < 0.001$ (false discovery rate) and a cluster size of 50 voxels. For each participant, differences in functional activity were averaged across all significant voxels in each ROI where a significant enhancement was found during emotional, compared to neutral, picture viewing.

[1] IAPS (Lang et al., 2008) catalog numbers for each content are—erotic: 4,597, 4,599, 4,624, 4,626, 4,641, 4,647, 4,658, 4,659, 4,660, 4,664, 4,668, 4,669,4,670, 4,680, 4,681, 4,687, 4,693, 4,694, 4,698, 4,800, 4,810 (pleasure: $M = 6.76$; $SD = 0.44$; arousal: $M = 6.35$; $SD = 0.55$); families: 2,040, 2,045, 2,057, 2,058, 2,070, 2,071, 2,080, 2,151, 2,152, 2,155, 2,158, 2,160, 2,224, 2,311, 2,340, 2,341, 2,345, 2,347, 2,391, 2,398, 2,655 (pleasure: $M = 7.56$; $SD = 0.43$; arousal: $M = 4.84$; $SD = 0.40$); neutral objects: 2,514, 5,120, 5,395, 5,510, 5,530, 7,026, 7,030, 7,032, 7,040, 7,050, 7,057, 7,100, 7,130, 7,140, 7,160, 7,190, 7,234, 7,235, 7,500, 7,700, 7,710 (pleasure: $M = 5.03$; $SD = 0.40$; arousal: $M = 3.13$; $SD = 0.39$); neutral people: 2,032, 2,036, 2,101, 2,102, 2,190, 2,200, 2,210, 2,215, 2,305, 2,308, 2,312, 2,359, 2,374, 2,377, 2,390, 2,393, 2,400, 2,411, 2,441, 2,590, 2,595 (pleasure: $M = 4.95$; $SD = 0.70$; arousal: $M = 3.49$; $SD = 0.46$); contamination: 1,275, 1,280, 2,446, 2,720, 7,359, 7,380, 8,230, 9,008, 9,031, 9,042, 9,140, 9,180, 9,182, 9,291, 9,301, 9,302, 9,320, 9,322, 9,325, 9,373, 9,832 (pleasure: $M = 3.06$; $SD = 0.83$; arousal: $M = 5.04$; $SD = 0.69$); violence: 1,026, 1,114, 1,205, 1,300, 1,303, 1930, 1932, 3,000, 3,051, 3,069, 3,120, 3,130, 3,150, 3,261, 3,500, 6,230, 6,243, 6,250, 6,550, 9,909, 9,921 (pleasure: $M = 2.74$; $SD = 0.97$; arousal: $M = 6.46$; $SD = 0.57$).

[2] For the first cohort of participants (approximately 80), a later recognition test assessed memory performance following RSVP presentation. These data are not presented here.

TABLE 1 Diagnostic and demographic information of anxiety/mood disorder sample and healthy controls

Principal diagnosis	*N*	# Female	Age (*SD*)	# Caucasian	# College graduate
Social phobia	55	24	27 (11)	43	26
Generalized anxiety disorder	32	26	28 (9)	27	18
Post-traumatic stress disorder	13	12	34 (14)	8	0
Mood disorder[a]	12	9	37 (16)	5	2
Specific phobia	11	8	33 (16)	9	3
Panic disorder[b]	10	7	27 (9)	7	2
Other[c]	29	14	38 (13)	25	17
All patients	162	124	31 (13)	124	87
Controls	35	24	34 (16)	24	19

[a]Includes patients diagnosed with major depressive disorder or dysthymia. [b]Includes patients both with and without agoraphobia. [c]Includes anxiety not otherwise specified ($N = 7$), obsessive-compulsive disorder ($N = 4$), adjustment disorder ($N = 4$), personality disorder ($N = 7$), substance abuse ($N = 2$), disorder of written expression ($N = 1$), hypochondriasis ($N = 1$), dysphoric disorder ($N = 1$), trichotillonamia ($N = 1$), and insomnia ($N = 1$).

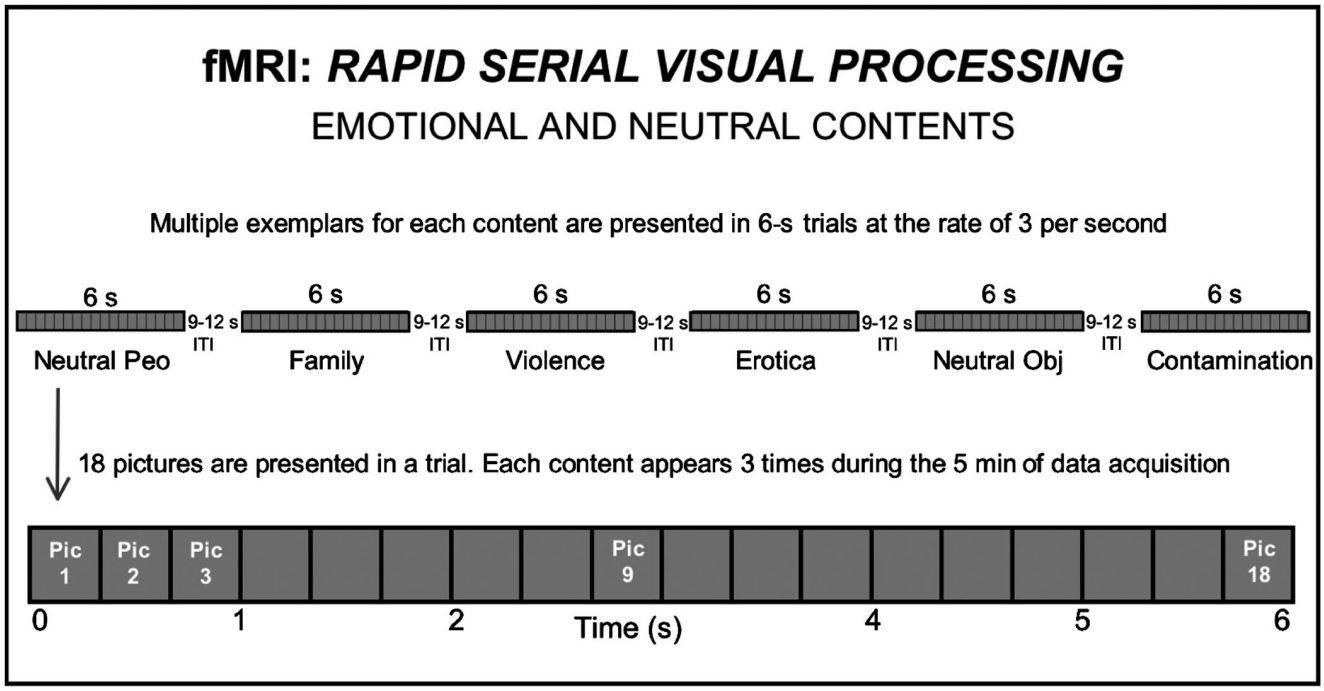

FIGURE 1 The RSVP paradigm used during fMRI acquisition. ITI = intertrial interval

2.4 | Psychopathology assessment

Questionnaires measuring anxiety and depression included the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), the State-Trait Anxiety Inventory (STAI; Speilberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), the Illness Intrusiveness Rating Scale (IIRS; Bieling, Rowa, Antony, Summerfeldt, & Swinson, 2001), the Panic and Agoraphobia Scale (PAS; Bandelow, 1995), and the Mood and Anxiety Symptoms Questionnaire (MASQ; Watson et al., 1995). The Posttraumatic Diagnostic Scale (PDS; Foa, 1996; Foa et al., 1997) was used to measure trauma, in which participants report the (a) number and types of trauma experienced, and, for the most severe trauma only (b) severity, indexed by whether life was endangered (self or other) and degree of terror/helplessness; (c) experienced symptoms; and (d) degree of interference in various aspects of life functioning. For the current sample of patients, the trauma experience identified as most severe was most frequently a naturally occurring life event (e.g., life-threatening illness, accident, natural disaster, etc.; 72%) or assault (sexual and nonsexual, 28%).

Following previous research (Cuthbert et al., 2003; Lang et al., 2016), scores on each questionnaire[3] were standardized across the patient sample and submitted to a principal component analysis on the correlations, followed by varimax rotation, which produced three factors (see Table 2) with eigenvalues greater than 1, including a factor of (a) negative affect (35% of variance; high loadings for BDI, STAI, and MASQ subscales of depressed mood and anhedonic depression), (b) anxious arousal (20% of variance; high loadings for PAS and MASQ subscales of anxious arousal and anxious mood), and (c) trauma exposure (19% of variance; high loadings for all four subscales of the PDS).

Primary analyses assessed functional brain activity in the amygdala, inferotemporal, and occipital visual cortex, as it varied with the three psychopathology factors of negative affect, anxious arousal, and trauma. In addition, the relationship of BOLD activity to individual trauma factor subscales—number of post-traumatic events, severity, symptomology, and functional interference—were assessed to provide more detailed information regarding effects of these variables.

3 | RESULTS

3.1 | Emotional reactivity in the amygdala and ventral visual cortex

As Figure 2 illustrates, three regions in the axial slice selection prompted functional activity that was significantly enhanced when viewing emotional, compared to neutral, scenes, replicating previous studies (e.g., Sabatinelli et al., 2005, 2009). Emotional pictures (either pleasant or unpleasant) prompted enhanced functional activity in the amygdala, $F(1, 161) = 105.1$, $p < 0.0001, \eta_p^2 = 0.40$, inferotemporal cortex, $F(1, 161) = 130.3$, $p < 0.0001$, $\eta_p^2 = 0.45$, and inferior occipital gyrus, $F(1, 161) = 89.3$, $p < 0.0001$, $\eta_p^2 = 0.36$, which is illustrated in the accompanying BOLD waveforms in Figure 2 (right).

Functional activity in the calcarine fissure, on the other hand, was uniformly enhanced, as previously reported for healthy participants (Sabatinelli et al., 2009), showing no difference as a function of hedonic content, $F(1, 161) < 1$, $p = 0.74$; mean functional activity = 1.07 and 1.08 for emotional and neutral scenes, respectively (see Figure 2, bottom right). Because BOLD differences in the two visual processing regions—inferotemporal cortex and inferior occipital gyrus—were highly correlated, $r = 0.93$, $F(1, 160) = 1{,}036.1$, $p < 0.0001$, functional activity in these regions was averaged into a single region comprising ventral visual cortex (see Table 3).

BOLD changes when viewing emotionally engaging pictures in the amygdala and the ventral visual cortex showed a strong positive correlation, $r = 0.62$, $F(1, 160) = 102.3$, $p < 0.0001$, replicating previous studies with healthy participants (Sabatinelli et al., 2005, 2009). To identify patients who varied in amygdala reactivity, the difference in BOLD activity when viewing emotional compared to neutral pictures was used to divide patients into successively increasing quintiles ($Ns = 32, 33, 33, 32, 32$). As illustrated in Figure 3 (center), functional activity in the ventral visual cortex shows a strong covariation with amygdala quintile, with increasing BOLD differences in ventral visual cortex as amygdala emotional activity increases. The correlation between emotional reactivity differences in the amygdala and ventral visual cortex was high ($r = 0.99$), and, as illustrated in Figure 3, BOLD differences in emotional reactivity in the amygdala (left) and ventral visual cortex (right) are similar in both regions for participants in each amgydala quintile.

As Figure 4 (inset) illustrates, functional activity in the amygdala significantly increased across quintiles when viewing unpleasant, $F(4, 57) = 11.8$, $p < 0.0001$, linear $p < 0.0001$, or pleasant scenes, $F(4, 157) = 5.0$, $p = 0.001$, linear $p < 0.0001$, and significantly decreased across quintiles when viewing neutral contents, $F(4, 157) = 28.1$, $p < 0.0001$, linear $p < 0.0001$, prompting the least difference in amygdala emotional activity for those in the first quintile and the greatest difference for those in the fifth quintile.

3.2 | Psychopathology factors and BOLD activity during emotional picture viewing

Variation in the amplitude of BOLD activity in the amygdala when viewing emotional scenes was did not vary as a function of either negative affect, $F(1, 160) < 1$, $p = 0.77$, or anxious arousal, $F(1, 160) < 1$, $p = 0.81$. Across amygdala emotional reactivity quintiles, neither of these factor scores (and no individual questionnaire loading on these factors) was significantly different. Similarly, for activity in the visual cortex, neither negative affect, $F(1, 160) = 1.48$, $p = 0.22$, nor anxious arousal, $F(1, 160) = 1.29$, $p = 0.26$, were related to emotional differences in BOLD activity.

Heightened functional activity in the amygdala for emotional, compared to neutral, scenes, however, varied significantly with the trauma factor, $r = -0.23$, $F(1, 160) = 8.9$, $p = 0.003$. As illustrated in Figure 4, for patients in the first quintile, who showed the least difference in amgydala activity when viewing emotional scenes, trauma factor scores were dramatically high, whereas patients in the fifth quintile, who were the most emotionally reactive, had the lowest trauma scores. The bivariate correlation between BOLD changes (emotional minus neutral) at each quintile and the trauma factor scores show a strong inverse relationship between amygdala emotional reactivity and reported trauma, $r = -0.91$ (see Figure 4). Consistent with the tight coupling between functional activity in the amygdala and the ventral visual cortex, BOLD activity when viewing emotional, compared to neutral, scenes

[3] Data for eight of the162 participants who were missing either specific items or questionnaires were imputed using the MICE package (van Buuren & Groothuis-Oudshoorn, 2011). Results are identical if these eight participants are omitted from analyses.

TABLE 2 Questionnaire scores (mean and standard error) for healthy controls and patients, and the highest loadings for each of the three significant psychopathology factors (in bold) of negative affect, anxious arousal, and trauma

	Controls	Patients			
Questionnaire	**Mean (*SE*)**	**Mean (*SE*)**	**Negative affect**	**Anxious arousal**	**Trauma**
Beck Depression Inventory-II	4.4 (1)	18.3 (0.9)*	**0.85**	0.25	0.20
Trait anxiety (STAI)	30.5 (1.5)	52.7 (1)*	**0.86**	0.28	0.09
Illness intrusiveness scale	19.5 (1.6)	47.4 (1.6)*	**0.70**	0.37	0.22
MASQ: mixed symptoms	24.5 (1.4)	40.3 (1)*	**0.71**	0.53	0.15
MASQ: depressed mood	18 (1)	32.6 (0.9)*	**0.82**	0.33	−0.03
MASQ: anhedonia	50.2 (2)	71.4 (1.2)*	**0.87**	0.12	−0.02
MASQ: anxious mood	15.3 (0.8)	25.5 (0.7)*	0.46	**0.77**	0.02
MASQ: anxious arousal	19.4 (0.6)	29.4 (0.9)*	0.38	**0.80**	0.15
Panic and agoraphobia scale	1.9 (0.7)	13.1 (0.8)*	0.23	**0.77**	0.22
PDS: number of traumatic events	2.2 (0.3)	2.4 (0.1)	−0.09	0.12	**0.79**
PDS: trauma severity	2.6 (0.3)	2.5 (0.1)	−0.09	0.25	**0.65**
PDS: PTSD symptoms	3.2 (1.2)	11.2 (1)*	0.28	0.08	**0.81**
PDS: functional impairment	0.7 (0.2)	2.2 (0.2)*	0.33	−0.06	**0.78**

Note. MASQ = Mood and Anxiety Symptoms Questionnaire; PDS = Posttraumatic Diagnostic Scale.
*Group difference between patients and controls significant at $p < 0.01$.

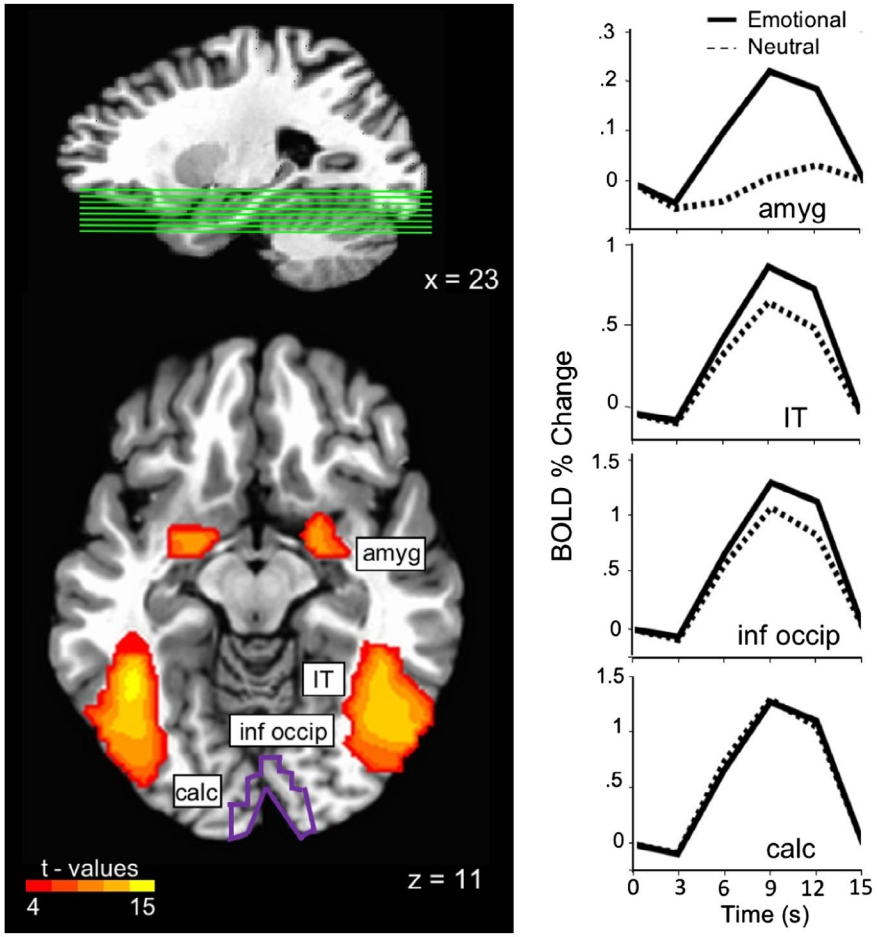

FIGURE 2 Left—Top: Sagittal image illustrates the slice selection that covers the regions of interest. Bottom: Axial slice illustrates regions (filled) in which functional activity was enhanced when viewing emotional, compared to neutral, scenes and included the amygdala, inferotemporal (IT) cortex, and inferior occipital cortex. In calcarine cortex (unfilled), functional activation did not vary by picture content. Right—BOLD waveforms illustrating functional activity when viewing emotional (unpleasant or pleasant), compared to neutral, scenes averaged over significant voxels in each region

TABLE 3 Cluster size, peak voxel location (Talairach space), and BOLD change for regions of interest in the selected slices

Brain region	Cluster size	% Δ pleasant	% Δ neutral	% Δ unpleasant	+ L + P + I	*t*
Amygdala	110	0.13	−0.001	0.22	−19 4 9	9.3
Inferotemporal cortex	809	0.74	0.55	0.75	41 49 11	15.6
Inferior occipital gyrus	298	1.07	0.84	1.02	41 54 9	12.8
Calcarine gyrus	182	1.06	1.07	1.07		

Note. Coordinates identify the peak voxel and its *t* value in each region.

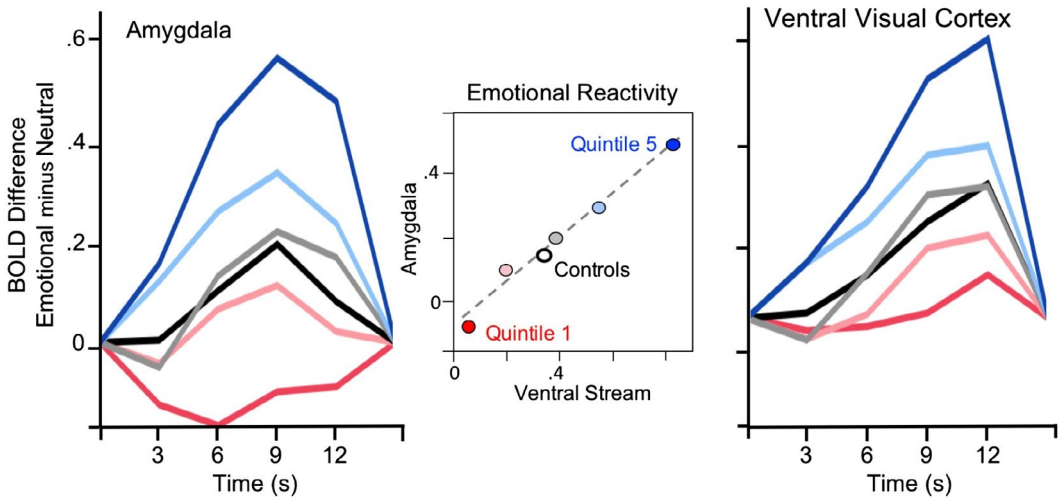

FIGURE 3 Left: BOLD difference waveforms (emotional minus neutral) in the amygdala are plotted for the patient groups in each amygdala emotional reactivity quintile, and healthy controls. Right: BOLD difference waveforms (emotional minus neutral) in ventral visual cortex for the patient groups in each amygdala emotional reactivity quintile, and healthy controls. Center: Mean BOLD difference (emotional minus neutral) in the amygdala and ventral visual stream for the patient groups in each amygdala emotional reactivity quintile, and healthy controls. Quintile 1 = dark red; Quintile 2 = pink; Quintile 3 = gray; Quintile 4 = light blue; Quintile 5 = bright blue; healthy controls = black

in the visual regions was also significantly associated with the trauma factor, $r = -0.15$, $F(1, 160) = 3.90$, $p = 0.049$.

When the relationship between the individual scales of the PDS and emotional activity in amygdala was assessed, three subscales—the number of traumatic events, trauma severity, and functional impairment—showed significant linear correlations, with higher scores associated with the smallest differences in amygdala activity when viewing emotional, compared to neutral, scenes, Fs(1, 160) = 5.2, 13.7, and 5.4, respectively, $ps < 0.05$. When individual PDS subscales scores were assessed over amygdala quintiles (see Table 4), trauma severity differed significantly, $F(4, 157) = 3.2$, $p = 0.01$.

3.3 | Demographic differences in trauma and BOLD activity

Not surprisingly, trauma factor scores increased with age, $F(1, 160) = 27.2$, $p < 0.0001$, and were slightly higher for women, $F(1, 160) = 6.9$, $p = 0.01$. However, age and gender were not related to BOLD differences in emotional reactivity in either the amygdala (gender: $F(1, 160) < 1$, $p = 0.70$; age: $F(1, 160) < 1$, $p = 0.39$), or the ventral visual cortex (gender: $F(1, 160) < 1$, $p = 0.24$; age: $F(1, 160) < 1$, $p = 0.96$).

3.4 | Clinical diagnosis, assessed severity, and control subjects

Trauma factor scores increased with the incidence of comorbid disorders, $r = 0.17$, $F(1, 160) = 4.8$, $p = 0.03$, as well as with the clinician's judgment of disorder severity, $r = 0.19$, $F(1, 116) = 14.99$, $p < 0.001$. However, neither of these measures predicted differences in BOLD changes when viewing emotional scenes in either the bilateral amygdala or ventral visual cortex. Table 5 shows that the principal DSM-IV diagnoses for patients were widely distributed across the amygdala quintiles of emotional reactivity, with a similar proportion of patients diagnosed with each disorder in each quintile, χ^2 (24, $n = 162$) = 18.7, $p = 0.77$. The possible influence of treatment medications on the BOLD differences was also assessed, resulting in no significant effects.[4]

[4] Thirty-one of the 162 patients reported recurrent use of psychotropic medication. Most frequently, these were selective serotonin reuptake inhibitors (50%), serotonin and/or norepinephrine reuptake inhibitors (22%). No differences emerged between medicated and nonmedicated patients in emotional reactivity indexed by BOLD changes when viewing emotional, compared to neutral, scenes in the amygdala, $F(1, 160) = 1.09$, $p = 0.30$.

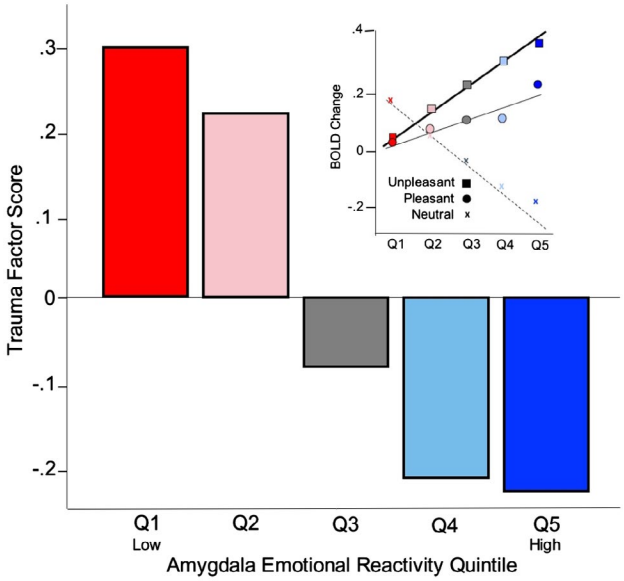

FIGURE 4 Mean trauma scores for anxiety and mood disorder patients covary inversely across amygdala emotional reactivity quintiles, such that those showing the least emotional discrimination in the amygdala report the highest trauma. Inset: Functional activity increases across amygdala emotional reactivity quintiles when viewing either pleasant or unpleasant scenes and decreases when viewing neutral scenes

Healthy control participants had significantly lower scores than patients on all individual questionnaires loading on the negative affect and anxious arousal factors (see Table 2; all p values < 0.01). And, whereas scores on the number of experienced traumas and reported severity did not differ for patients and controls, patients reported more subsequently experienced distress that included greater PTSD symptomology, $F(1, 195) = 12.8$, $p < 0.001$, and more functional impairment, $F(1, 195) = 9.3$, $p < 0.01$ (see Table 2). As illustrated in Figure 3, in both the amygdala and the ventral visual cortex, emotional reactivity for healthy controls was significantly larger than for the most distressed patients in the first quintile (ps < 0.05) and significantly smaller than patients scoring lowest on the trauma factor in the fourth (ps < 0.05) and fifth quintiles (ps < 0.05).

4 | DISCUSSION

For anxiety and mood disorder patients overall, BOLD changes during the RSVP picture task closely paralleled patterns observed in previous studies investigating functional activity during scene processing in healthy participants (e.g., Bradley et al., 2003; Lang et al., 1998; Sabatinelli et al., 2005, 2009). Thus, enhanced BOLD activity was found when participants viewed emotional, compared to neutral, scenes in the amygdala and in inferotemporal and inferior occipital cortex. When individual differences among patients were examined, however, BOLD activity in both the amygdala and ventral visual cortex covaried significantly with trauma: Patients showing the least amygdala discrimination among scenes (emotional minus neutral) reported the highest trauma scores, whereas those showing the largest BOLD differences in the amygdala had the lowest trauma scores.

Additional psychopathology factors of negative affect and anxious arousal that were previously found to relate to psychophysiological reactivity (Cuthbert et al., 2003; Lang et al., 2016) did not covary with BOLD changes in the amygdala or ventral visual cortex during emotional scene viewing. Furthermore, the principal diagnoses of patients were broadly distributed across amygdala emotional reactivity quintiles, with no discernible pattern, suggesting that differences in functional activity in the amygdala were unrelated to nomothetic diagnostic categories. And, although both the incidence of comorbid disorders and clinician-judged increase in disorder severity were related to trauma scores, neither of these measures was directly related to differences in functional brain activity in either the bilateral amygdala or ventral visual cortex when viewing emotional scenes.

In the amgydala, BOLD changes when viewing emotionally arousing (pleasant or unpleasant), compared to neutral, scenes increased linearly across the five quintiles and was least in amplitude for those with the highest trauma scores and greatest for the least distressed patients. This finding is analogous to psychophysiological reactions measured during trauma imagery in PTSD patients (Lang et al., 2016; McTeague et al., 2010), in which reduced or "blunted"

TABLE 4 Posttraumatic diagnostic scale (PDS) scores (and standard deviation) for each of the quintiles defined by the difference in functional activity in the amygdala when viewing emotional, compared to neutral, scenes

Posttraumatic diagnostic scale (PDS)	Amygdala emotional reactivity					Group comparison
	Q1	Q2	Q3	Q4	Q5	
Number of traumatic events	2.9 (2.0)	2.5 (1.4)	2.6 (2.1)	1.8 (1.5)	2.0 (1.8)	$F(4, 157) = 2.08$ $p = 0.09$
Trauma severity	3.2 (1.4)	2.8 (1.9)	2.4 (1.8)	1.8 (1.6)	2.2 (1.5)	$F(4, 157) = 3.02$ $p = 0.01$
PTSD symptoms	13.6 (16.0)	12.6 (11.2)	8.0 (11.0)	10.9 (12.7)	11.0 (13.2)	$F(4, 157) < 1$ $p = 0.48$
Functional impairment	2.6 (2.6)	3.1 (3.4)	1.8 (2.9)	2.2 (3.0)	1.3 (2.2)	$F(4, 157) = 1.86$ $p = 0.12$

Note. Q1–Q5: least to greatest difference in functional activity.

TABLE 5 Number/proportion of patients with the same principal diagnosis (DSM-IV) in each of the amygdala reactivity quintiles

Principal diagnosis	Q1 *n*/%	Q2 *n*/%	Q3 *n*/%	Q4 *n*/%	Q5 *n*/%
Social phobia	13/41	10/31	9/28	14/44	9/28
Generalized anxiety disorder	4/13	10/31	7/22	2/6	9/28
Post-traumatic stress disorder	3/9	3/9	2/6	2/6	3/9
Mood disorder	2/6	2/6	5/16	3/9	0
Specific phobia	2/6	2/6	1/3	4/13	2/6
Panic disorder	2/6	1/3	2/6	2/6	3/9
Other	6/19	5/16	7/22	5/16	6/19

Note. Quintiles are ordered from least (Q1) to greatest (Q5) difference in functional activity when viewing emotional, compared to neutral, scenes in the amygdala.

psychophysiological reactions were found in patients reporting multiple trauma experiences and high severity of disorder. Importantly, several previous fMRI studies have reported reduced BOLD activity when viewing emotionally engaging pictures that are similar to the findings reported here. Thus, Brunetti and colleagues (2010) assessed reactivity in the amygdala for PTSD or non-PTSD victims of a bank robbery, in which participants viewed blocked trials of emotionally unpleasant and neutral scenes. For the non-PTSD victims, BOLD changes in the amygdala when viewing unpleasant, compared to neutral, scenes were enhanced; whereas, for PTSD patients, amygdala BOLD activity did not differ as a function of hedonic content but was equivalent whether unpleasant or neutral scenes were presented. Hendler et al. (2003) reported a similar finding for veterans viewing combat and noncombat pictures, in which functional activity in the amygdala did not differ as a function of the emotional content of the visual stimuli for those diagnosed with PTSD.

The current data are not only consistent with these findings but indicate that, in general, trauma experience is associated with blunted functional activity in both the amygdala and visual cortex when processing emotional, compared to neutral, scenes. In addition, for the patients reporting the greatest trauma severity, BOLD changes when viewing neutral scenes were significantly elevated compared to patients reporting the least trauma, confirming a lack of emotional discrimination. This pattern of functional activation is consistent with Mueller-Pfeiffer et al. (2013) who found a reduction of BOLD activity specifically in ventral visual cortex for PTSD patients, prompting them to make the interesting suggestion that "the observed deficits in sensory processing might explain difficulties that PTSD patients have with complex sensory environments, even in the absence of emotional interference" (p. 536).

Moreover, the current data suggest that a deficit in visual sensory processing—a failure to discriminate motivational cues—is not limited to PTSD but, instead, is present across the spectrum of internalizing disorders and is not limited to aversive stimuli but is also found for appetitive cues. Given the strong covariation between functional activation in the amygdala and ventral visual cortex observed here, together with data supporting re-entrant amygdala-visual processing (Sabatinelli et al., 2009), the deficits in visual cortical processing found for those exposed to trauma could reflect effects of chronic stress on amygdala circuitry or function (McEwen, 2017; Vyas, Miltra, Shankaranarayana Rao, & Chattarji, 2002) or, alternatively or in addition to, HPA axis dysfunction (Ross, Foster, & Ionescu, 2017).

The number of reported traumas, trauma severity, and functional impairment were all significantly related to amygdala emotional reactivity. Moreover, the trauma severity subscale, which reports whether the traumatic event directly endangered life (one's self or another), accounted for significant variance in the emotional picture-driven BOLD activity across amygdala quintiles. This finding is relevant to issues raised in the development of DSM-5 criteria for PTSD (Adler, Wright, Bliese, Eckford, & Hoge, 2008) in which trauma severity was dropped as a primary measure of PTSD diagnosis, judging that it might exclude individuals (especially military personnel) who met all other criteria. A second justification for dropping the severity measure was that a subjective response did not "add predictive ability to the objective definition" (e.g., Pai, Suris, & North, 2017). The significant covariation of the trauma severity scale with an objective measure of brain physiology in the current data set merits clinical consideration in future patient evaluations.

Patients and healthy control participants did not differ on trauma scales that assessed the individual's exposure to, or severity of, experienced trauma but did differ substantially in reported incidence of subsequent PTSD symptomology as well as functional impairment, confirming that not all who experience an intense traumatic experience develop PTSD. Thus, perhaps not surprisingly, it is measures of trauma sequelae occurring after a similarly extreme traumatic exposure that discriminated between patients and healthy controls. For measures of subsequent PTSD symptoms, including re-experiencing, intrusive thoughts, bad dreams, etc., as well as reports of functional life impairment, patients reported significantly greater distress than controls.

The sample of anxiety and mood disorder patients in the present study were a subset of a larger group who participated in a variety of laboratory procedures (e.g., Lang et al., 2017); unfortunately, only half of the anxiety and mood disorder patients were willing to enter the MRI scanner. Thus, the sample may be somewhat biased toward less avoidant anxiety patients and perhaps accounts for the lack of relationship between functional brain activity and the underlying psychopathology factors of negative affect and/or anxious arousal. Furthermore, eye movements were not monitored during the fMRI session, and eye closure (despite instructions to the contrary) could conceivably have contributed to the results. Against this possibility is the finding of high amplitude BOLD changes in primary striate cortex (i.e., calcarine gyrus) during picture viewing that was equivalent for emotionally engaging and neutral scenes and, importantly, did not vary across patients in each of the amygdala reactivity quintiles.

In summary, transdiagnostic effects of trauma in the anxiety and mood disorders have not been extensively investigated in the past, due in part to the dominance of an earlier paradigm that emphasized the targeting of specific DSM disorders. With the encouragement of the RDoC initiative, however, studies exploring how specific dimensional factors relate to differences in neural, biological, and psychophysiological systems are discovering commonalities across patients in different diagnostic categories that suggest not only new classification schemes but may also help develop new treatment interventions. In the current study, functional brain activity in the amgydala-ventral visual cortex circuit was disrupted during emotional processing, both for pleasant and unpleasant cues, and this deficit covaried transdiagnostically with patients' reports of the frequency and severity of experienced trauma and the subsequent development of PTSD symptoms and functional impairment. Trauma and their sequelae are clearly an important environmental vulnerability factor that may play a causal, significant contributory role in the dysfunctional emotional processing found across the anxiety and mood disorders.

ACKNOWLEDGEMENTS

Thanks to Drs. Cyd Strauss and Evelyn Sullivan for conducting and supervising the clinical assessments, to Vanessa Dominguez and Charlesynquette Duncan for patient contact and data entry, to Sherry Zhou for assistance with questionnaire scoring, and to Christopher Sege, Robert Henderson, and Mathias Weymar for assistance in data acquisition. David Herring is now at Murray State University, Murray, KY. This research was supported by NIMH grants MH094386 and MH098078 to P.J.L.

REFERENCES

Adler, A. B., Wright, K. M., Bliese, P. D., Eckford, R., & Hoge, C. W. (2008). A2 diagnostic criterion for combat-related posttraumatic stress disorder. *Journal of Traumatic Stress*, *21*(3), 301–308. https://doi.org/10.1002/jts.20336

Amaral, D. G., Price, J. L., Pitkanen, A., & Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In J. P. Aggleton (Ed.), *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction* (pp. 1–66). New York, NY: Wiley-Liss.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Association.

Bandelow, B. (1995). Assessing the efficacy of treatments for panic disorder and agoraphobia. II. The panic and agoraphobia scale. *International Clinical Psychopharmacology*, *10*(2), 73–81. https://doi.org/10.1097/00004850-199506000-00003

Bandelow, B., Späth, C., Tichauer, G. A., Broocks, A., Hajak, G., & Rüther, E. (2002). Early traumatic life events, parental attitudes, family history, and birth risk factors in patients with panic disorder. *Comprehensive Psychiatry*, *43*(4), 269–278. https://doi.org/10.1016/j.psychres.2003.07.008

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory–II*. San Antonio, TX: Psychological Corporation.

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*(6), 885–908. https://doi.org/10.1037/a0017376

Bieling, P. J., Rowa, K., Antony, M. M., Summerfeldt, L. J., & Swinson, R. P. (2001). Factor structure of the Illness Intrusiveness Rating Scale in patients diagnosed with anxiety disorders. *Journal of Psychopathology and Behavioral Assessment*, *23*(4), 223–230. https://doi.org/0882-2689/01/1200-0223/0

Bradley, M. M., Costa, V. D., Ferrari, V., Codispoti, M., Fitzsimmons, J. R., & Lang, P. J. (2015). Imaging distributed and massed repetitions of natural scenes: Spontaneous retrieval and maintenance. *Human Brain Mapping*, *36*, 1381–1392. https://doi.org/10.1002/hbm.2278

Bradley, M. M., Sabatinelli, D., Lang, P. J., Fitzsimmons, J. R., King, W. M., & Desai, P. (2003). Activation of the visual cortex in motivated attention. *Behavioral Neuroscience*, *117*(2), 369–380. https://doi.org/10.1037/0735-7044.117.2.369

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., … Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*, *17*(5), 875–887. https://doi.org/10.1016/S0896-6273(00)80219-6

Brown, T. A., DiNardo, P. A., & Barlow, D. H. (1994). *Anxiety disorders interview schedule for DSM-IV (ADIS-IV)*. San Antonio, TX: Psychological Corporation.

Brunetti, M., Sepede, G., Mingoia, G., Catani, C., Ferretti, A., Merla, A., … Babiloni, C. (2010). Elevated response of human amygdala to neutral stimuli in mild post traumatic stress disorder: Neural correlates of generalized emotional response. *Neuroscience*, *168*(3), 670–679. https://doi.org/10.1016/j.neuroscience.2010.04.024

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and*

Biomedical Research, *29*(3), 162–173. https://doi.org/10.1006/cbmr.1996.0014

Cuthbert, B. N., Lang, P. J., Strauss, C., Drobes, D., Patrick, C. J., & Bradley, M. M. (2003). The psychophysiology of anxiety disorder: Fear memory imagery. *Psychophysiology*, *40*(3), 407–422. https://doi.org/10.1111/1469-8986.00043

Felmingham, K., Williams, L. M., Kemp, A. H., Liddell, B., Falconer, E., Peduto, A., & Bryant, R. (2010). Neural responses to masked fear faces: Sex differences and trauma exposure in posttraumatic stress disorder. *Journal of Abnormal Psychology*, *119*(1), 241–247. https://doi.org/10.1037/a0017551

Foa, E. (1996). *Posttraumatic diagnostic scale manual*. Minneapolis, MN: National Computer Systems.

Foa, E., Cashman, L., Jaycox, L., & Perry, K. (1997). The validation of a self-report measure of PTSD: The posttraumatic diagnostic scale. *Psychological Assessment*, *9*(4), 445–451. https://doi.org/10.1037/1040-3590.9.4.445

Frank, D. W., & Sabatinelli, D. (2014). Human thalamic and amygdala modulation in emotional scene perception. *Brain Research*, *1587*, 69–76. https://doi.org/10.1016/j.brainres.2014.08.061

Freese, J. L., & Amaral, D. G. (2006). Synaptic organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. *Journal of Comparative Neurology*, *496*(5), 655–667. https://doi.org/10.1002/cne.20945

Hendler, T., Rotshtein, P., Yeshurun, Y., Weizmann, T., Kahn, I., Ben-Bashat, D., … Bleich, A. (2003). Sensing the invisible: Differential sensitivity of visual cortex and amygdala to traumatic context. *NeuroImage*, *19*(3), 587–600. https://doi.org/10.1016/S1053-8119(03)00141-1

Hughes, K. C., & Shin, L. M. (2011). Functional neuroimaging studies of post-traumatic stress disorder. *Expert Review of Neurotherapeutics*, *11*(2), 275–285. https://doi.org/10.1586/ern.10.198

Insel, T. R., & Cuthbert, B. N. (2015). Medicine. Brain disorders? Precisely. *Science*, *348*(6234), 499–500. https://doi.org/10.1126/science.aab2358

Junghofer, M., Sabatinelli, D., Bradley, M. M., Schupp, H., Elbert, T., & Lang, P. J. (2006). Fleeting images: Rapid affect discrimination in the visual cortex. *NeuroReport*, *17*(2), 225–229. https://doi.org/10.1097/01.wnr.0000198437.59883.bb

Lane, R. D., Chua, P. M., & Dolan, R. J. (1999). Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. *Neuropsychologia*, *37*(9), 989–997. https://doi.org/10.1016/S0028-3932(99)00017-2

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual (Technical Report A-8)*. Gainesville, FL: University of Florida.

Lang, P. J., Bradley, M. M., Fitzsimmons, J. R., Cuthbert, B. N., Scott, J. D., Moulder, B., & Nangia, V. (1998). Emotional arousal and activation of the visual cortex: An fMRI analysis. *Psychophysiology*, *35*(2), 199–210. https://doi.org/10.1111/1469-8986.3520199

Lang, P. J., McTeague, L. M., & Bradley, M. M. (2016). RDoC, DSM, and the reflex physiology of fear: A biodimensional analysis of the anxiety disorders spectrum. *Psychophysiology*, *53*(3), 336–347. https://doi.org/10.1111/psyp.12462

Lang, P. J., Herring, D. R., Duncan, C., Richter, J., Sege, C. T., Weymar, M., … Bradley, M. M. (2017). The startle-evoked potential: Negative affect and severity of pathology in anxiety/mood disorders. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(7), 626–634. https://doi.org/10.1016/j.bpsc.2017.07.006

McEwen, B. S. (2017). Neurobiological and systemic effects of chronic stress. *Chronic Stress*, *1*, 1–11. https://doi.org/10.1177/2470547017692328

McTeague, L. M., Lang, P. J., Laplante, M.-C., Cuthbert, B. N., Shumen, J. R., & Bradley, M. M. (2010). Aversive imagery in posttraumatic stress disorder: Trauma recurrence, comorbidity, and physiological reactivity. *Biological Psychiatry*, *67*(4), 346–356. https://doi.org/10.1016/j.biopsych.2009.08.023

Mueller-Pfeiffer, C., Schick, M., Schulte-Vels, T., O'Gorman, R., Michels, L., Martin-Soelch, C., … Hasler, G. (2013). Atypical visual processing in posttraumatic stress disorder. *NeuroImage: Clinical*, *3*, 531–538. https://doi.org/10.1016/j.nicl.2013.08.009

Pai, A., Suris, A. M., & North, C. S. (2017). Posttraumatic stress disorder in DSM-5: Controversy, change, and conceptual consideration. *Behavioral Sciences*, *7*(1), 7. https://doi.org/10.3390/bs7010007

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., … Pitman, R. K. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: A functional MRI study. *Biological Psychiatry*, *47*(9), 769–776. https://doi.org/10.1016/S0006-3223(00)00828-3

Ross, R. A., Foster, S. L., & Ionescu, D. F. (2017). The role of chronic stress in anxious depression. *Chronic Stress*, *1*, 1–10. https://doi.org/10.1177/2470547016689472

Sabatinelli, D., Bradley, M. M., Fitzsimmons, J. R., & Lang, P. J. (2005). Parallel amygdala and inferotemporal activation reflect emotional intensity and fear relevance. *NeuroImage*, *24*(4), 1265–1270. https://doi.org/10.1016/j.neuroimage.2004.12.015

Sabatinelli, D., Lang, P. J., Bradley, M. M., Costa, V. D., & Keil, A. (2009). The timing of emotional discrimination in human amygdala and ventral visual cortex. *Journal of Neuroscience*, *29*(47), 14864–14868. https://doi.org/10.1523/JNEUROSCI.3278-09.2009

Shi, C., & Davis, M. (2001). Visual pathways involved in fear conditioning measured with fear-potentiated startle: Behavioral and anatomic studies. *Journal of Neuroscience*, *21*(24), 9844–9855. https://doi.org/10.1523/JNEUROSCI.21-24-09844.2001

Spiegler, B. J., & Mishkin, M. (1981). Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus-reward associations. *Behavioral Brain Research*, *3*(3), 303–317. https://doi.org/10.1016/0166-4328(81)90002-4

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press.

Starr, S., & Moulds, M. L. (2006). The role of negative interpretations of intrusive memories in depression. *Journal of Affective Disorders*, *93*, 125–132. https://doi.org/10.1016/j.jad.2006.03.001

van Buuren, S., & Groothuis-Oudshoorn, K. (2011). Mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software*, *45*, 1–67. https://doi.org/10.18637/jss.v045.i03

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., & Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nature Neuroscience*, *7*(9), 1271–1278. https://doi.org/10.1038/nn1341

Vyas, A., Miltra, R., Shankaranarayana Rao, B. S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *Journal of Neuroscience*, *22*(15), 6810–6818. https://doi.org/10.1523/JNEUROSCI.22-15-06810.2002

Watson, D., Weber, K., Assenheimer, J. S., Clark, L. A., Strauss, M. E., & McCormick, R. A. (1995). Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression

symptom scales. *Journal of Abnormal Psychology*, *104*(1), 3–14. https://doi.org/10.1037/0021-843X.104.1.3

Wendt, J., Weike, A. I., Lotze, M., & Hamm, A. O. (2010). The functional connectivity between amygdala and extrastriate visual cortex activity during emotional picture processing depends on stimulus novelty. *Biological Psychology*, *86*(3), 203–209. https://doi.org/10.1016/j.biopsycho.2010.11.009

Wild, J., Hackmann, A., & Clark, D. M. (2008). Rescripting early memories linked to negative images in social phobia: A pilot study. *Behavior Therapy*, *39*(1), 47–56. https://doi.org/10.1016/j.beth.2007.04.003

How to cite this article: Sambuco N, Bradley M, Herring D, Hillbrandt K, Lang PJ. Transdiagnostic trauma severity in anxiety and mood disorders: Functional brain activity during emotional scene processing. *Psychophysiology*. 2020;57:e13349. https://doi.org/10.1111/psyp.13349