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Greater Early Posttrauma Activation in the Right Inferior Frontal Gyrus Predicts Recovery From Posttraumatic Stress Disorder Symptoms

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ABSTRACT

BACKGROUND: Posttraumatic stress disorder (PTSD) has been associated with altered emotion processing and modulation in specific brain regions, i.e., the amygdala, insula, and medial prefrontal and anterior cingulate cortices. Functional alterations in these regions, recorded shortly after trauma exposure, may predict changes in PTSD symptoms.

METHODS: Survivors (N = 104) of a traumatic event, predominantly a motor vehicle accident, were included. Functional magnetic resonance imaging was used to assess brain activation 1, 6, and 14 months after trauma exposure (T1, T2, and T3, respectively). Participants performed the Shifted-attention Emotional Appraisal Task, which probes 3 affective processes: implicit emotional processing (of emotional faces), emotion modulation by attention shifting (away from these faces), and emotion modulation by appraisal (of the participants' own emotional response to these faces). We defined regions of interest based on task-related activations, extracted beta weights from these regions of interest, and submitted them to a series of analyses to examine relationships between neural activation and PTSD severity over the 3 time points.

RESULTS: At T1, a regression model containing activations in the left dorsolateral prefrontal cortex, bilateral inferior frontal gyrus (IFG), and medial prefrontal cortex during emotion modulation by appraisal significantly predicted change in PTSD symptoms. More specifically, greater right IFG activation at T1 was associated with greater reduction in symptom severity (T1–T3). Exploratory analysis also found that activation of the right IFG increased from T1 to T3.

CONCLUSIONS: The results suggest that greater early posttrauma activation during emotion appraisal in the right IFG, a region previously linked to cognitive control in PTSD, predicts recovery from PTSD symptoms.

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While most individuals experience at least one traumatic event during their lifetime (1), only some (1.7%–9.2%) develop posttraumatic stress disorder (PTSD) (2). Alterations in emotion processing and regulation have been reported in PTSD, including altered attentional bias to trauma-related cues (3), rumination, emotional suppression (4), impaired cognitive appraisal of emotions (5), higher impulsivity (6), and difficulty choosing an effective emotion regulation strategy (7). Initial evidence suggests that emotion dysregulation is associated with greater PTSD symptoms and predicts PTSD symptom trajectories (8,9).

Previous functional neuroimaging research has identified PTSD-related alterations in regions involved in emotion processing such as the amygdala and insula and in emotion regulatory circuitry comprising the dorsolateral prefrontal cortex (dlPFC), medial PFC (mPFC), and anterior cingulate cortex (ACC) (10). More specifically, studies have suggested that greater activations of the amygdala and insula and lower activations of the mPFC and ACC reflect neural processes underlying emotion regulation deficits in PTSD. However, it is still unclear whether these alterations constitute stable risk factors or are associated with changes in PTSD symptoms over time.

While early PTSD symptoms are significant risk indicators of prolonged PTSD (11,12), the underlying involvement of neuronal activities is not clear. Most studies linking PTSD symptoms with neurobiological alterations have been cross-sectional and retrospective, with observations often gathered a long time after the traumatic event (10), and therefore could not inform the role of the latter in the development and persistence of PTSD symptoms. An early posttrauma data collection and longitudinal follow-up are thus required for a better understanding of the role of early neurobiological alterations in PTSD symptom progression.

Preliminary evidence suggests that frontal activation during emotion regulation is associated with change in PTSD symptoms. More specifically, 2 weeks after trauma exposure, dorsal mPFC (dmPFC) activation during appraisal of fearful faces was associated with greater PTSD symptoms 2 weeks and 3 months after trauma (13). In a different study, greater activation of the ventral mPFC (vmPFC) and right inferior frontal gyrus

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(IFG), together with lower activation of the dlPFC during appraisal, predicted greater symptom improvement over a 24-month treatment course (14). Because the dlPFC and IFG are known to be involved in attentional control and vigilance to novel stimuli (15), it is possible that altered activation of regions that support executive function and attentional processes is involved in PTSD symptom development and maintenance. More studies involving larger groups are needed to resolve potential inconsistencies in the literature.

The current investigation aimed to examine the potential role of the early posttrauma function of the regions involved in emotion regulation in predicting change in PTSD symptoms in a large group of individuals recently exposed to trauma. We studied the same individuals 1, 6, and 14 months after exposure to a traumatic event, aiming to detect neural predictors of PTSD symptom progression. In addition, we examined changes in neural activation over time. While several large studies have examined patterns of neural function as predictors of PTSD symptoms following trauma [e.g., (16–18)], to our knowledge, this study is the first to specifically examine emotion processing and modulation, using functional magnetic resonance imaging (MRI) at multiple time points over the span of more than a year. We studied the activation patterns that underlie 3 affective processes: implicit emotional processing, emotion modulation by attention shifting, and emotion modulation by appraisal of threat faces. Based on preliminary reports in the literature (13,14), we hypothesized that activation within the PFC during emotion modulation by appraisal at baseline would be predictive of change in PTSD symptoms over the 14-month period after trauma. We included trauma survivors with both low and high PTSD symptoms to test the hypothesis that such prediction would be specific to change in symptoms (e.g., recovery) and would not represent a priori resilience. Given the association between emotional dysregulation and risk for PTSD (8), we explored whether neural activation during other emotion processing and/or regulation strategies, for example attention switch, could also be predictive of clinical outcome.

METHODS AND MATERIALS

Participants

This study is part of a larger project examining PTSD development during the first 14 months following trauma exposure (19). Included in this report are 104 adult civilians who were admitted to a general hospital's emergency department (ED) after experiencing a traumatic event and performed an emotion processing and modulation task in the MRI scanner. Of note, while this study enrolled trauma survivors with PTSD symptoms within 1 month after trauma, it oversampled the high-symptoms groups to generate a large enough sample of participants with PTSD at the end of the study. It also included a group of participants with low PTSD symptoms who reported symptoms at the initial phone interview but did not meet criteria for PTSD status at the clinical interview [for details, see (19)]. Of the initial sample, 6 participants were excluded due to excessive head motion during MRI scanning (see below) or data loss at T1, resulting in 98 participants with clinical and MRI data at T1. Of these participants, 82 and 85 participants also completed a clinical assessment and had Clinician-Administered PTSD Scale (CAPS) scores at the 6-month (T2) and 14-month (T3) follow-ups, respectively. For analysis of neural change across time points, there were 56 and 38 participants with clinical and MRI data at T1 and T2, and at T1 and T3, respectively (Figure 1). There was no difference in T1 CAPS scores between the participants included in the various analyses across the 3 time points (all $ps \geq .74$). For a description of demographic and clinical characteristics of the participants included in the different analyses, see Table 1.

Within the analyzed sample ($n = 98$), the most common trauma was motor vehicle accidents (92.86%). The rest were physical assault (3.06%) and other trauma types (4.08%) including terror attack, near-drowning accident, robbery, and animal attack. Exclusion criteria included head injury or coma upon arrival to the ED, contraindications for MRI scanning, known medical conditions that interfere with ability to give informed consent, current substance abuse disorder, current suicidal ideation, a current or past psychotic disorder, preexisting PTSD, and use of psychotropic medication or recreational drugs during the week prior to assessment. Preexisting PTSD was determined by 1) self-reported prior PTSD diagnosis (i.e., prior to their recent traumatic experience) or by 2) self-reported past trauma (unrelated to their recent ED admission), which was associated with the reported PTSD symptoms in the current study. Exclusion criteria were assessed during the initial phone screening within 1 month after admission to the ED, as well as during a clinical assessment at each of the time points. All participants gave written informed consent in accordance with the Declaration of Helsinki. The study was approved by the ethics committee at Tel-Aviv Sourasky Medical Center (reference No. 0207/14).

Clinical Assessments

We were mainly interested in examining whether neural activation shortly after the trauma could predict PTSD symptoms, as well as change in PTSD symptoms, over the 14-month follow-up period. We administered a combined instrument that scored both CAPS-IV (20) and CAPS-5 (21) items, as the transition from DSM-IV-TR to DSM-5 criteria took place during the study (19). When testing associations with symptoms, CAPS-5 scores were used as the main outcome measure. For secondary analysis, we classified participants based on their PTSD status, which was inferred when a participant met one of the following criteria: 1) met DSM-IV diagnostic criteria for PTSD, 2) met DSM-5 diagnostic criteria for PTSD, or 3) endorsed CAPS-IV symptom severity of $\geq$40. After PTSD status was determined for each time point, 3 trajectory groups were created: 1) low symptoms, i.e., no PTSD at both T1 and T3; 2) remission, i.e., PTSD at T1 but not at T3; and 3) nonremission, i.e., PTSD at both T1 and T3 (Table 1). Two participants who fell short of PTSD status at T1 but had PTSD at later time points were included in the nonremission group. While both the remission and nonremission groups had greater CAPS T1 scores than the low symptoms group (both $ps < .001$), CAPS T1 scores were also greater in the nonremission than in the remission group ($p = .004$). We use the term trajectory to refer to the analysis of these 3 trajectory groups, an approach that was intended to shed further light on the progression of symptoms over the 14-month period after trauma and is consistent with a recent report from the same cohort (22).

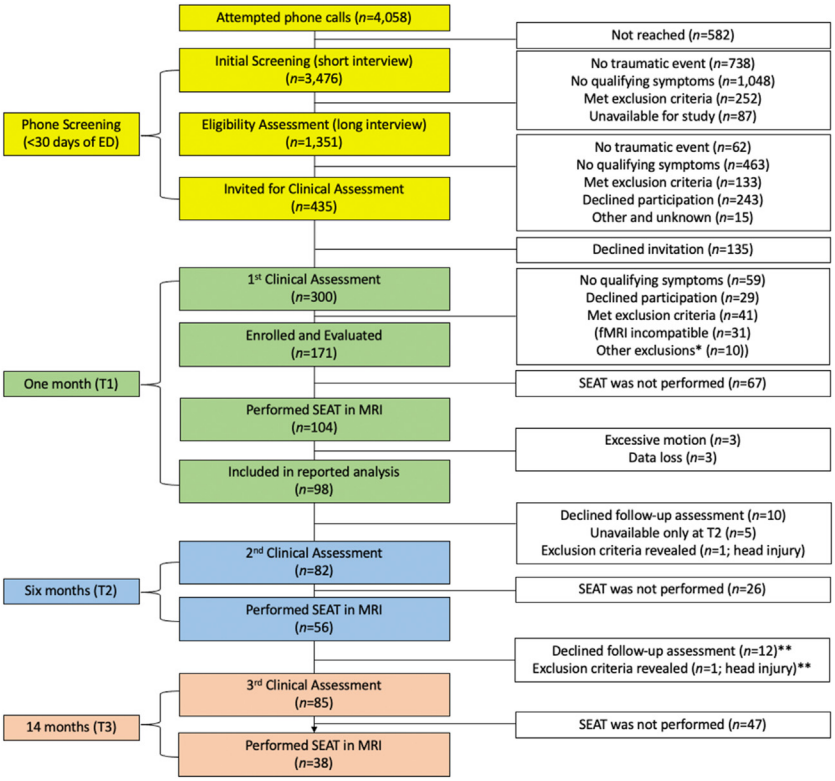


Figure 1. CONSORT diagram depicting the inclusion and exclusion of participants in this report. *Other exclusions (n = 10) included serious medical/surgical condition requiring clinical attention (n = 5), chronic posttraumatic stress disorder before the current event (n = 2), current substance use disorder (n = 1), head injury (n = 1), and no traumatic event (n = 1). **Number of participants is out of the initial reported sample (n = 98). ED, emergency department; fMRI, functional magnetic resonance imaging; SEAT, Shifted-attention Emotion Appraisal Task.

Computer Task

Participants completed the Shifted-attention Emotion Appraisal Task (SEAT) [originally modified from (23)], which has been shown to consistently activate/deactivate brain regions implicated in emotion processing and regulation (anterior insula and amygdala, dlPFC, vmPFC, and dmPFC) (13,14,24,25). Participants viewed compound images of neutral or threat faces superimposed on indoor/outdoor

Table 1. Demographic and Clinical Characteristics of the Participants Included at the Different Time Points

	n	Gender, Female, %	Age, Years, Mean (SD)	CAPS-5 Score, T1, Mean (SD)	CAPS-5 Score, T2, Mean (SD)	CAPS-5 Score, T3, Mean (SD)
Associations With Activation at T1						
Participants with MRI and CAPS data at T1	98	56.12%	33.36 (11.26)	24.15 (11.67)	–	–
Participants with MRI data at T1 and CAPS data at both T1 and T2	82	60.98%	34.04 (11.26)	23.57 (11.66)	24.57 (12.66)	–
Participants with MRI data at T1 and CAPS data at both T1 and T3	85	60%	33.81 (11.3)	24.08 (11.89)	–	10.69 (10.1)
Exploratory: Change in Activation						
Participants with MRI and CAPS data at both T1 and T2	56	60.71%	34.56 (12.09)	24.21 (12.11)	14.48 (10.06)	–
Participants with MRI and CAPS data at both T1 and T3	38	65.79%	35.21 (12.75)	24.16 (12.45)	–	10.82 (9.53)
Trajectory Groups[a]						
Low symptoms	22	40.91%	35.86 (13.07)	10.27 (4.59)	6.91 (8.42)	3.45 (4.67)
Remission	42	61.9%	32.83 (11.36)	26.45 (7.74)	13.87 (8.24)[b]	7.81 (6.51)
Nonremission	21	76.19%	33.62 (9.27)	33.81 (11.32)	23.25 (7.06)[c]	24.05 (7.49)

CAPS, Clinician-Administered PTSD Scale; MRI, magnetic resonance imaging; PTSD, posttraumatic stress disorder; T, time point.

[a]Trajectory groups were based on PTSD status: 1) low symptoms indicates no PTSD at both T1 and T3; 2) remission indicates PTSD at T1 but not at T3; and 3) nonremission indicates PTSD at both T1 and T3.

[b]Based on n = 38 due to 4 remission group participants who were not available at T2.

[c]Based on n = 20 due to 1 nonremission participant who was not available at T2.

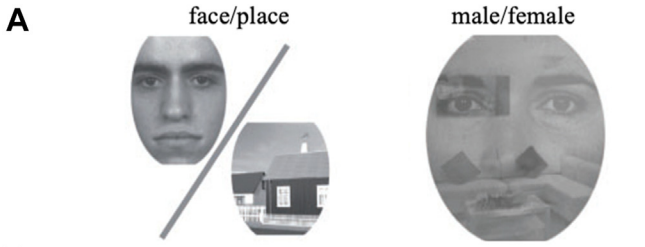
scenes (Figure 2A). Before each image, one of 4 prompts appeared: 1) male/female (identify the gender of the person based on the facial appearance), to probe implicit emotional processing; 2) indoor/outdoor (determine if the background scene was indoors or outdoors), to probe emotion modulation by shifting attention away from the face; 3) like/dislike (report if the participant liked or disliked the face), to probe emotion modulation by appraisal; and 4) face/place (indicate if the image was a face or a place), to control for brain activation associated with viewing faces and scenes alone. Trials were randomly presented in an event-related design. Each session included 3 runs of 55 trials each (15 male/female, 15 indoor/outdoor, 15 like/dislike, 10 face/place). Trials comprised a prompt for 750 ms, a blank screen for 250 ms, and a compound image for 1500 ms. A fixation cross was presented during the intertrial interval (jittered duration: 3–7.2 seconds).

Data Acquisition and Analysis

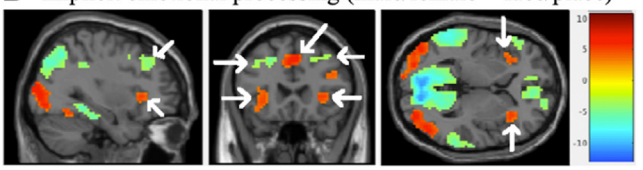
MRI scans were acquired with a Siemens 3T MAGNETOM Prisma scanner using a 20-channel head coil. For high-resolution whole-brain structural images, a sagittal T1-weighted magnetization-prepared rapid acquisition gradient-echo sequence was acquired (repetition time/echo time = 2400/2.29 ms, flip angle = 8°, field of view = 224 × 224 mm^2, voxel size = 0.7 × 0.7 × 0.7 mm^3). Functional whole-brain scans were acquired in an interleaved order using a T2*-weighted echo-planar imaging sequence (repetition time/echo time = 2000/28 ms, flip angle = 90°, field of view = 220 × 220 mm^2, voxel size = 3 × 3 × 3 mm^3, 36 slices per volume, 185 volumes per run).

MRI data preprocessing and analysis were performed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm-statistical-parametric-mapping/; Wellcome Centre for Human Neuroimaging) according to standard procedures. More specifically, functional images were slice-time corrected with sinc interpolation, realigned, and coregistered to the structural images; normalized to the Montreal Neurological Institute standard brain; and smoothed with a 5-mm kernel. Data were visually inspected to ensure adequate quality as well as accuracy of coregistration and normalization steps. Runs with more than 3 mm of motion in any plane (x, y, z, pitch, roll, yaw) were excluded from further analyses. Excessive motion resulted in the exclusion of 28 runs across 18 scan sessions, including the exclusion of 3 participants at T1 who had excessive motion during all 3 runs. All motion parameters and their derivatives were included as nuisance regressors in the subject-level analysis. A mask threshold of 0.5 was applied during first-level analysis.

Consistent with prior studies using the SEAT (13,14,24,25), regions of interest (ROIs) were defined based on task-related

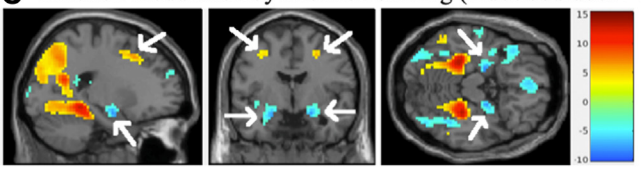


B Implicit emotional processing (male/female > face/place)



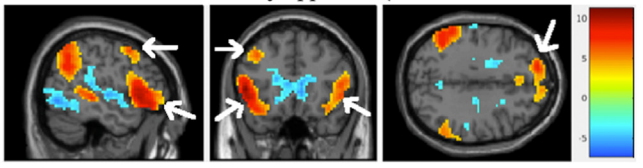
Region	Coordinates (x, y, z)	Cluster K	Ze	Cluster p (FWE-corrected)
dACC	3, 23, 44	163	5.89	<.001
Bilateral insula	L: -33, 23, -4 R: 33, 23, 2	88 42	4.36 4.69	.002 .050
Bilateral dlPFC	L: -24, 20, 41 R: 33, 32, 38	208 164	-5.29 -4.60	<.001 <.001

C Emotion modulation by attention shifting (indoor/outdoor > male/female)



Region	Coordinates (x, y, z)	Cluster K	Ze	Cluster p (FWE-corrected)
Bilateral dlPFC	L: -21, 14, 47 R: 27, -4, 47	81 61	5.67 4.93	.004 .017
Bilateral amygdala	L: -18, -7, -16 R: 21, -7, -13	151 74	-7.23 -7.56	<.001 .007

D Emotion modulation by appraisal (like/dislike > male/female contrast)



Region	Coordinates (x, y, z)	Cluster K	Ze	Cluster p (FWE-corrected)
dlPFC	L: -48, 11, 47	193	6.00	<.001
Bilateral IFG	L: -54, 23, 5 R: 54, 26, -4	688 352	Inf 7.31	<.001 <.001
mPFC	-15, 53, 38	530	6.80	<.001

Figure 2. **(A)** Examples of Shifted-attention Emotion Appraisal Task stimuli; **(B–D)** Task-based contrast maps on the Shifted-attention Emotion Appraisal Task across all participants at time point T1. Coordinates represent the center of each region-of-interest sphere extracted for analyses along with corresponding cluster size (K), Ze (peak-level Z-equivalent score), and familywise error (FWE)–corrected *p* value. Maps were generated by xjView with initial $p \leq .001$ and cluster size = 40. dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; L, left; mPFC, medial PFC; R, right.

Table 2. Summary of Primary Analyses: Prediction of Symptoms Based on Neural Activation at T1

Time Point of Predicted Symptoms		Implicit Emotional Processing	Emotion Modulation by Attention Shifting	Emotion Modulation by Appraisal
T1	*F*	1.155	1.038	1.309
	p	.337	.392	.273
T2	*F*	0.652	0.634	0.050
	p	.661	.640	.995
T3	*F*	0.478	0.303	0.476
	p	.792	.875	.753

Linear regression models included regions of interest that had significant activation in each task condition (Figure 2): Implicit emotional processing (dorsal anterior cingulate cortex, bilateral insula, bilateral dorsolateral prefrontal cortex [PFC]), emotion modulation by attention shifting (bilateral dorsolateral PFC, bilateral amygdala), and emotion modulation by appraisal (left dorsolateral PFC, bilateral inferior frontal gyrus, medial PFC). None of the models was significant.

T, time point.

activations across all participants at T1, independent of their PTSD status. More specifically, we identified clusters in the contrast maps for each task condition which 1) were significant ($p < .050$ familywise error corrected after initial thresholding at $p \leq .001$ uncorrected), and 2) represented regions that underlie emotion processing and modulation, which have been successfully probed using the SEAT in prior studies (dorsal ACC [dACC], insula, dlPFC, amygdala, IFG, mPFC) (Figure 2). ROIs were defined as 5-mm-radii spheres at each identified cluster, except for the amygdala ROI, which was a 3-mm sphere (26) and was centered at the peak of activation of each cluster. This method allowed us to define the ROIs that were most specific to our overall cohort task effects for each contrast of interest (implicit emotional processing: male/female > face/place; emotion modulation by attention shifting: indoor/outdoor > male/female; emotion modulation by appraisal: like/dislike > male/female). We then extracted beta weights from significant ROIs and submitted them to a series of analyses in IBM SPSS Statistics version 28 (https://www.ibm.com/products/spss-statistics). Separate linear regression models were constructed for neural activation during each task condition (implicit emotional processing, emotion modulation by attention shifting, emotion modulation by appraisal) at T1, with all ROIs for each corresponding contrast included in each model (Figure 2). Models were used to predict CAPS scores at each time point, as well as change in CAPS scores between time points (T1, T2, T3, T1–T2, T1–T3) (Tables 2 and 3).

Then, we used the ImCalc function of SPM12 to test change in neural activation (T1–T2, T1–T3) (Table 4). Beta weights from each ROI in each corresponding construct of interest were extracted from the generated difference maps and submitted to analysis in SPSS. We performed one-sample *t* tests to determine whether any of the ROIs had a change in activation significantly different from 0 and correlation analysis to test the relationship between change in activation and change in CAPS score. Due to the limited number of participants who had MRI data from the SEAT at T2 and T3 ($n = 56$ and $n = 38$, respectively) (Table 1), these analyses were exploratory and provide preliminary evidence that awaits further replication. Accordingly, statistical corrections for multiple exploratory analyses were not applied.

RESULTS

Task-Based Neural Activations

First, we examined task-based neural activations across all participants at T1 to compare them to previously established SEAT-related patterns of activations as a quality control and procedures validation in the given cohort. During implicit emotional processing (male/female > face/place contrast), as predicted, there were significant activations in regions associated with emotion processing (dACC and bilateral insula) and deactivation in regions associated with emotion modulation (bilateral dlPFC) (Figure 2B). Reciprocally, during emotion modulation by attention shifting (indoor/outdoor > male/female contrast), there were robust activations in regions associated with attention modulation (bilateral dlPFC) and robust deactivation in regions associated with emotion processing (bilateral amygdala) (Figure 2C). During emotion modulation by appraisal (like/dislike > male/female contrast), there were robust activations in both emotion processing and regulatory regions (left dlPFC, bilateral IFG and mPFC) (Figure 2D), consistent with previous findings [e.g., (14,24)].

Table 3. Summary of Primary Analyses: Prediction of Change in Symptoms Based on Neural Activation at T1

Time Points of Predicted Change in Symptoms		Implicit Emotional Processing					Emotion Modulation by Attention Shifting				Emotion Modulation by Appraisal			
		dACC	Left Insula	Right Insula	Left dlPFC	Right dlPFC	Left dlPFC	Right dlPFC	Left Amygdala	Right Amygdala	Left dlPFC	Left IFG	Right IFG	mPFC
T1–T2	β	−0.057	−0.057	0.026	0.059	−0.029	0.059	0.008	−0.065	−0.106	0.045	−0.101	0.110	0.023
	p	.709	.723	.862	.598	.789	.583	.944	.584	.390	.723	.421	.301	.860
T1–T3	β	0.056	0.093	−0.174	0.075	−0.024	−0.020	0.179	−0.066	−0.047	0.157	−0.134	0.210[a]	−0.067
	p	.717	.555	.246	.508	.829	.853	.150	.584	.715	.213	.268	.042[a]	.608

Linear regression models included regions of interest that had significant activation in each task condition and controlled for Clinician-Administered PTSD Scale at T1.

dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; mPFC, medial PFC; PTSD, posttraumatic stress disorder; T, time point.

[a]Significant finding.

Table 4. Summary of Exploratory Analyses of the Change in Neural Activation

Time Points of Change in Neural Activation		Implicit Emotional Processing					Emotion Modulation by Attention Shifting				Emotion Modulation by Appraisal			
		dACC	Left Insula	Right Insula	Left dlPFC	Right dlPFC	Left dlPFC	Right dlPFC	Left Amygdala	Right Amygdala	Left dlPFC	Left IFG	Right IFG	mPFC
T1–T2	*t*	0.034	0.059	−0.608	1.010	−0.353	−0.367	−0.456	−0.011	0.243	−0.045	−0.954	0.508	0.495
	p	.973	.953	.546	.317	.726	.715	.650	.991	.809	.964	.344	.613	.622
T1–T3	*t*	−0.121	0.317	−0.440	0.430	0.322	−1.289	−1.375	−0.582	−0.612	−1.212	−1.447	−2.065[a]	−0.316
	p	.905	.753	.662	.670	.749	.206	.177	.564	.544	.233	.156	.046[a]	.754

dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; mPFC, medial PFC; T, time point.
[a]Significant finding.

Associations Between Neural Activations at T1 and PTSD Symptoms Across Time

We used regression models to examine activation in ROIs at T1 as predictors of PTSD symptoms across all 3 time points. Activations during implicit emotional processing (male/female > face/place), emotion modulation by attention shifting (indoor/outdoor > male/female), and emotion modulation by appraisal (like/dislike > male/female) did not predict PTSD symptoms at any of the time points (all *p*s > .27) (Table 2). When examining activation in ROIs at T1 as predictors of change in PTSD symptoms after controlling for baseline symptom severity at T1, activation in the right IFG during emotion modulation by appraisal was the only region that significantly contributed to the prediction (model: $R^2 = 0.403$, $F_{5,79} = 10.675$, $p < .001$; right IFG: $\beta = 0.210$, $sr^2 = 0.032$, $p = .042$) (Figure 3). Due to gender differences in CAPS scores at all 3 time points (females > males) (all *p*s < .050), we re-ran the regression model while controlling for gender and confirmed that it was not driving our finding (right IFG: $\beta = 0.211$, $p = .039$). No other region contributed significantly to any of the models (all *p*s ≥ 1.50) (Table 3).

Post Hoc Analysis of Trajectory Groups

We followed up on the main finding with post hoc independent-samples *t* tests to compare activation of the right IFG during emotion modulation by appraisal (like/dislike > male/female) at T1 between the 3 trajectory groups. More specifically, we compared activation in the remission (participants who had PTSD at T1 but not at T3) group to the nonremission (participants with PTSD at both T1 and T3) and the low symptoms (participants without PTSD at both time points) groups. As hypothesized, at T1, the remission group had greater right IFG activation than the nonremission (trend level, $t_{61} = 1.599$, one-sided $p = .058$) and low symptoms (trend level, $t_{62} = 1.392$, one-sided $p = .084$) groups (Figure 4).

Exploratory: Change in Neural Activations Across Time

We examined the change in activation within ROIs across the 3 time points to better understand the dynamics of candidate neurobiological mechanisms involved. We observed an increase in activation in the right IFG from T1 to T3 during emotion modulation by appraisal (like/dislike > male/female) ($t_{37} = -2.065$, $p = .046$). Given the association between right IFG activation and change in PTSD symptoms, we hypothesized that an increase in right IFG activation would be associated with decrease in PTSD symptoms. A post hoc analysis confirmed this hypothesis and showed a negative correlation between change in right IFG activation (T1–T3) during emotion modulation by appraisal and change in PTSD symptoms (T1–T3) (trend level; $r = -0.248$, one-tailed $p = .067$) (Figure 5). No other changes were found in neural activations across all other ROIs and task conditions (all *p*s > .100) (Table 4).

DISCUSSION

In participants with recent trauma exposure, we examined whether neural activation during emotion processing and modulation predicts change in PTSD symptoms during the first critical year following trauma. We also performed an exploratory analysis to examine changes in neural activation and their association with changes in PTSD symptoms (i.e., if greater activation contributes to better recovery, does an increase in activation in the same region contribute to recovery?). Of note, because we recruited participants with high PTSD symptom severity 1 month after trauma (19), we aimed to study the progression of PTSD symptoms rather than acute stress symptoms that develop shortly after the trauma and often go away within the first month.

The SEAT (13,14,24,25,27–32) was used to probe the neural circuitry involved in implicit emotional processing, attentional modulation of emotion, and emotion modulation by appraisal. Consistent with prior studies, we defined ROIs based on activations across all participants at T1 and independent of their PTSD status to account for potential variability due to neuroanatomical variations related to cohort differences. Robust neural activation patterns during this task were consistent with other samples [e.g., (13,14,24,25)] and included activation/deactivation patterns in the insula, dACC, amygdala, dlPFC, mPFC, and IFG. Other significant patterns outside these a priori ROIs were not the focus of this investigation [e.g., deactivation of the default mode network, as seen during implicit emotional processing (Figure 2B), might occur during the performance of any demanding cognitive or emotional task (33)].

A model that included early activation of the left dlPFC and the bilateral IFG and mPFC during emotion modulation by appraisal (like/dislike > male/female) predicted change in PTSD symptoms across the 14-month period after trauma. This was driven by the association between greater right IFG activation and reduction in PTSD symptoms. The potential contribution of activation/deactivation patterns in other ROIs

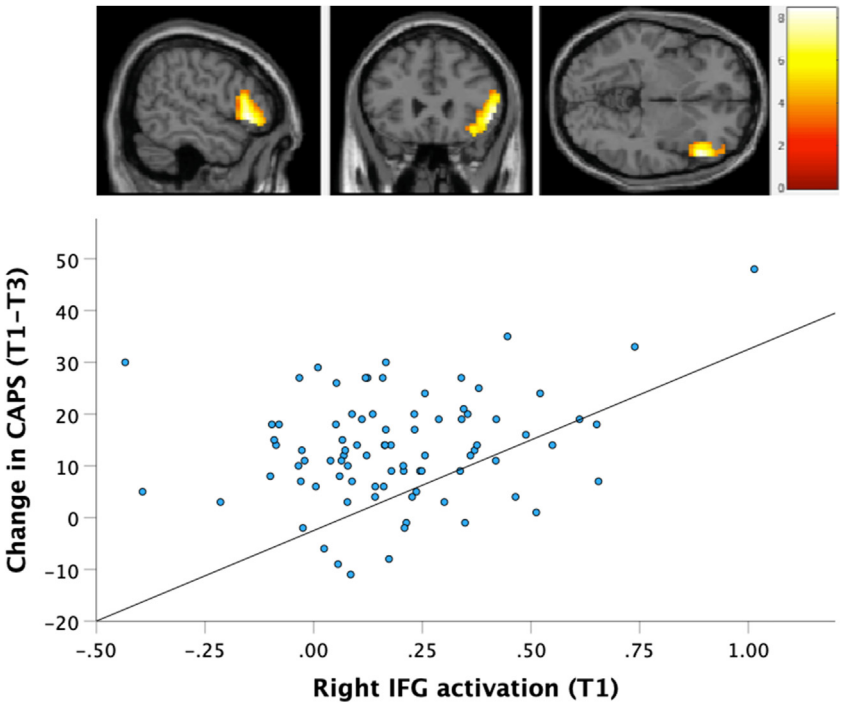


Figure 3. Activation in the right inferior frontal gyrus (IFG) (top) contributed significantly to the linear regression model that predicted change in Clinician-Administered PTSD Scale (CAPS) scores from time points T1 to T3 and controlled for baseline symptom severity at T1 (bottom; $\beta = 0.210$, $sr^2 = 0.032$, $p = .042$). Beta values were extracted from a 5-mm-radii region-of-interest sphere centered at the activation peak (54, 26, −4).

did not reach statistical significance in this model. In the exploratory analysis, an increase in right IFG activation during emotional modulation by appraisal was the only identified neural change over the course of 14 months after trauma, further highlighting the role of this region, as well as cognitive appraisal (9), in PTSD symptom change after trauma.

The coordinates of bilateral IFG in the current study are consistent with the ventral attention network parcellation (34) [also see (15)], which is involved in alerting attention and maintaining vigilance for novel/unexpected stimuli (35). There is evidence that the right IFG also plays a role in modulation of attentional biases for emotional information and specifically in the disengagement of attention from negative stimuli (36). The right IFG also subserves the suppression of impulses and actions [i.e., response inhibition (37)], as well as the shift between affective and cognitive domains, where the emotional significance of stimuli could affect inhibitory processes (38). It has been argued that altered response inhibition could

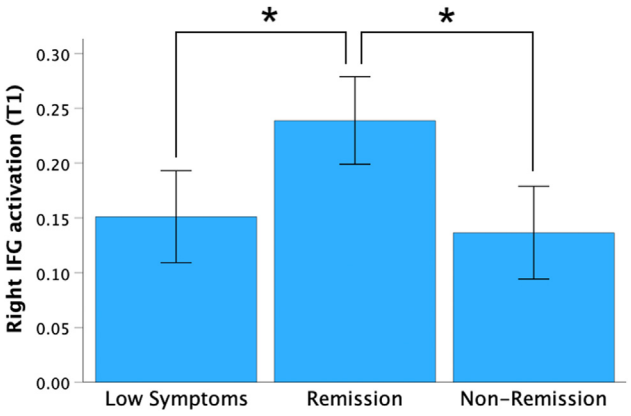


Figure 4. Activation of the right inferior frontal gyrus (IFG) during emotion modulation by appraisal at time point T1 in symptom trajectory groups. The remission group had greater right IFG activation than the nonremission and low symptoms groups at T1. Asterisks represent trend-level differences ($.050 < p < .100$). Error bars indicate SEM.

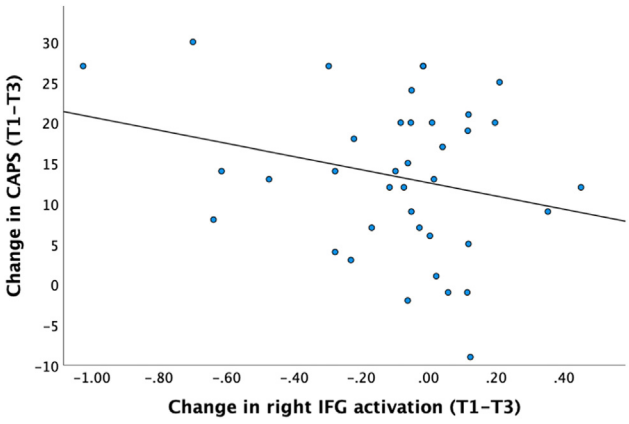


Figure 5. Negative correlation between change in right inferior frontal gyrus (IFG) activation (time points T1–T3) during emotion modulation by appraisal and change in posttraumatic stress disorder symptoms (T1–T3) (trend level, $p = .067$). CAPS, Clinician-Administered PTSD Scale; PTSD, posttraumatic stress disorder.

contribute to the impaired cognitive control that is seen in PTSD (39), and indeed, reduced activation of the right IFG was reported in veterans with PTSD during a response inhibition task ["stop signals" (40,41)]. It is possible that the greater right IFG activation during emotion modulation by appraisal during the SEAT represents a top-down modulation and enhanced control over the response to negative faces. This, in turn, could represent better overall emotional regulation (42), which can lead to better recovery after trauma as we observed in the current study.

With particular relevance to, and in agreement with, our findings, two recent prospective studies found that activation of the right IFG predicted PTSD symptom severity. First, Powers *et al.* (43) demonstrated that greater right IFG activation during response inhibition within 2 months after trauma predicted less PTSD symptoms 6 months after trauma. Second, greater right IFG activation during emotion modulation by appraisal during the SEAT predicted greater reduction in PTSD symptoms over the course of treatment (14). Our study provides compelling evidence for the role of the right IFG in PTSD symptom progression and suggests that increased activation over time could underlie recovery from PTSD symptoms.

Several limitations of this study should be noted. First, although our dropout rate was low, some participants did not perform the SEAT during the follow-up time points, limiting the analysis of the change in neural activation after trauma. While we were able to detect a significant change in right IFG activation 14 months after trauma, a statistical correction for multiple comparisons was not applied in these exploratory analyses. In addition, while its association with change in CAPS scores was in the expected direction, the association was at trend-level significance, possibly due to the lower *n* compared with the T1 analysis. Relatedly, while there have been several published studies with repeated SEAT measurements (13,14,25), there has not been a report of the test-retest reliability of this task. However, it should be noted that both the long duration of 6 to 8 months between time points and the lack of cognition-based processes that can be readily learned make practice effects less likely. Moreover, the association with CAPS scores further supports the notion that our finding is not merely the result of a time effect. With these considerations in mind, future work should directly address this concern by examining test-retest reliability. Taken together, the preliminary findings from these exploratory analyses should be treated with caution and replicated in future research.

Second, while the current longitudinal investigation provided us with the opportunity to compare participants with distinct symptom trajectories, secondary post hoc analyses were underpowered to examine these effects, and the findings were at trend level. Because these findings are relevant to understanding potential links between neural activation and PTSD symptom change after trauma, we opted to report but not interpret them. Future studies should attempt to replicate our results in larger samples. Third, the fact that participants who completed MRI scans at T2 had lower symptoms suggests that T2 (6 months after trauma) may reflect a less stable and more fluctuating level of symptoms, which could have contributed to the negative findings involving T2. Fourth, our sample consisted of ED-admitted civilians who predominantly had experienced one type of traumatic event (motor vehicle accidents), thus limiting generalizability to other types of trauma. Finally, future work could investigate associations between neural activation and specific PTSD symptom clusters, as well as include a non–trauma-exposed group to test the effect of trauma exposure on neural patterns (44).

Conclusions

To our knowledge, this is one of the first and the largest study to date to investigate neural activation during emotional processing and modulation as a predictor of PTSD symptoms in recent trauma survivors. While a few large studies have provided important evidence for the utility of acute functional MRI data to predict PTSD symptoms [e.g., (16–18)], they tested other cognitive processes (e.g., resting-state, threat/reward reactivity, and inhibitory engagement), followed participants for shorter periods of time (e.g., 3–6 months), and importantly, did not include scans at follow-up time points to investigate neural changes over time. Furthermore, the preferential enrollment of trauma survivors with high acute PTSD symptoms in the current study enabled us to investigate the differential trajectories of early posttrauma symptoms. Our findings demonstrate that greater right IFG activation during emotion modulation by appraisal predicts greater recovery after trauma. They further suggest that such activation may increase during the 14 months after trauma, a neural change that could serve as a neurobiological mechanism that underlies trauma recovery, consistent with the reported adaptive role of the right IFG in trauma-exposed individuals. Future research with larger samples at the follow-up time points is needed to confirm the findings from our exploratory longitudinal neuroimaging analysis.

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ClinicalTrials.gov: Neurobehavioral Moderators of Post-traumatic Disease Trajectories; https://www.clinicaltrials.gov/study/NCT03756545; NCT03756545.

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